PIPERAZINE BASED SUBSTANCES OF ABUSE: A NEW PARTY PILLS ON BULGARIAN DRUG MARKET

I. Nikolova, N. Danchev
Medical University, Faculty of Pharmacy, Department "Pharmacology, Pharmacotherapy & Toxicology", Sofia, Bulgaria
Correspondence to: Nikolai Danchev
E-mail: ndanchev@pharmfac.net

ABSTRACT

A new 'family" of drugs, the piperazines, has emerged on the European drug market as new designer drugs for the last few years. The key members of the group that have been used for non-medical recreational purposes are BZP (Benzylpiperazine, A2, Frenzy, Nemesis), TFMPP (1-[3-(trifluoro-methyl)phenyl]piperazine), mCPP (meta-chlorophenylpiperazine, 1-(3-Chlorophenyl)-piperazine). Piperazines are psychoactive drugs and clearly not without risks. With stimulant effects comparable to amphetamines but with a lower potency and differential global scheduling status, they have been sold as a supposed legal alternative to ecstasy. Currently, in Bulgaria these piperazines are not controlled drugs. Other European countries have banned or are going to ban some piperazines. This review provides a summary of current knowledge on recreational piperazines, the current situation in the Bulgaria and the experience in some countries.

Introduction

A new 'family" of drugs, the piperazines, has emerged on the European drug market as new designer drugs for the last few years. The key members of the group that have been used for non-medical recreational purposes are BZP (Benzylpiperazine, A2, Frenzy, Nemesis), TFMPP (1-[3-(trifluoro-methyl) phenyl]piperazine), mCPP (meta-chlorophenylpiperazine, 1-(3-Chlorophenyl)-piperazine). These piperazines are usually mixed with caffeine and a range of vitamins and binders to make party pills. Despite their frequently being marketed as "natural" or "herbal" highs, these chemicals are purely synthetic. Piperazine (1,4-hexahydropyrazine) is a heterocyclic compound used as a main ingredient of anthelmintics by altering cell membrane permeability and causing hyperpolarization of the membrane. The piperazine ring and piperazine derivatives are important cyclic components in industrial field as raw materials for hardener of epoxy resins, corrosion inhibitors, insecticides, accelerators for rubber, urethane catalysts and antioxidants. Piperazines are psychoactive drugs and clearly not without risks. With stimulant effects comparable to amphetamines but with a lower potency and differential global scheduling status, they have been sold as a supposed legal alternative to "Ecstasy".

The active components are partially freely available. Currently, in Bulgaria these piperazines are not controlled drugs. Other European countries have banned or are going to ban some piperazines. This review provides a summary of current knowledge on recreational piperazines, the current situation in Bulgaria and the experience in some countries, before discussion and recommendations on pragmatic ways forward.

BZP is a recreational drug with euphoric, stimulant properties. BZP was originally synthesized in 1944 from the pepper plant as a potential anthelmintic (antiparasitic) agent for use in farm animals. It was discovered that BZP had side effects and was largely abandoned as a worm treatment. It appears in the literature in the 1970s when it was investigated as a potential antidepressant medication, but rejected when research reported that BZP had amphetamine-like effects and was liable to abuse. BZP acts as a non-selective serotonin receptor agonist on a wide variety of serotonin receptors; binding to $5HT_{2A}$ receptors may explain its mild hallucinogenic effects at high doses, while partial agonist or antagonist effects at the $5HT_{2B}$ receptors may explain some of BZPs peripheral side effects, as this receptor is expressed very densely in the gut, and binding to $5HT_3$ receptors may explain the common side effect of headaches, as this receptor is known to be involved in the development of migraine headaches. BZP is an alpha2-adrenoreceptor antagonist, like yohimbine, which inhibits negative feedback, causing an increase in released noradrenaline. Unlike Viagra (a drug from the same family), however, BZP does not appear to have an effect on sexual performance.

Its dopamine and serotonin agonist mechanism of action is believed to be similar to MDMA and both animal studies and human clinical studies have demonstrated that the pharmacological effects of BZP are qualitatively similar to those of amphetamine. Taken on its own, it acts as a mild stimulant, about 10% the strength of normal "speed" or amphetamine. Public health risks of BZP are similar to those of amphetamine.

The amphetamine-like effects of BZP attracted the attention of drug abusers. BZP is often marketed ostensibly as a "dietary supplement" to avoid meeting stricter laws that apply to medicines and drugs, despite the fact that BZP has no dietary value. Some retailers claim that BZP is a "natural" product, describing it as a "pepper extract" or "herbal high," when in fact the drug is entirely synthetic, and has not been found to occur naturally.

Users report wakefulness, euphoria, increased vigilance, alertness, and a general feeling of well being. The perception of certain sensations such as taste, colour or music may be subjectively enhanced. The average duration is longer than that of dextroamphetamine, typically lasting 4-6 hours, but when it is mixed with other piperazines, the effects become more euphoric, even psychedelic, lasting up to 8 hours. BZP is often taken in combination with TFMPP, a noncontrolled substance, in order to enhance its spectrum of effects and has been promoted to youth population as substitute for MDMA at all-night dance parties. It may also be abused alone for its stimulant effects. BZP is generally administered orally as either powder or tablets and capsules. Other routes of administration included smoking and snorting.

As with most sympathomimetic stimulants there appear to be significant side effects associated with BZP use. BZP reportedly produces insomnia and a mild to severe hangover after the drug effect wears off. The major side effects include dilated pupils, dryness of the mouth, extreme alertness, pruritus, confusion, agitation, tremor, dystonia, headache, dizziness, anxiety, insomnia, vomiting, chest pain, tachycardia, hypertension, palpitations, collapse, hyperventilation, hyperthermia, and problems with urine retention. The more severe toxic effects include psychosis, renal toxicity, and seizure.

It does not appear to be very addictive and no deaths have been reported following a sole ingestion of BZP, although there have been at least two deaths from the combination of BZP and MDMA. Research into BZP's tolerance is sparse. Anecdotal evidence from online sources claim tolerance to the central action of BZP will develop quickly. Due to tiredness associated with the body's recovery from stimulants, such as BZP, it is uncommon for users to be able to sustain a week-long intake.

BZP is banned in many countries in Europe, Japan, the USA, and Australia, but is available on a more or less restricted basis in many jurisdictions. BZP is legal and uncontrolled in many countries such as Canada and Ireland. BZP and related piperazines are not controlled under any UN convention, so the compounds themselves are legal throughout most of the world, although in most countries their use is restricted to pharmaceutical manufacturing and recreational use is unknown. BZP is, however, to be the subject of a European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) risk assessment, the results of which will determine what, if any, control will placed on BZP throughout the European Union. The risk assessment comes about as the result of a joint Europol – EMCDDA report which concluded that BZP needs to be looked at in more detail. The report concluded that the use of BZP can lead to medical problems even if the long effects are still unknown. Taking this concession as a basis, the European Commission has decided to ask the Council to place BZP under control of the UN Convention on Psychotropic Substances. On 4 March 2008, BZP was placed under control in the EU.

mCPP is a piperazine-based 5-HT receptor agonist. The CPP abbreviation should be treated with caution since the term 'CPP' is also used for the unrelated herbicide - 2-(4-chlorophenoxy)-propionic acid. Apart from the large number of variously substituted piperazines, there are two positional isomers of mCPP, namely 1-(4-chlorophenyl)piperazine (pCPP, para-CPP) and 1-(2-chlorophenyl piperazine, (oCPP, ortho-CPP). Since oCPP is an antagonist of the 5HT2C receptor, then it is unlikely to produce similar effects to mCPP. The positional isomer, pCPP has also been reported in some illicit products, but only limited investigations have been made on the properties of pCPP and oCPP. mCPP consists in interaction with various serotonin receptors, as well as adrenergic and dopaminergic receptors, which leads to secretion of serotonin.

A major use of mCPP is as an intermediate in the production of trazodone (antidepressant) and three related substances (nefazodone, etoperidone and mepiprazole), which differ only in the substituent attached to the piperazinylpropyl moiety. Trazodone and related drugs are metabolised in the liver to form the active metabolite mCPP by N-dealkylation at the piperazinyl nitrogen. It has been suggested that mCPP may contribute to the antidepressant efficacy of trazodone. Trazodone is a prescription drug that has marketing authorization in Bulgaria and a number of Member States.

Consumption of mCPP leads to broad neuroendocrinological, physiological and psychological effects. This compound is mainly taken due to its stimulating properties and hallucination similar to those that occur after taking of MDMA. In contrast to MDMA, however, an increase in blood pressure and heart rate was not observed. mCPP has not shown sympathomimetic activity; it does not increase the heart rate or blood pressure and has no influence on the ECG. There is a possibility that mCPP may interact with certain medicinal products and lead to the development of a serotonin syndrome. In terms of toxicity, little is known about the long- or short-term effects of mCPP. No fatal case due to, or involving, mCPP has ever been reported by a Member State. France and Belgium are the only two countries which reported intoxications involving mCPP. There is no evidence to indicate that mCPP has the potential to produce dependence in humans, and as far as is known, it has no major effects on cognitive functions.

Users of mCPP claimed that it acted as a stimulant at high doses and that it had similar spectrum to MDMA of both negative (dysphoria, anxiety) and positive (euphoria) effects.

The negative effects of mCPP, often typical of a serotonin syndrome, include anxiety, dizziness, confusion, depressive symptoms, feeling of being persecuted and aggressiveness shivering, sensitivity to light and noise, fear of losing control, nausea, vomiting, migraine and panic attacks. This has tended to limit the use of mCPP as a recreational drug. Unlike MDMA, mCPP lacks neurotoxic potential and mCPP releases 5HT without causing long-term depletion. The adverse effects of mCPP are more often seen in alcoholics, cocaine addicts and those who use drugs that also interact with 5HT receptors, such as MDMA. No fatal poisonings with mCPP have been reported.

There are no licensed medicinal uses of mCPP in the EU. Over the last year, in the majority of the Member States, mCPP-containing tablets, often designed to look like ecstasy, have increasingly been found in the context of various recreational activities (open-air dance/music festivals, dance clubs, rave scenes, street parades, etc.), where they are almost always sold/bought as the popular drug ecstasy.

In Europe, studies are being conducted on assessing risk linked to mCPP consumption and its possible inclusion on lists of controlled psychotropic substances due to the fact that this compound is increasingly frequently detected in ecstasy tablets that have been seized and sent to forensic and police laboratories for analysis. There have also been reports of over dosing and poisoning. In Greece, as of 20 January 2005, mCPP is subject to the same control measures that apply to other psychotropic substances such as MDMA. In December 2005, Denmark decided to control mCPP along with four other piperazines. Furthermore, in 2006-2007 control measures were introduced in Belgium (22 October 2006), Hungary (1 January 2006), Lithuania (1 July 2006) and Germany (1 March 2007). At least two other Member States – Slovakia and Latvia – have informed EMCDDA that they are considering control measures. In Finland, mCPP is included in Annex 1 of the list of medicinal products covered by the Medicines Act (395/1987). Furthermore, in both the Netherlands and Spain, such possibility for control exists under medicines related laws. Apart from the above nine Member States, mCPP is commercially available elsewhere without legal restriction. According to the World Health Organisation mCPP is not currently under assessment for potential control by the United Nations 1971 Convention. In the USA, BZP was placed into Schedule I of the Controlled Substances Act in 2003, but mCPP remains uncontrolled. Currently, this substance, in spite of demonstrated psychotropic properties, is still legal in most countries, although work is in progress in the European Union to ban it.

TFMPP (TMFPP, 1-(3-trifluoromethylphenyl)-piperazine) is a piperazine-based drug, related to benzylpiperazine. Pharmacologically, it behaves in a similar manner to phenethylamines (MDMA, MDE, 2-CB). TFMPP acts as a non-selective serotonin receptor agonist, in addition to boosting synaptic serotonin levels by blocking serotonin reuptake and increasing its release. It is not used medicinally, but has been sold as a recreational drug used as a "legal alternative" to illicit drugs such as LSD and MDMA. TFMPP has properties similar to the stimulant effects of ecstasy, but taken in larger doses it promotes hallucinogenic reactions. This poses an even greater risk to young adults who have taken ecstasy previously and accidentally overdose by trying to achieve the hallucinogenic effects. The psychoactive effect caused by a dose taken of TFMPP is sometimes described as being somewhere between empathogens such as MDMA and entheogens such as psilocybin, mescaline, or LSD.

TFMPP has only mild effects and is rarely administered by itself, and there has been little research into it as a single drug. It produces aversive effects in animals rather than self-administration, which explains the decision not to permanently make TFMPP an illicit drug. The combination of BZP and TFMPP, in a ratio of about 2:1 appears to be fairly common. Due to the similar mode of action of ecstasy on the serotonin system, BZP/TFMPP combination is sometimes advertised as a MDMA substitute. This combination has been described as having entactogenic body-effects similar to MDMA and/or MDEA, but generally without the strong empathogenic qualities of these phenethylamines. A meditative quietness, calm centeredness, contentedness, a warm flushing sensation, waves of euphoria, tactile pleasure, time dilation, and mild visual effects (similar to low-dose mescaline, LSD) have also been reported. So it would be more accurate to describe the combination of BZP and TFMPP as being closer to a combination of a weak dose of LSD mixed with amphetamine rather than comparing it to MDMA. However research has shown that in addition to the effects on serotonin, the combination results in an unexpectedly large amount of dopamine release that far exceeds what one would expect from the dopamine releasing properties of each drug alone added together. This suggests a strong degree of synergy between the two drugs. There have been no adverse contraindications reported between the two substances when combined, so far as we are aware.

BZP/TFMPP combination can cause a range of side effects including nystagmus, dehydration, seizures, jaw-clench, mild to severe nausea, vomiting, toxic psychosis (panic and extreme paranoia), high blood pressure, persistent headache, flu-like symptoms, stiff neck, post-trip exhaustion, impotence, anxiety, migraine muscle aches, as well as a come-down syndrome characterised by insomnia and loss of appetite. These side effects tend to be significantly worsened when the BZP/TFMPP mix is consumed alongside alcohol, especially the headache, nausea and hangover. These side effects tend to discourage abuse of TFMPP. It is difficult to say how many of these side effects are produced by TFMPP itself, as anxiety, headache and nausea are common to all piperazine drugs, and pills containing TFMPP are reported by users to produce comparatively more severe hangover effects than those containing only BZP.

Besides BZP, TFMPP and mCPP, the following piperazines, amongst others, have been synthesized and introduced onto the narcotics market:

MeOPP (4-methoxyphenylpiperazine, Paraperazine, 4-MeOPP) is a piperazine derivative with stimulant effects which has been sold as an ingredient in "Party pills", initially in New Zealand and subsequently in other countries around the world. The effects of MeOPP) is similar to ecstasy. The perception of certain sensations such as taste, colour or music may be subjectively enhanced. The average duration is shorter than that of BZP and does not have strong stimulant effects and is often mixed with stimulant piperazine derivatives such as BZP for a combined effect. Users report a ratio of meOPP 1:1 with BZP can bring a warming sense of empathy to the regular BZP experience.

pFPP (parafluorophenylpiperazine, flippiperazine, fluoperazine, 4-FPP) is a piperazine derivative with mildly hallucinogenic and euphoric effects. pFPP has been found in vitro to act mainly as a serotonin receptor agonist. It also inhibits the reuptake of serotonin and norepinephrine. pFPP has little stimulant effects, with its subjective effects derived mainly from its action as a $5HT_{1A}$ agonist. pFPP is active at doses between 20mg - 150mg, but higher doses cause a range of side effects including migraine headaches, muscle aches, anxiety, nausea and vomiting, which tend to discourage abuse..

BZP related compouns

2C-B-BZP (2-bromo-4,5-dimethoxy-benzylpiperazine) is related to BZP and shares the ring-substitution pattern of the psychedelic phenethylamine 2C-B (4-bromo-2,5-dimethoxyphenethylamine), although 2C-B-BZP is not a phenethylamine itself. 2C-B-BZP produces stimulant effects that last 3-6 hours, depending on the dose. 2C-B-BZP increase the effects of other compounds when combined. Side effects include headaches and nausea, similar to other piperazine derivatives used recreationally. The pharmacology of 2C-B-BZP is unknown. The toxicity of 2C-B-BZP is not known, although BZP, which is chemically related, has known toxicity.

MBZP (1-methyl-4-benzylpiperazine) is a stimulant drug which is a derivative of benzylpiperazine. The effects of MBZP are very similar to those of BZP, but the stimulant effect is slightly weaker and it seems to have less of a tendency to cause negative side effects such as headaches and nausea.

DBZP (dibenzylpiperazine) is a piperazine derivative often found as an impurity in the recreational stimulant drug benzylpiperazine (BZP). Presence of DBZP is a marker for low quality or badly made BZP. It can be made as a reaction byproduct during BZP synthesis, either because the reaction has been run at too high a temperature, or because an excess of benzyl chloride has been used. The toxicity of DBZP is unknown. It is not believed to have any stimulant effects in its own right, although this has not been tested.

Conclusions

A new breed of stimulant drugs from the same class as Viagra but with similar effects to ecstasy are being sold through Bulgaria and websites. The drugs, known as piperazines and marketed as party pills, are fuelling a boom in the "legal highs" trade as people search for safer, cleaner alternatives to illicit drugs that do not carry the risk of conviction. The pills contain a blend of the stimulant benzylpiperazine (BZP) and other less potent chemicals from the piperazine family. They are becoming increasingly popular as a legal alternative to ecstasy's active ingredient, MDMA, mainly because users say they appear to work.

In connection with the fact that new substances, previously unknown mixtures of substances, and substances containing high concentrations of earlier known drugs have started to appear on the narcotics market, an Early Warning System has been set up under the auspices of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), in order to react appropriately to new compounds and phenomena on the narcotics market and assess risks linked to them. In Bulgaria piperazines are still not included in controlled substances by means of Law for Control on Narcotic Substances and Precursors (LCNSP), as they are not on the list of Appendix 1, 2 and 3, but it is indispensable to include them since the continued, uncontrolled production, distribution and abuse of BZP, mCPP and TFMPP pose an imminent hazard to the public safety.

REFFERENCES

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