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4-Fluoroamphetamine in the Netherlands: more than a one-night stand

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ABSTRACT

Aims To investigate the temporal pattern of appearance of a new psychoactive substance (4-fluoroamphetamine) on the Dutch drug market, as well as its patterns of use and effects. **Design** Data from the Drug Information and Monitoring System (DIMS) was used to investigate the emergence of 4-fluoroamphetamine on the Dutch drug market. An on-line questionnaire was used to study its patterns of use and effects. **Setting** Dutch drug-related websites and social media. **Participants** A convenience sample of 249 life-time 4-fluoroamphetamine users was recruited through the internet. **Measurements** Samples containing 4-fluoroamphetamine were extracted from the DIMS database for further investigation. Patterns of use, settings of use and the subjective effects of 4-fluoroamphetamine, amphetamine and 3,4-methylenedioxymethamphetamine (MDMA) were investigated with the on-line questionnaire. **Findings** 4-Fluoroamphetamine was first encountered on the Dutch drug market, sold mainly as amphetamine or ecstasy (MDMA), between 2007 and 2009. These misrepresented drug samples declined when the MDMA and amphetamine markets recovered after a period of shortage, whereas purposefully bought 4-fluoroamphetamine samples showed an increase. Survey results showed that 4-fluoroamphetamine is used predominantly [77.1%, 95% confidence interval (CI) = 72.0–82.3] for its specific effects, rather than its legal status (17.7%, 95% CI = 10.7–22.1). The subjective effects of 4-fluoroamphetamine were compared with those of amphetamine and MDMA. Subjective effect scores of 4-fluoroamphetamine ranged between those of amphetamine and MDMA. **Conclusions** The stimulant 4-fluoroamphetamine is increasingly popular in the Netherlands, which might be due to its subjective effects profile, which lies intermediate between amphetamine and MDMA.

Keywords Amphetamine, MDMA, new psychoactive substance, questionnaire, reported effects, 4-fluoroamphetamine.

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INTRODUCTION

In recent years, the face of the global drug market has changed radically, due to the increasing availability of new psychoactive substances (NPS). The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reported a dramatic increase from 14 different NPS that were first detected in 2005 to 81 in 2013 [1]. Most of these substances appear to be substituted molecules of known drug classes already on the market, such as phenylethylamines or cathinones. In light of this expansive increase of NPS world-wide and their easy availability through the internet, it is important to monitor some of these substances in greater detail, especially their prevalence on the market and the extent in which they are actually used by drug consumers.

Some of the main reasons reported for using NPS were their relative safety, few side effects, cheapness, availability and stable quality [2,3], and there are studies that have suggested that NPS have been added to the repertoire of the already established club drugs, such as 3,4-methylenedioxymethamphetamine (MDMA) and cocaine, even after a ban [4,5], indicating that the choice of drug is not influenced solely by the legal status of the drug [3].

There has been a steady increase of drugs submitted to the Dutch Drug Information and Monitoring System (DIMS) that can be categorized as NPS [6]. Of these substances, 4-fluoroamphetamine seems to have gained

territory, as was revealed by study into the nightlife behaviour of 3335 Dutch partygoers in 2013 [7]; see Table 1. Last month use is particularly striking, as it was at almost the same level as ketamine or γ-hydroxybutyric acid (GHB), well-established drugs of choice among partygoers in the Netherlands [6,8–10].

4-Fluoroamphetamine (often termed 4-FA or 4-FMP by the users) belongs to the class of phenethylamines. In animals, it has a neurostimulatory action by inhibiting the dopamine (DA), 5-hydroxytryptamine (5-HT) and noradrenaline (NE) re-uptake and accelerates secretion of these monoamines [11,12]. It was also shown that 4-fluoroamphetamine was more potent in 5-HT release than amphetamine [13]. To our knowledge, however, to date there are no pharmacological studies on the effects of 4-fluoroamphetamine in humans.

The aim of this study is to investigate the pattern of emergence of 4-fluoroamphetamine on the Dutch drug market, its patterns of use and some of its subjective effects in humans. DIMS data are used to show the trend of 4-fluoroamphetamine on the drug market. In addition, through means of an on-line questionnaire, this study will investigate patterns of use. Furthermore, subjective effects of 4-fluoroamphetamine are compared to those of the established illicit drugs amphetamine and MDMA.

METHODS

Participants

Participants for the on-line 4-fluoroamphetamine questionnaire were recruited through a number of websites, such as Twitter, Facebook and Unity, a peer-education project in the Netherlands for alcohol and drugs. The Global Drug Survey (GDS) uses the same Dutch channels of recruitment [14], so this sample was expected to represent the 4-fluoroamphetamine-using subsample. Similar to the GDS, this survey was based on opportunistic sampling and was considered the most feasible to obtain this kind of sentinel population. Completing the questionnaire was voluntary, anonymous, took approximately 15–20 minutes to complete and respondents were obliged to agree to a statement of informed consent. Participants had to be 18 years or older and the final inclusion criterion was life-time use of 4-fluoroamphetamine. The survey ran between 1 May and 1 July, 2014, and 4-fluoroamphetamine was not scheduled at that time.

Table 1 Life-time, last year and last month use of new psychoactive substances (NPS) among Dutch partygoers aged 15–35 years ($n = 3335$).

NPS	*Life-time % (n)*	*Last year % (n)*	*Last month % (n)*
4-fluoroamphetamine	9.9 (330)	8.5 (284)	3.8 (127)
Mephedrone	5.2 (173)	2.5 (84)	0.7 (23)
Methylone	4.2 (140)	2.2 (72)	0.5 (17)
Methoxetamine	3.0 (100)	2.3 (77)	0.3 (10)
6-APB	2.9 (97)	2.1 (69)	0.6 (20)
Spice	2.3 (77)	1.3 (43)	0.6 (20)

Source: Trimbos Institute [7].

Measurements

Questionnaire

The questionnaire was conducted with Limesurvey, an online survey programme. The first part dealt with age, gender and patterns of use. In the second part, participants were asked about the effects of 4-fluoroamphetamine. First, they were given the option of choosing the main positive effect and the three most frequent adverse effects. Then, participants were asked to rate the effects of 4-fluoroamphetamine, amphetamine and MDMA in terms of the following 12 typical adjectives for stimulatory and entactogenic effects, obtained from the scientific literature [15,16]: intensity, stimulation, alertness, euphoria, connectedness to others, talkative/sociable, self-confidence, changed sensory perception, irritability, confusion, dizziness and craving. Effects were scored on a five-point Likert scale, with 1 being very weak and 5 being very strong.

Monitoring and chemical analysis of drug samples

DIMS is a scientific surveillance monitor which continuously monitors the Dutch illegal drug market by analysing consumer samples [17]. Drugs can be submitted by consumers to have their chemical contents analysed and to obtain information and advice on risk reduction. For this study, samples that contained 4-fluoroamphetamine and/or were sold as 4-fluoroamphetamine were examined. The DIMS methodology is described in detail elsewhere [17].

Statistical analysis

Mixed-effects linear regression models were used to compare subjective effects, with substance (MDMA, amphetamine and 4-fluoroamphetamine) as fixed effect. First, variables were converted into cases to allow for a comparison of effects between and within the subjects, as subjects could have reported effects on more than one substance. Responses to each substance were converted into cases, with subject as case identification, so three cases ('MDMA', 'amphetamine', '4-fluoroamphetamine') for each subject were created. Then, linear mixed-effects regression was executed with 4-fluoroamphetamine as reference category. This model was designed to compare effects between and within the subjects. It also dealt with the fact that there were missing responses for some of the effects or some of

the participants. Co-dependence in the data due to some respondents having used more than one substance (within-subject) was taken into account by a random intercept for subject. To reduce the likelihood of type I errors in the tests, the critical *P*-value of 0.05 was divided by 12, leaving a Bonferroni-adjusted significance level of 0.004. All data were analysed with SPSS version 21.

RESULTS

4-Fluoroamphetamine in consumer drug samples

Between 2007 and 2013, 474 samples containing 4-fluoroamphetamine were analysed by the DIMS laboratory. In Fig. 1, numbers of samples are shown, sold either as 4-fluoroamphetamine or as another drug. This latter category could be considered as misrepresented drugs, with 4-fluoroamphetamine as adulteration or substitution. 4-Fluoroamphetamine was being misrepresented mainly as amphetamine and ecstasy. Since 2009, there has been a steady decline in misrepresented drugs containing 4-fluoroamphetamine. Conversely, samples bought purposely as 4-fluoroamphetamine have increased ($R^2 = 0.885$, $P<0.001$) (Fig. 1).

Questionnaire

Patterns of use

In total, 288 participants responded to the questionnaire, 249 of whom were included for further analysis [66% male; mean age: 25.4 years; standard deviation (SD) = 5.7]. The majority had first used 4-fluoroamphetamine in 2013. Approximately half ($n = 116$, 46.6%, 95% confidence interval (CI) = 40.6– 53.6) used it in the last 12 months. Sixty-eight participants (27.3%, 95% CI = 22.3–33.6) used 4-fluoroamphetamine in the last 30 days, 33 participants (13.3%, 95% CI = 9.4–17.7) used in the last week and the remainder used more than a year ago. Most typical settings were festivals (33.3%), dance parties (28.4%), clubs (16.3%) or after-parties (10.5%). A total of 111 participants (44.6%, 95% CI = 38.6–50.6) obtained 4-fluoroamphetamine from friends, 70 participants (28.1%, 95% CI = 22.9–34.1) bought it through a web shop and the remainder obtained it elsewhere. Most participants ($n = 192$, 77.1%, 95% CI = 72.0–82.3) used 4-fluoroamphetamine because of its specific effects; only a minority (44 participants, 17.7%, 95% CI = 10.7–22.1) used it because of its legal status.

Effects

Two hundred and thirty-one participants (92.8%, 95% CI = 88.8–95.6) reported that they swallowed and 18 participants (7.2%, 95% CI = 4.0–10.0) snorted the drug. Snorting was reported as being very painful to the intranasal cavities. Doses used were: 50–100 mg (44 participants, 17.6%, 95% CI = 12.9–22.1); 100–150 mg (105 participants, 42.2%, 95% CI = 33.7–46.2); more than 150 mg (48 participants, 19.2%, 95% CI = 12.4–22.5); the remainder did not know. Duration of effects reported: less than 4 hours (57 participants, 22.9%, 95% CI = 17.7–28.1); 4–6 hours (110 participants, 44.2%, 95% CI = 37.8–50.2); 6–8 hours (54 participants, 21.7%, 95% CI = 16.5–26.9) and more than 8 hours (28 participants, 11.2%, 95% CI = 7.6–15.3). Table 2 lists the reported positive effects and adverse effects.

Effects of 4-fluoroamphetamine compared to MDMA and amphetamine

The reported effect scores of 4-fluoroamphetamine for 'stimulation', 'alertness', 'euphoria', 'connectedness with others' and 'changed sensory perception' differed significantly from those of amphetamine and MDMA and ranged between both substances (Table 3). The effect scores for 'stimulation' and 'alertness' were highest for amphetamine and 'euphoria', 'connectedness with others' and 'changed sensory perception' were lowest. The effect scores for 'intensity', 'confusion' and 'dizziness' differed only between

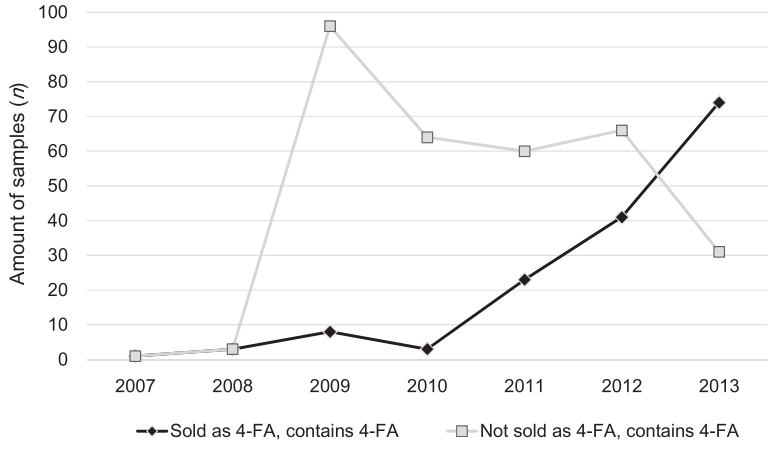

Figure 1 Samples submitted at the Drug Information and Monitoring System (DIMS) containing 4-fluoroamphetamine, either sold as 4-fluoroamphetamine (4-FA) or as another drug

Table 2 Reported positive and adverse effects of 4-fluoroamphetamine; for adverse effects, multiple answers were possible.

Effects	*n*	*%*	*95% CI*
Positive			
Stimulatory	145	58.2	51.4–64.3
Euphoria	69	27.9	22.1–33.3
Empathic	24	9.6	6.0–13.3
Sedative	11	4.3	1.1–5.6
Adverse			
Difficulty falling asleep	133	53.4	47.4–59.0
Dry mouth	109	43.8	37.4–50.2
Jaw tension/cramp	106	42.6	36.2–49.0
Elevated heartbeat	92	36.9	30.9–43.4
Sweating/high body temperature	83	33.3	27.7–39.4
Lowered mood in the days after use	49	19.7	14.9–24.5
Muscle weakness in days after use	46	18.5	13.7–23.3
Nausea	17	4.8	3.6–10.0
The drug had no effect	16	6.4	3.6–9.6
Tachycardia	29	11.6	8.0–15.7
Headache	21	8.4	5.2–12.4
Loss of memory (while intoxicated)	17	6.8	4.0–10.4
Unpleasant hallucinations	3	1.2	0.0–2.8
Difficulty breathing	2	0.8	0.0–2.0
Tolerance (higher dose needed after first use)	16	6.4	3.6–9.6
Other	6	2.4	1.0–4.6

CI = confidence interval.

4-fluoroamphetamine and MDMA, with effect scores being lower for 4-fluoroamphetamine. The effect scores 'talkative/sociable' and 'irritability' differed between 4-fluoroamphetamine and amphetamine only, with effect scores for 'talkative/sociable' being higher and for 'irritability' being lower for 4-fluoroamphetamine. The effect score of 4-fluoroamphetamine for 'craving' differed from both amphetamine and MDMA and was lowest. The effect score for 'self-confidence' did not differ between all three drugs.

DISCUSSION

This study suggests that 4-fluoroamphetamine is a NPS that has sustained throughout the years and has occupied its own niche on the Dutch drug market. This is in contrast to many other NPS that disappeared almost as quickly as they appeared on the drug market [6,17–20]. In addition, there is evidence pointing towards a role of 4-fluoroamphetamine on drug markets of other countries, such as Spain, Denmark and Germany [21–23].

Because of a shortage in precursors for MDMA and amphetamine in Europe during 2008 and 2009, producers switched to more available alternatives or synthesizing new compounds not yet under control [24], and it seems plausible that 4-fluoroamphetamine emerged as a substitute [17,24]. However, by 2013, purposely bought 4-fluoroamphetamine samples outnumbered misrepresented drugs containing 4-fluoroamphetamine. This reversal could imply that 4-fluoroamphetamine was actually fulfilling the needs of drug consumers and gained its own territory on the drug market. The fact that many participants buy 4-fluoroamphetamine from a friend might suggest that it is more widely available than most other NPS, which are only for sale on-line. The survey data suggest further that 4-fluoroamphetamine is used mainly for recreational purposes and not because of its legal status, in agreement with previous studies [2,3].

The majority reported on 4-fluoroamphetamine as a stimulant, with typical adverse effects reported for other psychostimulants, such as MDMA and amphetamine [25]. 4-Fluoroamphetamine might be hypothesized to have some entactogenic effects, as it was more potent in 5-HT release than amphetamine [13]. Subjective effects indeed suggest that 4-fluoroamphetamine has a profile intermediate between that of amphetamine and MDMA. 4-Fluoroamphetamine seemed to resemble amphetamine more closely with regard to 'stimulation' and 'alertness'. Conversely, 4-fluoroamphetamine scored higher on 'euphoria' and 'connectedness to others' than amphetamine, but lower than MDMA. This may indicate stimulatory properties combined with some entactogenic properties.

The 4-fluoroamphetamine effect scores for 'intensity', 'confusion' and 'dizziness' did not differ from amphetamine, and were significantly lower than for MDMA. 'Changed sensory perception' was substantially lower than for MDMA, but higher than for amphetamine. It is well known that MDMA can cause perceptual side effects, as it potently stimulates the 5-HT system and its receptors [25,26]. Apparently, 4-fluoroamphetamine behaves more like a typical stimulant, with less potent 5-HT stimulation. However, it is striking that 4-fluoroamphetamine seems to have a similar sociable effect to MDMA. The typical sociable effects of MDMA have always been ascribed to its potent 5-HT activity [27,28]. Irritability seemed a property attributed mainly to amphetamine and not to 4-fluoroamphetamine or MDMA, which may lie in a much stronger stimulation of NE and DA of amphetamine [29].

Taken together, 4-fluoroamphetamine induced less confusion, changes in perception and dizziness than MDMA and its effects are less intense, which might make it more compatible with certain settings in which users want to maintain a higher level of control over their behaviour. Conversely, 4-fluoroamphetamine seemed to induce greater entactogenic feelings than amphetamine, which might make it more attractive for users who prefer using drugs in a social context.

Table 3 Linear mixed effects regression models for the subjective effects reported by the participants, effects of amphetamine and 3,4-methylenedioxymethamphetamine (MDMA) were compared to 4-fluoroamphetamine (4-FA) in each model.

					95% Confidence interval	
	Estimate	*SE*	*t-value* (*d.f.*)	*P-value*	*Lower limit*	*Upper limit*
Intensity (intercept)	3.18	0.07	47.34 (478)	<0.001	3.05	3.31
Amphetamine versus 4-FA	–0.14	0.10	–1.46 (342)	0.146	–0.34	0.05
MDMA versus 4-FA	1.29	0.09	14.00 (318)	<0.001	1.11	1.47
Stimulation (intercept)	3.85	0.07	56.21 (479)	<0.001	3.72	3.99
Amphetamine versus 4-FA	0.48	0.11	4.48 (340)	<0.001	0.27	0.69
MDMA versus 4-FA	-0.37	0.10	-3.71 (312)	<0.001	-0.57	-0.18
Alertness (intercept)	3.90	0.07	55.86 (469)	<0.001	3.77	4.04
Amphetamine versus 4-FA	0.50	0.10	4.92 (326)	<0.001	0.30	0.71
MDMA versus 4-FA	–1.34	0.10	–13.90 (303)	<0.001	–1.53	-1.15
Euphoria (intercept)	3.56	0.06	57.30 (480)	<0.001	3.44	3.69
Amphetamine versus 4-FA	–1.10	0.09	–12.02 (340)	<0.001	–1.28	-0.92
MDMA versus 4-FA	1.07	0.08	12.51 (317)	<0.001	0.90	1.24
Connectedness to others (intercept)	3.61	0.07	51.54 (470)	<0.001	3.47	3.75
Amphetamine versus 4-FA	–0.99	0.10	–9.80 (331)	<0.001	–1.19	-0.79
MDMA versus 4-FA	0.91	0.09	9.72 (309)	<0.001	0.73	1.10
Talkative/ sociable (intercept)	4.11	0.08	54.55 (453)	<0.001	3.96	4.26
Amphetamine versus 4-FA	–0.44	0.10	–4.23 (334)	<0.001	–0.64	-0.23
MDMA versus 4-FA	–0.06	0.10	–0.60 (314)	0.56	–0.25	0.13
Self-confidence (intercept)	3.80	0.08	48.80 (311)	<0.001	3.65	3.96
Amphetamine versus 4-FA	–0.10	0.08	–1.16 (312)	0.246	–0.26	0.07
MDMA versus 4-FA	–0.04	0.08	–0.54 (302)	0.588	–0.19	0.11
Changed sensory perception (intercept)	2.70	0.08	33.26 (352)	<0.001	2.54	2.86
Amphetamine versus 4-FA	–0.43	0.09	–4.57 (315)	<0.001	–0.62	-0.25
MDMA versus 4-FA	1.18	0.09	13.53 (303)	<0.001	1.00	1.35
Irritability (intercept)	1.69	0.08	21.07 (331)	<0.001	1.53	1.85
Amphetamine versus 4-FA	0.73	0.09	8.32 (317)	<0.001	0.56	0.90
MDMA versus 4-FA	0.02	0.08	0.03 (307)	0.977	–0.16	0.16
Confusion (intercept)	1.91	0.08	25.31 (370)	<0.001	1.77	2.06
Amphetamine versus 4-FA	–0.09	0.09	–0.95 (325)	0.341	–0.26	0.09
MDMA versus 4-FA	1.42	0.08	17.10 (313)	<0.001	1.26	1.58
Dizziness (intercept)	1.43	0.07	20.39 (316)	<0.001	1.29	1.57
Amphetamine versus 4-FA	–0.03	0.07	–0.41 (314)	0.685	–0.18	0.12
MDMA versus 4-FA	0.49	0.07	7.07 (304)	<0.001	0.35	0.62
Craving (intercept)	2.49	0.09	26.70 (386)	<0.001	2.30	2.67
Amphetamine versus 4-FA	0.76	0.11	6.73 (328)	<0.001	0.54	0.99
MDMA versus 4-FA	0.66	0.10	6.27 (314)	<0.001	0.45	0.86

SE = standard error.

Some limitations should be mentioned regarding the current study. An inherent shortcoming of this type of study is that self-reports were used to analyse patterns of use and effects. Also, it cannot be determined whether participants actually used 4-fluoroamphetamine or another substance, and whether users were able to report accurately on dose or other aspects of the drug. Whereas the Bonferroni correction of the *P*-values controls for false positives, it may also lead to generating false negatives with multiple tests.

Despite these limitations, this study clearly shows an increase in the number of purposely bought 4-fluoroamphetamine samples on the drug market, confirming the status of 4-fluoroamphetamine as an upcoming drug on the Dutch drug market [7]. Furthermore, 4-fluoroamphetamine falls between the extremes of effects of amphetamine and MDMA and for some users combines the best of both worlds. This may suggest that 4-fluoroamphetamine has the potential to be more than just a transient NPS. This is an important insight for drug policymakers and prevention professionals. However, it should be emphasized that this study did not specifically address the potential toxicity of 4-fluoromaphetamine in the questionnaire, as the main focus was its appeal to drug users. Because many of its subjective (adverse) effects resemble those of other typical stimulants, similar toxicity patterns might be anticipated [30]. Therefore, future studies should focus on the possible (neuro-)toxicity of

4-fluoroamphetamine, to aid harm reduction and medical treatment of intoxications.

Declaration of interests

None.

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References

1. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) *European Drug Report 2013*. Lisbon, Portugal: EMCDDA; 2013.
2. van Amsterdam J. G., Korf D. J., Nabben A. L. W. M. *RIVM Rapport: Designer Drugs in Europe*. Bilthoven, the Netherlands: RIVM; 2013.
3. Carhart-Harris R. L., King L. A., Nutt D. J. A web-based survey on mephedrone. *Drug Alcohol Depend* 2011; **118**: 19–22.
4. Moore K., Dargan P. I., Wood D. M., Measham F. Do novel psychoactive substances displace established club drugs, supplement them or act as drugs of initiation? The relationship between mephedrone, ecstasy and cocaine. *Eur Addict Res* 2013; **19**: 276–82.
5. Ayres T. C., Bond J. W. A chemical analysis examining the pharmacology of novel psychoactive substances freely available over the internet and their impact on public (ill)health. Legal highs or illegal highs? *BMJ Open* 2012; **2**: e000977, 1–8.
6. van der Gouwe D. *DIMS Annual Report 2012*. Utrecht, the Netherlands: Trimbos Institute; 2012.
7. Goossens F. X., Frijns T., van Hasselt N. E., van Laar M. W. *The National Nightlife Survey 2013*. Utrecht, the Netherlands: Trimbos Institute; 2014.
8. Brunt T. M., van Amsterdam J. G., van den Brink W. GHB, GBL and 1,4-BD addiction. *Curr Pharm Des* 2014; **20**: 4076–85.
9. Brunt T. M., Koeter M. W., Hertoghs N., van Noorden M. S., van den Brink W. Sociodemographic and substance use characteristics of γ hydroxybutyrate (GHB) dependent inpatients and associations with dependence severity. *Drug Alcohol Depend* 2013; **131**: 316–9.
10. de Jong C. A., Kamal R., Dijkstra B. A., de Haan H. A. Gamma-hydroxybutyrate detoxification by titration and tapering. *Eur Addict Res* 2012; **18**: 40–5.
11. Marona-Lewicka D., Rhee G. S., Sprague J. E., Nichols D. E. Psychostimulant-like effects of p-fluoroamphetamine in the rat. *Eur J Pharmacol* 1995; **287**: 105–13.
12. Nagai F., Nonaka R., Satoh K. The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. *Eur J Pharmacol* 2007; **559**: 132–7.
13. Wee S., Anderson K. G., Baumann M. H., Rothman R. B., Blough B. E., Woolverton W. L. Relationship between the serotonergic activity and reinforcing effects of a series of amphetamine analogs. *J Pharmacol Exp Ther* 2005; **313**: 848–54.
14. Global Drug Survey (GDS). Available at: http://www.globaldrugsurvey.com/facts-figures/the-global-drug-survey-2014-findings. 2014 (accessed 1 December 2014).
15. Baylen C. A., Rosenberg H. A review of the acute subjective effects of MDMA/ecstasy. *Addiction* 2006; **101**: 933–47.
16. Sumnall H. R., Cole J. C., Jerome L. The varieties of ecstatic experience: an exploration of the subjective experiences of ecstasy. *J Psychopharmacol* 2006; **20**: 670–82.
17. Brunt T. M., Niesink R. J. The Drug Information and Monitoring System (DIMS) in the Netherlands: implementation, results, and international comparison. *Drug Test Anal* 2011; **3**: 621–34.
18. Ewald A. H., Fritschi G., Bork W. R., Maurer H. H. Designer drugs 2,5-dimethoxy-4-bromo-amphetamine (DOB) and 2,5-dimethoxy-4-bromo-methamphetamine (MDOB): studies on their metabolism and toxicological detection in rat urine using gas chromatographic/mass spectrometric techniques. *J Mass Spect* 2006; **41**: 487–98.
19. Ewald A. H., Fritschi G., Maurer H. H. Designer drug 2,4,5-trimethoxyamphetamine (TMA-2): studies on its metabolism and toxicological detection in rat urine using gas chromatographic/mass spectrometric techniques. *J Mass Spect* 2006; **41**: 1140–8.
20. Wood D. M., Looker J. J., Shaikh L., Button J., Puchnarewicz M., Davies S., *et al.* Delayed onset of seizures and toxicity associated with recreational use of Bromo-dragonFLY. *J Med Toxicol* 2009; **5**: 226–9.
21. Giné C. V., Espinosa I. F., Vilamala M. V. New psychoactive substances as adulterants of controlled drugs. A worrying phenomenon? *Drug Test Anal* 2014; **6**: 819–24.
22. Johansen S. S., Hansen T. M. Isomers of fluoroamphetamines detected in forensic cases in Denmark. *Int J Leg Med* 2012; **126**: 541–7.
23. Röhrich J., Becker J., Kaufmann T., Zörntlein S., Urban R. Detection of the synthetic drug 4-fluoroamphetamine (4-FA) in serum and urine. *Forensic Sci Int* 2012; **215**: 3–7.
24. Brunt T. M., Poortman A., Niesink R. J., van den Brink W. Instability of the ecstasy market and a new kid on the block: mephedrone. *J Psychopharmacol* 2011; **11**: 1543–7.
25. Peiró A. M., Farré M., Roset P. N., Carbó M., Pujadas M., Torrens M., *et al.* Human pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) after repeated doses taken 2 h apart. *Psychopharmacology (Berl)* 2013; **225**: 883–93.
26. Litjens R. P., Brunt T. M., Alderliefste G. J., Westerink R. H. Hallucinogen persisting perception disorder and the serotonergic system: a comprehensive review including new MDMA-related clinical cases. *Eur Neuropsychopharmacol* 2014; **24**: 1309–23.
27. Wolff K., Tsapakis E. M., Winstock A. R., Hartley D., Holt D., Forsling M. L., *et al.* Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population. *J Psychopharmacol* 2006; **20**: 400–10.
28. Hysek C. M., Schmid Y., Simmler L. D., Domes G., Heinrichs M., Eisenegger C., *et al.* MDMA enhances emotional empathy and prosocial behavior. *Soc Cogn Affect Neurosci* 2013; **28**: 1645–52.
29. Gerra G., Avanzini P., Zaimovic A., Fertonani G., Caccavari R., Delsignore R., *et al.* Neurotransmitter and endocrine modulation of aggressive behavior and its components in normal humans. *Behav Brain Res* 1996; **81**: 19–24.
30. Fisk J. E., Murphy P. N., Montgomery C., Hadjiefthyvoulou F. Modelling the adverse effects associated with ecstasy use. *Addiction* 2011; **106**: 798–805.