Special feature: mini-review

Drug Testing and Analysis

Received: 16 November 2010 Revised: 28 February 2011 Accepted: 4 March 2011 Published online in Wiley Online Library: 28 April 2011

(www.drugtestinganalysis.com) DOI 10.1002/dta.285

Subjective effects in humans following administration of party pill drugs BZP and TFMPP alone and in combination

Joanne C. Lin,[a]* Reem K. Jan,[a] Rob R. Kydd[b] and Bruce R. Russell[a]

The use of piperazine derivatives, colloquially named 'party pills', has been escalating in New Zealand and worldwide since their introduction in the 1990s. Benzylpiperazine (BZP) is often used alone, or can be combined with trifluoromethylphenylpiperazine (TFMPP). Taken together as an oral dose, they have been reported to produce effects similar to 3, 4-methylenedioxymethamphetamine (MDMA). While the pharmacokinetic data have recently been published, little research has been conducted on the subjective effects of these piperazines on humans. This paper outlines the subjective effects observed following oral doses of BZP (200 mg) and TFMPP (60 mg) alone, or in combination (100/30 mg) compared to placebo. Participants were asked to comment on the subjective effects of each drug using three subjective rating scales – the Addiction Center Research Inventory (ARCI), the Profile of Mood States (POMS), and the Visual Analog Scales (VAS) – before and approximately 120 min after a single dose. BZP showed significant dexamphetamine-like stimulant effects, inducing euphoria, sociability, and drug liking, whereas TFMPP induced fewer stimulant-like effects and increased anxiety, via its serotonergic effects. The combination of BZP and TFMPP induced similar subjective effects, along with well-characterized dexamphetamine- and MDMA-like effects. These subjective data allow for obvious comparisons to be made between party pill drugs and other commonly known stimulants. However, despite estimates of over 20 million doses sold in New Zealand alone and increasing seizures by the Drug Enforcement Administration in the USA, there are no published cases of dependence worldwide. The long-term effects of regular party pill use are also unknown, and create the potential for future research. **Copyright © 2011 John Wiley & Sons, Ltd.**

Keywords: Benzylpiperazine (BZP); Trifluoromethylphenylpiperazine (TFMPP); Party pills; Human; Mood

Introduction

Piperazine derivatives were a relatively new group of recreational drugs found to have psychoactive effects. Benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) are perhaps the most commonly used constituents of this group of drugs, colloquially named 'party pills'. They became legally available and widely used in recreational settings in the 1990s, with use in New Zealand and around the world escalating from 2000.

In New Zealand, party pills were marketed as 'herbal highs' and safer alternatives to illicit substances such as the amphetamines. Users of party pills have described increased energy and alertness, enhanced confidence, and euphoria.[1] Drug websites, where users report their experiences and opinions, have reported that BZP and TFMPP taken together produce a similar 'high' to that experienced following administration of 3, 4-methylenedioxymethamphetamine (MDMA or 'Ecstasy'; Figure 1).[2]

Party pills have been sold over the Internet and marketed under many brand names worldwide. In New Zealand prior to April 2008, party pills were legally accessible by those 18 years of age and over. Since then, BZP and related analogues have been reclassified under the Misuse of Drugs Act (1975), placing them in the same class as cannabis. In the USA, BZP and TFMPP were placed on Schedule 1 of Controlled Substances Act in 2002 due to their potential to cause harm. However, in 2004 TFMPP was controversially removed from the Schedule due to lack of evidence of harm, and is currently not controlled by US Federal Law whereas BZP was 'permanently' placed in Schedule 1.[3] Despite this, there is evidence that the use of these drugs is still increasing – in 2004, there were 48 seizures of items identified as BZP by the American Drug Enforcement Administration (DEA), and in 2009 the number of seizures had increased to 13 822 despite being made illegal six years earlier.[4]

Due to the structural similarity of BZP to piperadine – a constituent of the piperine alkaloid found in black pepper – party pills were originally marketed 'herbal highs'. Some party pill formulations also contained amino acids, in addition to black pepper extract so were able to be advertised as 'herbal' products. However, despite these claims, BZP, TFMPP and other piperazine derivatives are purely synthetic.

Piperazine was originally synthesized by Wellcome Research Laboratories as a potential threadworm treatment in children. Although the anthelmintic properties of BZP, a derivative of piperazine, were never assessed, it was later found to reverse the effects of tetrabenazine, a dopamine (DA)-depleting agent

* *Correspondence to: Joanne C. Lin, School of Pharmacy, Faculty of Medical and Health Sciences, University of Auckland Private Bag 92019, Auckland, New Zealand. E-mail: joanne.lin@auckland.ac.nz*

a *School of Pharmacy, Faculty of Medical and Health Sciences, University of Auckland, New Zealand*

b *Department of Psychological Medicine, Faculty of Medical and Health Sciences, University of Auckland, New Zealand*

 Copyright © 2011 John Wiley & Sons, Ltd.

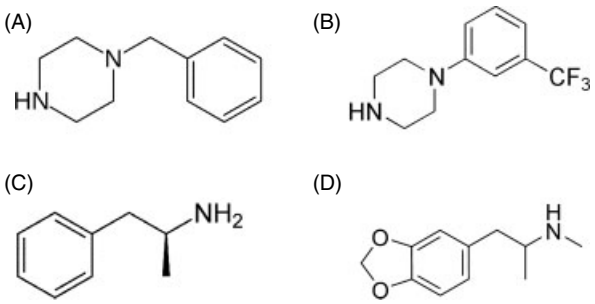

Figure 1. Structures of (A) N-benzylpiperazine (BZP), (B) 1-[3-trifluoromethylphenyl]-piperazine (TFMPP) (C) dexamphetamine and (D) 3, 4-methylenedioxymethamphetamine (MDMA).

Table 1. Summary of subjective effects of BZP (200 mg) and TFMPP (60 mg) alone and in combination (100/30 mg)

	BZP[26]	TFMPP[25]	BZP/TFMPP[27]
ARCI			
Euphoria	↑	–	–
Dysphoria	↑	↑	↑
Dexamphetamine-like effects	↑	↑	↑
POMS			
Tension/anxiety	–	↑	–
Depression/dejection	↓	–	–
Fatigue/inertia	↓	–	–
Confusion/bewilderment	↓	↑	–
Vigour/activity	↑	–	↑
Total mood disturbance	↑	–	–
VAS			
Drug effect	↑	–	↑
Good drug effect	↑	–	↑
Drug liking	↑	↑	↑
Stimulated	↑	↑	↑
High	↑	↑	–
Anxious	↑	–	–
Talkative	↑	–	–
Self-confident	↑	–	↑
Social	↑	–	–

that depresses vesicular monoamine accumulation in rats and mice.

BZP is chemically similar in structure to DA and the amphetamines. In humans, it is metabolized by hepatic cytochrome P450 (CYP) enzymes CYP2D6, CYP1A2, and CYP3A4, and predominantly excreted by the kidneys.[5,6] Contrary to earlier studies in humans suggesting that the physiological effects of BZP do not occur for up to two hours following oral administration,[7] more recent studies have shown that C_{max} is reached within 75 min.[5]

Nearly all studies to date investigating the central mechanism of action of BZP and TFMPP have been carried out in rats and monkeys. In rodents, BZP has been found to exert its central effects through interactions with DA, and to a lesser extent, serotonin (5-HT) transporters. Dose-dependent elevations of extracellular DA and 5-HT were seen following intravenous administration of BZP, however 5-HT release was only induced following high doses.[8] These effects are similar to those seen following amphetamine administration. In addition to the effects of BZP on DA and 5-HT, it has been suggested that BZP also causes peripheral release of noradrenaline (NA), due to its α_2-adrenoceptor-blocking properties.[9]

In contrast, TFMPP bears little resemblance to dopaminergic stimulants,[10,11] it does not exert any adrenergic effects[11] and its mechanism of action is almost exclusively serotonergic, resembling other serotonergic compounds such as lysergic acid diethylamide (LSD),[12] 1-[3-chlorophenyl]-piperazine (mCPP)[13] and fenfluramine.[14] Hence, TFMPP was, and still is, commonly used as a marker for 5-HT activity.[15,16]

Similarly to BZP, TFMPP is metabolized by the hepatic enzymes – predominantly CYP2D6, and to a lesser extent, CYP1A2 and CYP3A4.[17] Our laboratory has shown that following an oral TFMPP dose of 60 mg, C_{max} is reached within 90 min.[18]

TFMPP is relatively selective for 5-HT_1 and 5-HT_2 receptors, with little affinity for 5-HT_3 receptors.[19] TFMPP is an agonist at 5-HT_{2C} [20] and a partial agonist at 5-HT_{1A},[21] 5-HT_{1B} [11] and 5-HT_{2A} receptor[22] subtypes. It is also thought to inhibit gamma-aminobutyric acid (GABA) release possibly through activity at 5-HT_3 receptors.[23]

When administered together, BZP and TFMPP produce similar neurochemical effects to MDMA in rats but are three-fold less potent with respect to stimulating monoamine release. However, the amount of DA released when BZP and TFMPP were co-administered was greater than the summed effects of either drug alone, suggesting a synergistic effect on DA transmission.[8]

Until recently, the subjective effects of BZP and TFMPP alone and in combination have not been well studied. In animal studies, BZP has been shown to induce self-administration behavior by monkeys, as well as place preference in rats – a phenomenon unique to drugs with rewarding effects.[24] However, the discriminative properties of TFMPP did not generalize to amphetamine, nor was it self-administered by monkeys.[10] In early human studies, equipotent doses of BZP and amphetamine produced indistinguishable subjective effects and both drugs were considered desirable by former amphetamine addicts,[7] whereas the subjective effects of TFMPP have anecdotally been reported as mildly psychedelic, similar to those produced by LSD and psilocybin.[2]

This paper outlines the results of three randomized double-blind, placebo-controlled trials investigating the subjective effects of BZP (200 mg), and TFMPP (60 mg), as well as BZP in combination with TFMPP (100/30 mg) in human males Table 1.[25–27]

Rating scales

The subjective effects of placebo and drug were evaluated using subjective rating scales both before and 120 min after placebo or drug administration – the Addiction Research Center Inventory (ARCI), Profile of Mood States (POMS) and Visual Analog Scales (VAS).[28]

A shortened version of the ARCI form was used to determine drug-induced effects. The questions were categorized into five empirically derived scales that have proved sensitive for psychoactive drugs.[28] These scales measured sedation (Phenobarbital-Chlorpromazine-Alcohol Group, or PCAG scale), drug-induced euphoria (Morphine-Benzedrine Group, or MBG scale), stimulant-like effects (Benzedrine, or BG scale), dysphoria (Lysergic Acid Diethylamine, or LSD scale) and dexamphetamine-like effects (Amphetamine, or A scale).

The POMS standard form, described by McNair *et al.*[29], is used to clinically evaluate mood states. The form was composed

Copyright © 2011 John Wiley & Sons, Ltd.

of 65 separate items, which assessed the tension/anxiety (T), depression/dejection (D), anger/hostility (A), fatigue/inertia (F), vigor/activity (V), confusion/bewilderment (C) and total mood disturbance (TMD) felt by the participant at that point in time. Each item was graded on a five-point Likert scale (ranging from 'not at all' to 'extremely') and thus assesses the total mood disturbance of the participant. These were graded according to the POMS standard scoring grid, where each point of the five-point scales corresponded to one or more of the seven abovementioned categories.

Visual analog scales were used to assess momentary changes in mood within individual participants. This consisted of 22 scales -100 mm horizontal lines, each labelled with an adjective (drug effect, good drug effect, bad drug effect, drug liking, stimulated, high, anxious, sedated, down, hungry, friendly, miserable, on edge, alert, tired, talkative, self-confident, paranoid, social, irritable, confused, and sick). Zero mm on the line corresponded to 'not at all' and 100 mm corresponded to 'extremely'. Participants were required to place a mark on each line indicating how they felt at that moment.

Subjective effects

ARCI

BZP administration produced significant increases in euphoria (MBG), dysphoria (LSD) and dexamphetamine-like effects (A).[26] These effects are similar to those seen following administration of other stimulants such as dexamphetamine.[30] In addition to the acute pleasurable effects caused by stimulants such as MDMA and dexamphetamine, dysphoria-related effects can also occur. MDMA has shown a consistent and reproducible increase in score on the LSD scale, and there is evidence that dexamphetamine-induced dysphoria is more variable and dose-dependent.[31–34] Foltin and Fischman suggested that the increase in LSD score following MDMA was due to a time-dependent rebound effect.[28] This is likely as, unless the drug was continuously infused, the euphoric effects are expected to diminish, resulting in a relatively less euphoric state. The subjective effects of TFMPP were found to be similar to other serotonergic agents such as LSD,[12] mCPP[13] and fenfluramine;[14] this was not unexpected given their ability to modulate 5-HT receptors. TFMPP administration caused an increase in the LSD and A scales.[25] As mentioned, these effects are also observed with MDMA and fenfluramine.[28] The combination of BZP and TFMPP produced similar changes as those seen with BZP and TFMPP alone, increasing the LSD and A scales.[27]

POMS

BZP was associated with significant changes in five of the seven POMS scales – decreased depression/dejection (D), fatigue/inertia (F) and confusion/bewilderment (C) with increased vigor/activity (V) and total mood disturbance (TMD)[22b]. These effects – with the exception of decreased anger/hostility (A) and increased tension/anxiety (T) – overlap with a number of well-characterized effects of stimulants such as dexamphetamine.[28,32] TFMPP caused an increase in T, which is thought to be mediated by the 5-HT_{1B} receptor, along with an increase in C.[25] Similar changes were observed following mCPP administration.[34] Administration of BZP and TFMPP in combination did not cause significant changes in all of the expected scales; BZP/TFMPP only increased V.[27] This may be due to a dose effect, as only half the dose of BZP and TFMPP was given in combination, and more changes may be seen with higher doses of one or both drugs in combination.

VAS

A number of changes on VAS scales were seen following BZP administration – increased drug effect, good drug effect, drug liking, stimulated, high, anxious, talkative, self-confident and social.[26] TFMPP increased ratings of drug liking, high, and stimulated.[25] These overlap with a number of effects seen following dexamphetamine administration – specifically good drug effect, drug liking, stimulated, high, and talkative.[28,30,34] BZP and TFMPP administration resulted in similar effects – increased drug effect, good drug effect, drug liking, stimulated, and self-confident. These effects are also observed following MDMA administration.[32,34]

These subjective data allow for obvious comparisons to be made between the party pill drugs BZP and TFMPP and other commonly known stimulants, which support pre-clinical research suggesting similar mechanisms of action. BZP alone, through predominantly dopaminergic action, shares a number of subjective effects with dexamphetamine, while TFMPP alone produces fewer stimulant-like effects via interactions with 5-HT receptors, and more closely mimics the effects of serotonergic agent LSD. The combination of BZP and TFMPP induced a mixture of effects attributable to DA and 5-HT, which are also observed following MDMA administration. However, exclusive reliance on subjective effects does not take into account external variables which need to be considered when assessing whether or not a drug is likely to cause addiction;[28] these factors include personality traits and history of the user, the physical setting and environment in which the drugs are used.

In humans, BZP-related side-effects resulting in emergency department admission have been associated with high plasma levels of BZP, and co-administration of alcohol increased the likelihood of distressing symptoms.[35] Adverse effects have also been reported following combined BZP/TFMPP administration; however, these were subsequent to very high doses of each drug (300/74 mg) in addition to six standard units of alcohol – the recommended safe upper limit of alcohol consumption in one session.[36] There have also been case series of confirmed toxicity associated with the use of TFMPP in combination with BZP, with clinical features – such as dissociative-type symptoms – that are not typical of previous reports of BZP toxicity. The authors conclude that these symptoms were most likely due to the ingestion of TFMPP.[37] More systematic approaches to toxicological screening and further assessment of the objective and subjective effects of these drugs would provide more precise information, and aid in the legislative scheduling of novel compounds.

Dexamphetamine is well known to induce dependence if used on a recreational basis. However, it has been claimed that dependence on MDMA is unlikely to become a serious problem due to the decrease in pleasurable effects with increasing frequency of use.[38] The increase in unpleasant effects would diminish the incentive to continue using the drug in a manner likely to cause dependence – a phenomenon observed with use of hallucinogens.[38] This may also be true of the party pill drugs when taken in combination as hallucinogenic effects have been anecdotally reported following the use of TFMPP alone.[2]

There have been anecdotal reports of dependence on party pills from a telephone-based survey undertaken by Wilkins *et al*.[1] However, due to the lack of specific measures of dependency for a wide range of party pills, the Short Dependence Scale was used,

Copyright © 2011 John Wiley & Sons, Ltd.

with a cut-off point validated for amphetamine dependency only. Despite estimates of over 20 million doses sold in New Zealand alone and increasing number of seizures within the USA,[4] there have been no published cases of dependence reported worldwide. This may be due to the slow absorption of these drugs, as they are usually taken orally, which is thought to affect the speed with which drug dependence is induced, or the unpleasant side-effects as described by some users which may limit the extent to which BZP is abused.[39] The long-term effects of regular party pill use are still unknown so there is a need for further research.

References

[1] C. Wilkins, M. Girling, P. Sweetsur, T. Huckle, J. Huakau, *Legal Party Pill Use in New Zealand: Prevalence of use, availability, health harms and 'gateway effects' of benzylpiperazine (BZP) and triflourophenylmethylpiperazine (TFMPP)*, Centre for Social and Health Outcomes Research and Evaluation (SHORE), Massey University, Auckland **2006**.
[2] Erowid. *Erowid Experience Vaults: Piperazine Reports 2010.* Available at: http://www.erowid.org/chemicals/piperazines **2010**, Accessed 3 October 2010.
[3] FDA. *U.S. Food and Drug Administration.* Available at: http://www.fda.gov **2008**, Accessed 30 October 2010.
[4] DEA. *Drug Enforcement Administration – Drugs and Chemicals of Concern: N-benzylpiperazine.* Available at: http://www.deadiversion.usdoj.gov/drugs_concern/bzp_tmp/bzp_tmp.htm **2010**, Accessed 15 September 2010.
[5] U. Antia, H. S. Lee, R. R. Kydd, M. D. Tingle, B. R. Russell, *Forensic Sci. Int.* **2009**, *186*, 63.
[6] R. F. Staack, G. Fritschi, H. H. Maurer, *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2002**, *773*, 35.
[7] H. Campbell, W. Cline, M. Evans, J. Lloyd, A. W. Peck, *Eur. J. Clin. Pharmacol.* **1973**, *6*, 170.
[8] M. H. Baumann, R. D. Clark, A. G. Budzynski, J. S. Partilla, B. E. Blough, R. B. Rothman, *Neuropsychopharmacology* **2005**, *30*, 550.
[9] K. Magyar, M. I. Fekete, K. Tekes, T. Torok, *Eur. J. Pharmacol.* **1986**, *130*, 219.
[10] W. E. Fantegrossi, G. Winger, J. H. Woods, W. L. Woolverton, A. Coop, *Drug Alcohol Depen.* **2005**, *77*, 161.
[11] L. Herndon, M. E. Pierson, R. A. Glennon, *Pharmacol. Biochem. Be.* **1992**, *43*, 739.
[12] K. A. Cunningham, B. A. Carroll, J. B. Appel, *Psychopharmacology (Berl.)* **1986**, *89*, 134.
[13] M. H. Baumann, D. C. Mash, J. K. Staley, *Neuroreport* **1995**, *6*, 2150.
[14] R. B. Rothman, M. A. Ayestas, C. M. Dersch, M. H. Baumann, *Circulation* **1999**, *100*, 869.
[15] S. B. Auerbach, N. Kamalakannan, J. J. Rutter, *Eur. J. Pharmacol.* **1990**, *190*, 51.
[16] F. Miranda, G. Orozco, D. N. Velazquez-Martinez, *Behav. Pharmacol.* **2002**, *13*, 303.
[17] R. F. Staack, L. D. Paul, D. Springer, T. Kraemer, H. H. Maurer, *Biochem. Pharmacol.* **2004**, *67*, 235.
[18] U. Antia, M. D. Tingle, B. R. Russell, *J. Pharm. Pharmacol.* **2009**, *61*, 877.
[19] D. W. Robertson, W. Bloomquist, D. T. Wong, M. L. Cohen, *Life Sci.* **1992**, *50*, 599.
[20] P. J. Conn, E. Sanders-Bush, *J. Pharmacol. Exp. Ther.* **1987**, *242*, 652.
[21] P. Schoeffter, D. Hoyer, *Naunyn. Schmiedebergs Arch. Pharmacol.* **1989**, *339*, 675.
[22] M. S. Grotewiel, H. Chu, E. Sanders-Bush, *J. Pharmacol. Exp. Ther.* **1994**, *271*, 1122.
[23] I. Cloëz-Tayarani, C. Harel-Dupas, G. Fillion, *Fund. Clin. Pharmacol.* **1992**, *6*, 333.
[24] E. Meririnne, M. Kajos, A. Kankaanpaa, T. Seppala, *Basic Clin. Pharmacol. Toxicol.* **2006**, *98*, 346.
[25] R. K. Jan, J. C. Lin, H. Lee, J. L. Sheridan, R. R. Kydd, I. J. Kirk, B. R. Russell, *Psychopharmacology (Berl.)* **2010**, *211*, 347.
[26] J. C. Lin, N. Bangs, H. Lee, R. R. Kydd, B. R. Russell, *Psychopharmacology (Berl.)* **2009**, *207*, 439.
[27] J. C. Lin, R. K. Jan, H. Lee, M. A. Jensen, R. R. Kydd, B. R. Russell, *Psychopharmacology (Berl.)* **2010**, *214*, 761.
[28] R. W. Foltin, M. W. Fischman, *Drug Alcohol Depen.* **1991**, *28*, 3.
[29] D. M. McNair, J. W. P. Heuchert, E. Shilony, *MHC Inc.* **2003**, 7–8.
[30] J. P. Zacny, H. de Wit, *Pharmacol. Biochem. Be.* **1989**, *34*, 791.
[31] J. Camí, M. Farré, M. Mas, P. N. Roset, S. Poudevida, A. Mas, L. San, R. de la Torre, *J. Clin. Psychopharmacol.* **2000**, *20*, 455.
[32] L. D. Chait, E. H. Uhlenhuth, C.-E. Johanson, *Psychopharmacology* **1985**, *86*, 307.
[33] W. R. Martin, J. W. Sloan, J. D. Sapira, D. R. Jasinski, *Clin. Pharmacol. Ther.* **1971**, *12*, 245.
[34] M. Tancer, C.-E. Johanson, *Drug Alcohol Depen.* **2003**, *72*, 33.
[35] P. Gee, M. Gilbert, S. Richardson, G. Moore, S. Paterson, P. Graham, *Clin. Toxicol.* **2008**, *46*, 802.
[36] I. Thompson, G. Williams, B. Caldwell, S. Aldington, S. Dickson, N. Lucas, J. McDowall, M. Weatherall, G. Robinson, R. Beasley, *J. Psychopharmacol.* **2010**, *24*, 1299.
[37] D. M. Wood, J. Button, S. Lidder, J. Ramsey, D. W. Holt, P. I. Dargan, *J. Med. Toxicol.* **2008**, *4*, 254.
[38] H. Kalant, *CMAJ* **2001**, *165*, 917.
[39] A. C. Johnstone, R. A. Lea, K. A. Brennan, S. Schenk, M. A. Kennedy, P. S. Fitzmaurice, *J. Psychopharmacol.* **2007**, *21*, 888.

Copyright © 2011 John Wiley & Sons, Ltd.