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Review

Benzylpiperazine: "A messy drug"

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ABSTRACT

Designer drugs are synthetic structural analogues/congeners of controlled substances with slightly modified chemical structures intended to mimic the pharmacological effects of known drugs of abuse so as to evade drug classification. Benzylpiperazine (BZP), a piperazine derivative, elevates synaptic dopamine and serotonin levels producing stimulatory and hallucinogenic effects, respectively, similar to the well-known drug of abuse, methylenedioxymethamphetamine (MDMA). Furthermore, BZP augments the release of norepinephrine by inhibiting presynaptic autoreceptors, therefore, BZP is a "messy drug" due to its multifaceted regulation of synaptic monoamine neurotransmitters. Initially, pharmaceutical companies used BZP as a therapeutic drug for the treatment of various disease states, but due to its contraindications and abuse potential it was withdrawn from the market. BZP imparts predominately sympathomimetic effects accompanied by serious cardiovascular implications. Addictive properties of BZP include behavioral sensitization, cross sensitization, conditioned place preference and repeated self-administration. Additional testing of piperazine derived drugs is needed due to a scarcity of toxicological data and widely abuse worldwide.

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1. Introduction

Piperazine derivatives are a group of chemically modified designer drugs derived from piperazine, a six-membered ring with two oppositely positioned nitrogen atoms (Fig. 1a). The name designer drug was first created in the mid-1980s by Dr. Gary Henderson at the University of California for psychoactive compounds which are suitable for educational purposes. Piperazinic derivatives are divided into two classes, benzylpiperazines and phenylpiper-

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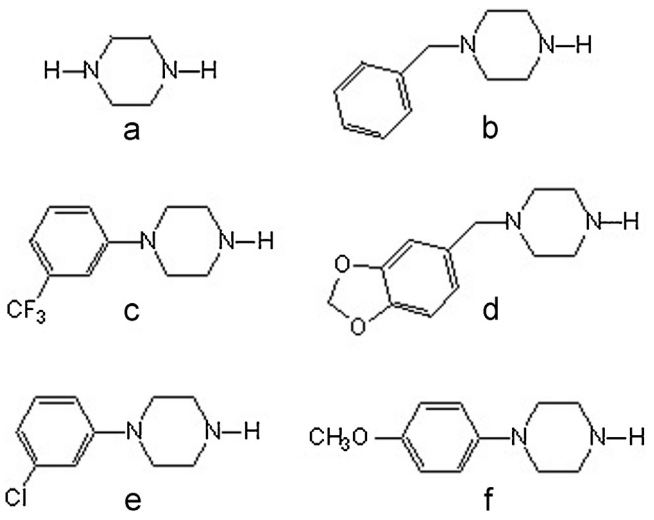

Fig. 1. Chemical structures of (a) piperazine, (b) benzylpiperazine, (c) TFMPP, (d) 1-(3,4-methylenedioxybenzyl)piperazine (MDBP), (e) 1-(3-chlorophenyl)piperazine (mCPP) and (f) 1-(4-methoxyphenyl)piperazine (MeOPP).

azines. The benzylpiperazines include *N*-benzylpiperazine (BZP) (Fig. 1b) and 1-(3,4-methylenedioxybenzyl)-piperazine (MDBP), the methylenedioxy analogue (Fig. 1d). Common phenylpiperazines abused are 1-(3-trifluoromethylphenyl) piperazine (TFMPP, Fig. 1c), 1-(3-chlorophenyl) piperazine (mCPP, Fig. 1e), and 1-(4-methoxyphenyl) piperazine (MeOPP) (Fig. 1f). Chemical modification of piperazine compounds enables clandestine manufacturers to avoid governmental bans and promotes widespread distribution under the pseudonyms "Rapture", "Frenzy", "Bliss", "Charge", "Herbal ecstasy", "A2", "Legal X", and "Legal E" (Arbo et al., 2012). Other than the piperazines derivatives, the designer drugs also include cathinones (MDPV, mephedrone, methylone), synthetic cannabinoids, tryptamines and other botanical formulations. To make things much worse, numerous unrestricted and autonomous internet sites are significantly devoted to reveal the "fun/delightful" actions of these designer drugs. The information's provided are very attractive and inquisitive to the common public, which increases the interest in these designer substances leading to the abuse. However, the data provided are dubious and misjudged by the public. The word "legal" used in the designer drugs has been misunderstood by the common public as a harmless substance that gives pleasure. This misinterpreted concept on designer drugs can lead to the destruction of the future generation (Corazza et al., 2014; Iversen et al., 2014). Substances were deliberately manufactured as designer drugs to induce the abuse potential similar to MDMA and amphetamines. Primarly their pharmacological actions were targeting monoamine release, transporters, reuptake and the receptors. Major monoaminergic neurotransmitters affected are dopamine, norepinephrine and serotonin. Based on their structure, the designer drugs have differential and selective effect on dopamine, norepinephrine and serotonin release and neurotransmission.

Originally, BZP was synthesized by Burroughs, Wellcome & Co. of Wellcome Research Laboratories in the United Kingdom. BZP was tested as an anti-helminthic agent for the treatment of intestinal roundworm infestations (Haroz and Greenberg, 2006), but piperazine was preferred because of greater efficacy and fewer side effects (Gee et al., 2005; Johnstone et al., 2007). In the 1970's, BZP was examined as a potential antidepressant, but was not pursued due to abuse potential (Bye et al., 1973). In late 1990s, New Zealand youth popularized the legal party drug, seeking its stimulatory effects (confidence, talkativeness, euphoria, vigor, activity and enhanced socialization), and as a result, its use spread rampantly among New Zealand residents, due to a failure of regulation. In 2007, an estimated 5 million BZP pills were sold in New Zealand (Gee and Fountain, 2007). The majority of epidemiological and pharmacotoxicological data, including patterns of use, motivations and positive and adverse effects, pertaining to BZP use, emanates from New Zealand during 2000–2008 (Cohen and Butler, 2011). Students and workers, such as shift workers and truck drivers, abused the drug to increase alertness and enhance their physical and mental performance (Butler and Sheridan, 2007). Also, because of its anorectic properties, BZP was abused as an appetite suppressant among young women (Wilkins et al., 2006). BZP was also exploited in the performance enhancement arena, particularly the horse racing industry (Barclay, 2003) and athletics (Molly, 2005), but has since been prohibited. Based on various incidences, European Union formally and publicly warned regarding the new designer drugs exploitation particularly among youths. The warning clearly expressed its concerns regarding the use in humans, retail trade by means of an alternate but a fabricated and deceitful label, no formal and validated scientific background.

Similarly, in the United States, on September 20, 2002, BZP was temporarily scheduled, in accordance with the controlled substances act (CSA) of the United States, as a schedule I drug, a drug with a high liability for abuse with no recognized medical use (Drug Enforcement Administration, 2014a). This scheduling resulted from an inaccurate report by the Drug Enforcement Administration (DEA); BZP displays 10–20 times greater potency than amphetamine, when actually BZP is 10 times less potent than dexamphetamine (Stargate International, 2004). Based on the European Union report constructed largely on abuse potential, on March 18, 2004, BZP was permanently placed among schedule I drugs by DEA. Identified BZP cases reported to federal, state and local forensic laboratories peaked at 15,174 in 2009, while in 2013 there were 2548 reports, according to DEA's System to Retrieve Information from Drug Evidence (STRIDE) and the National Forensic Laboratory Information System (NFLIS) (Drug Enforcement Administration, 2014b).

2. Perception of safety

Due to its psychoactive properties, legal status in many countries, and false reputation of safety, the recreational use of piperazine derivatives has gained popularity as an alternative to amphetamine, in spite of a plethora of experimental, clinical, and epidemiological studies linking its use with the development of severe serotonin syndrome, hepatotoxicity, neurotoxicity, psychopathology, and potential for abuse (Schep et al., 2011). New Zealand users believed that legality protected the quality and purity of BZP, when manufacturers synthesized without controls. Product labels gave consumers false impressions that they knew exactly what they were buying. Many users underestimated the strength of the pills and characterized the effects as moderate. Moreover, BZP-party pills were socially accepted and widely available due to a lack of legislation. It has since been proposed that BZP may entice users into using other illicit drugs ("gateway") or it may provide illicit drug users a legal alternative (Sheridan and Butler, 2010). However, in New Zealand it is prohibited and the accessibility has declined immediately following its prohibition (Wilkins et al., 2014).

3. Patterns of use

Administered orally in capsule, tablet, pill, powder, or liquid form (Gee et al., 2005), the piperazine designer drugs frequently appear as adulterants of, or additives to, ecstasy, cocaine, amphetamine and ketamine products (EMCDDA, 2009). Other reported routes of administration include inhalation, insufflation