Forensic Science International 267 (2016) 25–34

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Review Article

An overview of emerging and new psychoactive substances in the United Kingdom

Shruti Beharry, Simon Gibbons *

Research Department of Pharmaceutical and Biological Chemistry, UCL School of Pharmacy, London WC1N 1AX, UK

ARTICLE INFO

Article history:
Received 14 March 2016
Received in revised form 1 August 2016
Accepted 4 August 2016
Available online 11 August 2016

Keywords:
New psychoactive substances
Psychostimulants
Lefetamine
Hallucinogens
LSD derivatives
Benzodiazepines

ABSTRACT

The purpose of this review is to identify emerging or new psychoactive substances (NPS) by undertaking an online survey of the UK NPS market and to gather any data from online drug forums and published literature. Drugs from four main classes of NPS were identified: psychostimulants, dissociative anaesthetics, hallucinogens (phenylalkylamine-based and lysergamide-based materials) and finally benzodiazepines. For inclusion in the review, the 'user reviewers' on drugs forums were selected based on whether or not the particular NPS of interest was used alone or in combination. NPS that were used alone were considered.

Each of the classes contained drugs that are modelled on existing illegal materials and will be covered by the UK New Psychoactive Substances Bill in 2016.

Contents

1. Introduction

New psychoactive substances (NPS), also inaccurately known as 'legal highs', are those materials which lie in the grey area of legislative control in most countries and are used recreationally by psychonauts and at raves. According to the European Monitoring Centre for Drugs and Drug Addiction's (EMCDDA) March 2015 report, the number of NPS is continuously increasing every year putting pressure on National Agencies to monitor these newly emerging drugs and to find solutions to reduce their harms [1]. The emergence of NPS has established itself as a global phenomenon appearing in some 94 countries worldwide as of December 2013 [2]. Furthermore, some NPS have much higher potency than the older drugs they are designed to replace while some are difficult to detect in body fluids [3]. NPS have rarely been studied for the purposes they are being used for and therefore pose a considerable and significant threat to the health of society. The aim of this paper is to cover the current landscape of available NPS just after the introduction of the PS Act in May 2016. Commonly encountered NPS and their effects and doses are discussed.

* Corresponding author.
E-mail address: simon.gibbons@ucl.ac.uk (S. Gibbons).

http://dx.doi.org/10.1016/j.forsciint.2016.08.013
0379-0738/

2. Methods

The NPS names were entered as keywords into the search engines Google and PubMed. Around ten of the most relevant results on Google were considered and all relevant literature on PubMed was taken into account for each substance. Information was gathered from manufacturer's websites, drug forums such as Bluelight, UK Chemical Research, Drugs-Forum, Reddit, TripSit and PsychonautWiki.

3. Results and discussion

3.1. Psychostimulants

3-Fluorophenmetrazine (3-FPM; (**1**)), also known as PAL-539 (Fig. 1), has recently emerged in the online market of 'research chemicals' and is currently legal to possess and supply in the UK as long as it is not for human consumption [4]. This compound is a relatively new substance and there are currently no scientific studies or literature pertaining to it. Psychonaut Wiki and drug forums such as Bluelight refer to the amphetamine-like its properties and 3-FPM is a close relative to the now no longer used anorectic drug phenmetrazine (**2**), the chemical backbone of which can be likened to amphetamine with the terminal amine in a morpholine ring. According to Psychonaut Wiki, 3-FPM has not been used in humans prior to 2014, however, psychonaut communities who have experience with the drug have put up rough 'guidelines' for its use. These suggest that a longest duration of action of 5–8 h occurs when taken orally with a dose of 25–50 mg orally or 20–35 mg as insufflation for what is referred to as a 'common' effect [5].

Physical effects described are increased energy levels, vasoconstriction, loss of thermoregulation, appetite suppression and an increased heart rate. Cognitive effects included increased motivation, focus and euphoria. Nonetheless, the stimulant effect was described as being less than that induced by substituted amphetamine compounds and users have referred to 'flu-like' symptoms with shivers [4,6]. Most of its effects could be inferred from the effects associated with phenmetrazine and other amphetamine-like drugs; therefore, part of this review will include some closely related compounds to which 3-FPM is related.

Phenmetrazine is of the phenylmorpholine class of compounds and was developed as an appetite suppressant (anorectic) to be used in conjunction with a low caloric intake diet in the short-term treatment of exogenous obesity [7]. It was marketed under the trade name Preludin and was allegedly used by the Beatles early during their career to cope with long hours of performance. It is an indirect-acting sympathomimetic agent with central stimulant effects, and its mode of action and effects are similar to those of dextroamphetamine [7,8]. Due to its high potential for abuse, considered to be more potent than amphetamine, it was withdrawn from the market [9]. It has been used recreationally and abused in Sweden in the 1950s and in the USA in the 1960s and 1970s before being removed completely from the market [10].

The mechanism of action is highly similar to amphetamine by blocking the noradrenaline and dopamine re-uptake transporters in the brain which leads to their prolonged presence and hence prolonged stimulation of post-synaptic receptors at the synapse [11,12].

Ritalin or methylphenidate (**3**) analogues such as 4-Me-TMP (**4**), made its appearance on the NPS market in April 2015 as a methylphenidate (**3**) replacement for the recently banned methylphenidate analogues EPH (**5**), PPH (**6**), IPH (**7**), 3,4-CTMP (**8**) and HDMP-28 (**9**) [13]. However, 4-Me TMP did not last long among psychonauts as it also was soon put under a Temporary Class Drug Order which took effect on the 27th June 2015 following recommendations made by the UK Advisory Council on the Misuse of Drugs (ACMD), based on its similarity to methylphenidate in effects and inferred adverse effects [14,15].

Currently there are no scientific studies specific to 4Me-TMP as a recreational drug. A search on PubMed using the keywords '4Me-TMP', '4-Methylmethylphenidate' returned no results as of 26th October 2015. Pharmacological data is limited with records of 4Me-TMP as one of the analogues of methylphenidate investigated in the treatment of cocaine dependence. It was found to be slightly more potent than methylphenidate at inhibiting the binding of [^{3}H]-WIN35 428, a cocaine analogue used in research on the dopamine transporter [16,17].

In psychonaut communities, 4Me-TMP has gained popularity as a psychostimulant during its short span of 'legality'. Users described it as the only 'research chemical' with effects closest to methylphenidate with a relatively lower potency that is concordant with available scientific pharmacological data [18]. Information regarding its effects in the human body can only be gleaned from reports of trips as posted or discussed on drug forums. Users reported euphoria, decreased appetite and need for sleep, increased alertness and focus and sexual arousal as positive and desired effects. Negative effects included increased sweating, tremors and tachycardia, however, the degree of the effects was subjective to the user. Depending on the dose administered, 4Me-TMP was reported to be recreational resulting in a clear head and enabling users to improve performance during work or study. Some users have recognised that as a methylphenidate analogue, 4Me-TMP may also have addictive potential, although so far, no compulsion to re-dose has been reported [19,20].

4Me-TMP has been mainly taken orally or by insufflation and oral doses vary from a recommended threshold of 25 mg to 90–125 mg as a heavy dose, with an onset of action within minutes and a duration of action of 4–6 h. For insufflation, doses are smaller with a threshold of 10 mg and a heavy dose of over 70 mg with an onset of action within minutes and a duration of action of 2–5 h. Doses are sometimes 'boosted' after 3 h of administration for a prolonged effect [18,19,21,22]. Varying degrees of harm from drug-drug interactions when using methylphenidate are also warned of on the TripSit website. For instance, concomitant use of stimulants and tramadol are said to increase the risks of seizures and are qualified as dangerous. Increased risk of serotonin syndrome is noted with simultaneous use with monoamine oxidase inhibitors and 2C-T-x compounds (e.g. **10**). Excessive anxiety with persistent thought-loop is also purported to occur when 4Me-TMP is used with psychedelics such as mescaline. 4Me-TMP as a psychostimulant is also said to decrease the perception of drunkenness and increase the risk of drinking excessively till the passing out point [21].

The forums threads on 4Me-TMP are relatively short possibly because of its short span of use as an NPS. Nevertheless, users have so far reported few negative effects and are positive about 4Me-TMP with people still seeking it out. New posts appear to come from users who are apparently based outside the UK for example in Sydney [18], which suggests that 4Me-TMP has spread globally. For the time being, there is still no scientific evidence specific to 4Me-TMP (26th October 2015) apart from its inferred effects from structural similarity to methylphenidate, to validate its permanent ban under UK law.

Methiopropamine (**11**) as an NPS was first reported following a seizure in Finland in January 2011 [23]. Its synthesis however, dates back to the 1940s when it was synthesised by Blicke and Burckhalter as an analogue of methamphetamine, where the phenyl ring was substituted with a thiophene ring in order to compare effects on blood pressure [24].

Since its appearance online as a research chemical in late 2010, methiopropamine has become an established NPS used