Benzofuran Analogs of Amphetamine, Emerging Novel Psychoactive Substances in Colombia: A Narrative Review

Erik García Muñoz*
Addiction Psychiatrist, ESE Hospital Carisma, Medellín, Colombia
Submission: April 23, 2018; Published: May 09, 2018
*Corresponding author: Erik García Muñoz, Addiction Psychiatrist Specialty, ESE Hospital Carisma, Medellín, Colombia, Tel: 3105017827; Email: dr.ekrgarciamun@gmail.com

Abstract
The use of novel psychoactive substances (NPS) is a growing phenomenon worldwide that harms user’s health and increases healthcare system costs. In September 2017, amphetamine-analog benzofurans (APB) were reported by the Sistema de Alertas Tempranas, a branch of Observatorio de Drogas de Colombia. At first, benzofurans use was globally reported as an adulterant of other psychoactive substances but, due to its legal status, its easy commercialization and because of government and doctors did not know those substances; they have noticeably been growing as a drug of choice. In the face of this new threat, this review tries to expose information expecting it will help in these needs. A wide bibliographical review was made regarding pharmacodynamic and pharmacokinetic characteristics, clinical effects and toxicity, and marketing strategies about 4-APB, 5-APB and 6-APB.

Keywords: Benzofuran; NPS; APB; Designer drugs; Benzofury; Legal high; 4-APB; 6-APB

Abbreviations: NPS: Novel Psychoactive Substances; APB: 2-Aminopropyl Benzofuran; NET: Noradrenaline Transport; DALY’s: Disability Adjusted Life Years; VPN: Virtual Private Networks

Introduction
Drug abuse is one of the major risk factors involved in disability worldwide. According with United Nations Office on Drugs and Crime, 5% of world population used this substances in 2015 and 0.6% suffered any substance-use disorder. These conditions generate an estimated 28 million of years of Disability Adjusted Life Years (DALY’s). In spite of that, psychoactive substances abuse remains high over the years [1].

As a result, monitoring policies in drug markets have been implemented. Drug Observatories have improved in tracking and now they have a more efficient data recollection across the globe. So, a growing drug seizure in most consumed psychoactive drugs or in their raw material can be observed, and it reduces their availability in the streets. Along with this, prohibition policies, a fast growth of mobile technologies and cryptocurrency have facilitated the use of novel psychoactive substances (NPS), also known as “Legal Highs” [2,3]. According with UNODC, there has been an annual increase of 50% in sales of NPS in the Darknet since 2013 until now. This can be recorded for less than 1% in the total of drug sales worldwide.

NPS are not controlled psychoactive substances as they are not scheduled by the Single Convention of Narcotic Drugs 1961, the Convention on Psychotropic Substances 1971 or by the Controlled Substances Act of each country. Those uncontrolled substances endanger individual and public health as badly as the drugs scheduled in Conventions mentioned above. These NPS include a variety of legally sold compounds. They are used because their effects are similar to the effects of the most used illegal substances [4,5]. Synthesis and merchandising of these products have increased over the years. According with UNODC, 483 NPS were reported until 2015.

This phenomenon is not strange in Colombia. According with the last report of Sistema de Alertas Tempranas from the National Observatory on Drugs, a total of 28 NPS were reported since 2007. Most of the reported substances are the same as those on other countries with and increasing market for phenylethilamines, synthetic cannabinoids and synthetic cathinones. Nevertheless, in September 2017 there was the first report about the presence of benzofurans in the country [6].

Despite the increase of reports related to these substances, literature respecting clinical data and health risk is scarce and diffuse. A lot of these manuscripts do not scope this situation in Latin America and, much less in Colombia. That implies a growing need to gather data concerning Colombia and spread
information to medical and chemical communities and to governmental authorities. The present review tries to cover this gap, in order to focus on the need for attention, for monitoring and for benzofurans legislation.

Method

A literature search was made in Pubmed, Google Scholar and EBSCO using the MeSH terms “benzofuran”, “benzofury”, “APB”, “4-APB”, “5-APB”, “6-APB”, “4-(2-aminopropyl) benzofuran”, “5-(2-aminopropyl) benzofuran” and “6-(2-aminopropyl) benzofuran” in title and abstract. Manuscripts reporting chemical, pharmacological and clinical characteristics, and case and forensic reports were considered. Also, manuscripts regarding policies, marketing and consumer characteristics were taken in account. Another search was made in free web bases and discussion blogs like erowid.com, energycontrol.com, cannabiscafe.net, psiconautas.org, blue-light.org, maps.org to gather information about marketing and subjective experiences from users. Thanks to this access, a search in the websites such as chemicalpowdershop.eu, researchchemicalworld.com, chem.eu, arrestspainmeds.org was implemented, in order to knowing aspects linked to commercialization of these molecules. Manuscripts regarding benzofuran derivative molecules like 5-MAPB, 2-CB-Fly, Bromo-Dragon FLY, 3-CB-Fly, bromo-2-dragonfly-5-butterfly, TFM-fly, 6-APDB were discarded. Research was limited to manuscripts in English and Spanish languages. No manuscripts were found in Spanish language.

Results

Chemical and Pharmacological Characteristics

Benzofurans are molecules whose structure contains a benzenic ring and one or two heterocyclic furan rings (Figure 1). Although the report of benzofuran derivatives as psychoactive substances is relatively recent, benzofuran derivatives have been widely used in medicine and chemistry from a long time. Antiarrhythmic drugs amiodarone and dronedarone, antifungal griseofulvin, antihypertensive drugs benziodarone and cloridamor, uricosuric agent benz bromarone, antipsychotic elopiprazole and antidepressant vilazodone are part of this group [7]. Besides this, benzofuran derivatives have been studied for their antitumoral, antiviral, antibiotic (including antimycobacterial), anti-inflammatory and antipyretic properties [8].

Benzofuran derivatives reported as NPS are amphetamine analogs 4-(2-aminopropyl) benzofuran (4-APB), 5-(2-aminopropyl) benzofuran (5-APB) and 6-(2-aminopropyl) benzofuran (6-APB). These molecules are structurally very similar to 3,4-metilenedioxymetamphetamine (MDMA) and to its active metabolite 3,4-metilenedioxymetamphetamine (MDA) [9].

Pharmacokinetics

Benzofuran derivatives are available in doses from 60 to 150mg. These are used orally because nasal ingestion is reported painful. The effects start one or two hours later, and they can last seven hours, according to users [10]. Metabolism data in humans are not available now. Nevertheless, in murine models 5-APB and 6-APB are hydroxylated at the furan ring, followed by a cleavage and a reduction resulting in an aldehyde compound, which is either oxidized to carboxylic acid or reduced to alcohol. Alcohol is further hydroxylated and both, alcohol and carboxylic acid, are glucuronated. The resulting metabolites are 3-carboxymethyl-4-hydroxy-amphetamine in the case of 5-APB and 4-carboxymethyl-4-hydroxy-amphetamine from the 6-APB metabolism. Apparently, the metabolism of these compounds is made by cytochrome p450 system with its CYP1A2, CYP2B6, CYP2C19 y CYP2D6 isofoms but this information requires confirmation in human laboratory studies because metabolites were obtained in low proportion and this analysis was made in other benzofuran derivatives. 5-APB and 6-APB metabolites are eliminated through urine [11,12].

Pharmacodynamics

The release of dopamine in the nucleus accumbens, the serotoninergic effects in the digestive tract and an increase in the locomotor activity were the main effect of the 5-APB administration in in vitro models. The blocking of the dopamine reuptake by antagonist actions to Dopa mine Transporter (DAT), the release of dopamine from the synaptic bottom and agonism to 5-HT2a, 5-HT2b and 5-HT2c serotoninergic receptors are the main mechanisms of benzofurans [13,14]. Additionally, benzofurans are strong antagonists of noradrenaline transport (NET). In higher concentrations, they also antagonize serotonin transporter (SERT). These characteristics provide more similarities to MDMA than amphetamine. Benzofurans also act at the vesicular monoamine transporters which generates a direct release of dopamine. 5-APB releases predominantly dopamine and noradrenaline while 6-APB releases predominantly serotonin though both molecules act in the three neurotransmission systems. Both molecules are ligands of the alpha 1a and alpha 2a receptors of noradrenaline system and 5-APB is also a weak inhibitor of the Monoamine Oxidase enzmye. None of these molecules act at the dopamine receptors [15,16].
Clinical Effects

Because of their agonism at different targets, a lot of effects could be dilucidated. They are nearly the same although users describe them as more intense [17,18]. Users expect entactogen and euphoriant effects which are generated due dopamine and serotonin release and also due agonism to 5-HT2a,b and c serotoninergic receptors. Agonism to 5-HT2a receptor has long been implied in the hallucinogen effect of some compounds like LSD and some benzofuran users report this effect [19].

Noradrenaline release and its reuptake inhibition by benzofurans might generate sympatomimetic symptoms like tachycardia, hypertension, hyperthermia with or without diaphoresis and headache. Along with that, it may appear panic attacks, agitation, anxiety, insomnia; also, trismus and xerostomia which may derive in lingual and gingival ulcerations. Due serotonin release, along with euphoric, entactogen and hallucinogenic effects, psychiatric symptoms like aggression, confusion and digestive symptoms like nausea, prolonged diarrhea, abdominal cramps and dizziness can occur. Muscular symptoms like myoclonus also may appear. Due dopamine release, psychotic symptoms may emerge which can last longer in time than the ones produced by other stimulants like mephedrone as it was reported by users [20].

Due the low availability of these molecules, addiction to benzofuran was not reported in humans. Nevertheless, in a rewarding-reinforcing animal model, it was demonstrated that mice reported preference for compartments where 5-APB was located but they did not increase their self-administration. It means that repeated use of benzofurans generates rewarding but not reinforcing effects [21].

Marketing Aspects

Although 6-APB was synthesized in 1993 with experimental purposes [22], its use as a NPS was first reported in 2010. Like many other NPS, benzofurans have been used as adulterants. According to the Sistema de Alertas Tempranas in Colombia, the report of these compounds was made because it was found in chemical analysis of other substances [23]. Nevertheless, the use of these compounds has been changed from an adulterant to an abuse substance in Netherlands and United Kingdom.

Its marketing is mainly centered on the internet through cryptomarkets. They are defined as anonym trading websites, usually found on the deep web or on social networks. Vendors use cryptocurrencies (like bitcoin or ethereum) as means for monetary exchanges and this websites also provides feedback from other users by ratings and comments [24]. The average users are 20 to 40 years old young men, with experience in using a wide variety of substances and able to use encrypted servers in order to access to the deep web-like Onion servers, virtual private networks (VPN) and proxy servers- to maintain their information the most private as possible. They also have a high-
education and require privacy. They are employees with high incomes looking for substances with less impact in their life and job [25]. Nowadays, specific motivations for benzofuran use are not published yet. Though, different motives for other NPS may be extrapolated. It might be mainly value for money, a better or a longer desired effect and a perception of better purity. Along with these motivations, a main incentive for benzofuran demand was the diminished production and availability of MDMA at mid-2000’s [26, 27]. Due the anonym services provided by servers, it is difficult to know if these parameters are the same for Colombian users.

6-APB is sold with the brand name of Benzofury and 4-APB and 5-APB seem to be adulterant compounds. Caffeine and other stimulant like synthetic cathinones are also adulterants found in Benzofury. Because the synthesis of 6-APB requires a controlled substance, 3-metoxypentamethine, most of Benzofury is sold as 5-APB due its synthesis may be suited using the legal substance dihydrobenzofuran [28]. Benzofury is sold as little packages with gray powder or brown-colored tablets. Paraphernalia of this product follows identical characteristics for other NPS: it is presented with labels like “for research porpoises”, “not for human consumption”, “not for sale” and “harmful”. This NPS may be purchased from US 20.00 dollars or £32 pounds per gram or US 9,000 per 10kg. 5-APB and 6-APB are controlled substances in United Kingdom, Portugal, Germany and Sweden besides in Florida and Minnesota in United States. 4-APB is not a controlled substance worldwide.

Toxicity

Due its mechanism of action, potentially mortal syndromes may appear in users. Serotonin syndrome might be produced because of the release of serotonin from synaptosomes, the reuptake inhibition, agonisms to several serotonin receptors and release of other monoamines which indirectly release more serotonin. There are several reports of this syndrome in MDMA users, especially when they combined it with other drugs implied in serotonin neurotransmission [29]. Besides, cathecolamine release and agonisms to its receptors may produce sympatomimetic syndromes with tachyarrhythmia, hypertensive crises and hyperthermia with rhabdomyolysis and myoglobinuria with subsequent acute renal failure.

It is noteworthy that a lot of NPS abusers combine them with other psychoactive substances, which may lead to pharmacological interactions. There are several reports in the databases about these risks. According with UK Advisory Council on the Misuse of Drugs, case reports regarding patients in emergency rooms with sympatomimetic syndrome and agitation related to benzofuran ingestion have been published since 2011 [30]. A case of 42 years old man, with loss of consciousness, tachycardia, hypertension and hyperthermia associated with the consumption of 1.5liters of beer, 0.75g of 5-APB and metoxetamine was reported in a case series about metoxetamine use, a ketamine analog NPS [31]. There is also a
report of a 21 years old male who combined cannabis and 0.4 mg of 6-APB. This subject developed a psychotic syndrome with paranoid delusional ideas, mind reading and agitation, resulting in a suicide attempt. The patient needed in-vitro treatment and psychotic features did not subside up to eight days [32,33]. Meningitis-like symptoms were developed in a 40 years old male with hypothyroidism and HIV- infection. Agitation, sympathomimetic symptoms, 39.2oC hyperthermia, myoclonus and supraventricular tachycardia were manifested in this patient who attended to the emergency room. Leukocytosis and rises in blood creatinine, lactic dehydrogenase, myoglobin, creatinine- kinase, alpha-amyrase and total bilirubin were reported in his laboratory test. After the initial management and 12hours later, the patient was awake and afibrile and declared himself as a Benzofurans user. Urinate analysis was positive for MDMA and amphetamines. Product analysis was positive for 2-APB and 4- methylcathinone [33].

Since 2011, several forensic reports in UK and later in many parts of the world associated with benzofurans have been stated. In some of these cases, combinations with legal drugs, like the antidepressant mirtazapine, and illegal drugs and NPS like methylypropan, 5-amnopropyl indol, alpha- methyltryptamine and other benzofuran analogs like 5-MAPB were reported [34-37]. Nonetheless, it seems that benzofurans do not produce a direct cytoxicity on neurons when they are exposed in vitro to high concentrations of these compounds.

Conclusion

NPS use is a growing global phenomenon and each day more prevalent in Colombia. For that reason, medical professionals must be informed about these substances and its reported effects.

Colombia is a noticeable market for MDMA and that is one of the reasons that an increase in benzofuran use may appear as adulterants as the raw materials for its production may become easier to get. That might result in major harms to health than the ones expected for ecstasy use. This may be demonstrated through case and forensic reports, which imply harmful or fatal accidental intoxications with 4-5- and 6-APB in individuals who consume ecstasy mislabeled tablets. Moreover, benzofurans are gaining reputation as a drug of choice and not exactly as adulterants because of their legal status and their easiness of marketing. They are sold as research chemical products and people only require a computer with internet access, a credit card and knowledge in deep web to buy it. Also, an increase in seizures, improves in drug trades monitoring, a diminished production of psychoactive substances or its low availability due the peace process with the guerrillas armed forces and an improve in drug detection tests may lead an increase of NPS use in Colombia.

Harms related to benzofurans have been reported. It is noticeable a large number of deaths related with their ingestion, considering a rather narrow use of this substances than other drugs. Besides, the number of benzofuran deaths is more than the ones related to other NPS use like 2-C’s series or 4-fluoromethylamphetamine. This fact must alert legal and forensic medicine services.

Nonetheless, there are some gaps in information. Long term use effects of these substances are not reported. Despite in-vitro studies have proved acute administration of benzofurans do not have neurotoxic activity, many psychoactive substances do not present it and it may appear only with chronic use. Data regarding Colombian consumers are not available due the report of the presence of benzofurans in the country was made thanks to detection in forensic laboratories of drug testing and not in consumers. This fact might be because there is a scarcity in urine and blood analysis of benzofuran metabolites in users and post-mortem cases due to the lack of laboratory reagents.

In order to discourage and diminish trading of benzofurans or their raw material, and in order of clarify the choice of this drugs, several efforts must be taken on benzofurans use. Those efforts must be taken on medical education and awareness of the clinical manifestations and presence of these substances in Colombia, also monitoring of potential new cases in MDMA and/or amphetamine intoxications, including forensic cases, analysis in forensic laboratories of ecstasy-labeled products by Observatorio de Drogasde Colombia, epidemiological studies mainly qualitative, field research and a legislation based on the evidence.

Acknowledgment

The author wants to thank Dr. Dulce Gabriela Licona Galicia, Dr. Ana María Restrepo, Mr. Adrián Heredia Hernandez and ESE Hospital Carisma clinical staff for their help in reviewing and preparation of the manuscript.

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