Psychopharmacology (2011) 214:761–768
DOI 10.1007/s00213-010-2081-7

ORIGINAL INVESTIGATION

Determining the subjective and physiological effects of BZP combined with TFMPP in human males

Joanne C. Lin · Reem K. Jan · HeeSeung Lee · Maree-Ann Jensen · Rob R. Kydd · Bruce R. Russell

Received: 13 September 2010 / Accepted: 27 October 2010 / Published online: 9 November 2010

Abstract
Rationale 'Party Pills' containing benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) have been used in a recreational context since the 1990s and, prior to April 2008, were legally available in New Zealand. Taken together, they have been reported to produce a 'high' similar to that produced by 3,4-methylenedioxymethamphetamine (MDMA).
Objectives There has been little research on the subjective effects of piperazines in humans. The purpose of this study is to further investigate the subjective and physiological responses following an oral dose of BZP combined with TFMPP in males.
Methods In a randomised, double-blind, placebo-controlled study the subjective and physiological effects of BZP/TFMPP were investigated in 36 healthy, non-smoking males (mean age 22±4 years). Participants were tested before and approximately 120 min after administration of a single dose of placebo (n=16) or 100/30 mg BZP/TFMPP (n=20). Participants were required to comment on the subjective effects using three rating scales—the Addiction Research Centre Inventory (ARCI), the Visual Analogue Scale (VAS) and the Profile of Mood States (POMS). Participants' blood pressure, heart rate and body temperature were also measured.
Results Statistical analysis using repeated-measures analysis of variance (ANOVA) and planned comparisons revealed that BZP/TFMPP significantly increases blood pressure and heart rate ($p<0.05$). Likewise, the subjective rating scales revealed that BZP/TFMPP has significant dexamphetamine-like effects, increases dysphoria and feelings of self-confidence ($p<0.05$).
Conclusion These physiological and subjective data reflect clear similarities between the effects of BZP/TFMPP and commonly known stimulants such as dexamphetamine and MDMA.

Keywords Benzylpiperazine (BZP) · Trifluoromethylphenylpiperazine (TFMPP) · Party pills · Human · Mood

Introduction

Piperazine derivatives, colloquially termed 'Party Pills', have been used in a recreational context since the 1990s, with their use in New Zealand and worldwide escalating since 2000—especially in young people in their late teens and early twenties (Wilkins et al. 2006). Benzylpiperazine (BZP) is a common constituent of party pills, and is frequently combined with trifluoromethylphenylpiperazine (TFMPP). Users of party pills have described feelings of enhanced confidence, increased alertness, energy and euphoria (Wilkins et al. 2006). Taken together, drug websites report them as being able to produce a 'high' similar to that produced by 3,4-

This research was funded by the Health Research Council of New Zealand.

J. C. Lin (✉) · R. K. Jan · H. Lee · M.-A. Jensen · B. R. Russell
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

R. R. Kydd
Department of Psychological Medicine,
Faculty of Medical and Health Sciences, University of Auckland,
Private Bag,
92019, Auckland, New Zealand

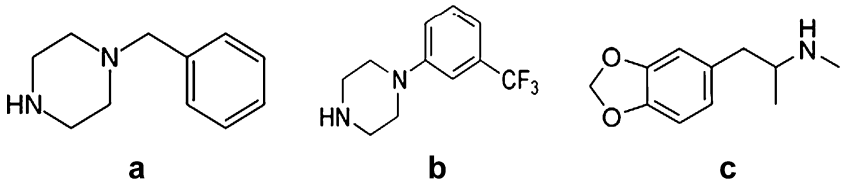

Fig. 1 Structures of **a** N-benzyl-piperazine (BZP), **b** 1-[3-trifluor-omethylphenyl]-piperazine (TFMPP) and **c** 3,4-methylene-dioxymethamphetamine (MDMA)

methylenedioxymethamphetamine (MDMA or 'Ecstasy'; Fig. 1; Erowid 2010).

In New Zealand and the United Kingdom, party pills have been marketed under many brand names and have been widely available from specific retailers and over the internet. The USA is among the many countries that have imposed restrictions on BZP. Due to the suspected potential of BZP to cause harm, it was permanently placed in schedule 1 of the United States Controlled Substances Act in 2004 (FDA 2008). Despite this, there is evidence that the use of these drugs is increasing in the USA, for example there were only 48 seizures of items identified as BZP in 2004 and in 2009 the figure increased to 13,822 (DEA 2010). In New Zealand prior to April 2008, the sale of party pills was legally allowed to those 18 years of age and over. Since then, BZP and other BZP analogues have been reclassified under the Misuse of Drugs Act (1975), placing them in the same class as cannabis.

The average dose of BZP in party pills supplied in New Zealand was initially about 50 mg, but has ranged from 70 to 250 mg in more recent products, with one product offering 500 mg per dose. The ratio of BZP to TFMPP in party pills ranged from 2:1 up to 10:1.

Because of the structural similarity of BZP to piperidine—a constituent of the piperine alkaloid found in black pepper, party pills were initially marketed as 'herbal highs' and claimed to provide a safer alternative to illicit substances such as the amphetamines. Many party pill formulations sold as 'herbal' did in fact contain black pepper extract and amino acids. However despite this BZP, TFMPP and the related piperazines are purely synthetic compounds.

Piperazine was originally trialled as a potential thread-worm treatment in children (White and Standen 1953). Although BZP itself, a derivative of piperazine, was never investigated for anthelmintic properties, it was later found to reverse the sedative effects of tetrabenazine, a dopamine (DA)-depleting agent that depresses vesicular monoamine accumulation in rats and mice (Miller et al. 1971, unpublished work).

Nearly all of the research to date carried out to determine the central mechanism of action of BZP has utilised rats and monkeys. In rodents, BZP interacts with DA, and to a lesser extent, serotonin (5-HT) transporters which mediate its central effects. Elevation of extracellular DA and 5-HT levels in the nucleus accumbens was shown to be dose-dependent following intravenous administration of BZP in male Sprague–Dawley rats. However 5-HT release was only affected following high doses (Baumann et al. 2005). These effects are comparable to those induced by amphetamine.

In addition to the effects of BZP on DA and 5-HT release, Magyar et al. (1986) suggested that it also induces noradrenaline (NA) release in the periphery, an effect attributed at the time to α_2-adrenoceptor-blocking properties.

BZP is chemically similar to DA and other amphetamines. It is primarily excreted by the kidneys, and degraded by the hepatic enzymes CYP2D6, CYP1A2 and CYP3A4 which also play a central role in its metabolism (Antia et al. 2009a). Early studies in humans investigating the effects of BZP suggested that physiological effects do not occur for up to 2 h following oral administration (Campbell et al. 1973); however, recent research has shown that C_{max} is reached within 75 min (Antia et al. 2009a) supporting the suggestion that the effects occur much sooner.

TFMPP was, and still is, commonly used as a marker for 5-HT activity due to its non-selective agonist activity at all 5-HT receptor subtypes (Miranda et al. 2002). It also causes presynaptic 5-HT transporter (SERT)-mediated 5-HT release (Auerbach et al. 1991). TFMPP is known to have an indirect effect on DA release through interactions with 5-HT receptors and GABA receptor blockade (Cloëz-Tayarani et al. 1992; Nissbrandt et al. 1992). In addition TFMPP has been shown to affect NA release—radioligand binding studies have shown that central and peripheral adrenoceptors are activated indirectly through 5-HT_{2C} receptors (Millan et al. 1998; Sawynok and Reid 1992). However, the effect of TFMPP on α- and β-adrenoceptors has not been well described in the literature.

The clinical effects of TFMPP in humans have recently been characterised. It has been shown to increase dysphoria and dexamphetamine-like effects, as well as increase feelings of tension and confusion (Jan et al. 2010). There have been anecdotal reports from people who have used TFMPP recreationally and described hallucinations and hyperthermia amongst other effects (Erowid 2010). In rodents, it is thought that stimulation of 5-HT_{1B} receptors

is responsible for behavioural changes such as reduced aggression and increased anxiety (Saudou et al. 1994). The hallucinogenic effects may be attributed to the involvement of 5-HT_1 and 5-HT_2 receptor subtypes (Appel and Callahan 1989). TFMPP-induced hyperthermia has also been shown in male Wistar rats (Klodzinska and Chojnacka-Wojcik 1992).

The hepatic enzymes that play a role in the degradation of BZP are also involved in the metabolism of TFMPP (Antia et al. 2009c) and recent research shows that C_{max} is reached in about 90 min following an oral dose (Antia et al. 2010).

Previous research designed to investigate the effects of BZP and TFMPP when administered together in Sprague–Dawley rats found that they produce similar neurochemical effects to MDMA but were threefold less potent with respect to stimulating monoamine release. The amount of DA released when BZP and TFMPP were co-administered was shown to be greater than the summed effects of either drug alone, suggesting a synergistic effect on DA transmission (Baumann et al. 2005).

Baumann et al. (2005) also suggested that BZP, in combination with TFMPP, has a relatively narrow therapeutic window as the seizure-inducing threshold was close to the threshold for monoamine release in rats. However, the wide dose range of BZP and TFMPP contained in party pill preparations, and the consequential use by approximately 400,000 users and a low-reported rate of BZP-induced seizures suggests otherwise (Wilkins et al. 2006).

Human studies investigating the pharmacokinetic interactions between BZP and TFMPP have shown that despite inhibition of TFMPP metabolism by BZP, the time to peak concentration and half-life of each agent remained unchanged (Antia et al. 2009b).

To date there are no published data about the subjective effects of BZP in combination with TFMPP and very little about BZP and TFMPP alone. Following on from work carried out by Campbell et al. (1973) and Bye et al. (1973), we investigated the physiological and subjective effects of BZP (200-mg oral) in female humans (Lin et al. 2009). BZP was found to increase systolic and diastolic blood pressure and heart rate, and increase stimulant effects, euphoria, dysphoria, sociability and drug liking on subjective rating scales. These data reflect a similarity between the effects of BZP and other commonly used stimulants such as amphetamine and MDMA. TFMPP (60 mg) was also found to have dexamphetamine-like effects. They provide a basis for investigating the effects of BZP when combined with TFMPP. BZP and TFMPP are frequently taken together and combined in party pill preparations in an attempt to produce the subjective effects induced by MDMA administration.

Materials and methods

Participants

Thirty-six non-smoking male participants (18–34 years of age, mean=22±4 years) volunteered to participate in this double-blind placebo-controlled experiment. Participants were recruited by word of mouth and posters. The Northern X Regional Ethics Committee of New Zealand approved this study; written consent was obtained from all participants before this research was undertaken.

Participants were excluded on the basis of a history of mental illness, cardiac disease, head trauma, epilepsy and recent or excessive drug use, which was defined as having engaged in binge drinking more frequently than once a month, or using cannabis or other recreational drugs more than twice a month or in the previous 7 days. Participants were also asked to compare their drug use against their peers and to classify themselves as light, regular or heavy users. Participants who considered themselves heavy users were excluded.

A questionnaire detailing medication history, recreational drug, party pill, alcohol and cigarette use, sleeping patterns and stress levels was completed by participants to ensure they were not drug naïve and reduce the likelihood of exaggerated subjective responses to BZP/TFMPP. This was also to ensure there were no potential drug interactions.

Drugs

Placebo (lactose) capsules and capsules containing BZP (100 mg) combined with TFMPP (30 mg) were manufactured by the School of Pharmacy, University of Auckland, using Good Manufacturing Practice. All capsules were identical in appearance, and administered with 200 ml of water.

Procedure

After fasting for 12 h and abstaining from alcohol the evening prior to the trial, participants were given a standard breakfast of water or decaffeinated tea or coffee and one or two pieces of toast with a sugar-free spread. Sugar is known to affect mood, for a review, see the work of Christensen (1993). Breakfast was given approximately 90 min before drug/placebo administration.

Following breakfast, participants completed three rating scales to determine their mood status.

Randomisation to placebo and BZP/TFMPP groups and administration was double-blind; participants were then given either BZP/TFMPP or placebo and required to wait 120 min in a low stimulus environment before repeating the mood rating scales. BZP and TFMPP have been shown to

reach peak concentration respectively around 75 and 90 min after administration (Antia et al. 2009a; Antia et al. 2010). Ambient temperature was also recorded.

Physiological measures

Heart rate, diastolic and systolic blood pressure were measured by a Microlife Automatic Blood Pressure Monitor A100 Plus, which has been validated and determined as suitable for clinical use by the British Hypertension Society (http://www.bhsoc.org/blood_pressure_list.stm). Body temperature of the participants was also measured using a WelchAllyn Suretemp Plus oral thermometer. These measures were recorded prior to and 120 min after BZP/TFMPP administration.

Subjective effects

The effects of placebo and BZP/TFMPP were evaluated using subjective rating scales completed by the participants both before and 120 min after drug or placebo administration—the Addiction Research Centre Inventory (ARCI), Visual Analogue Scale (VAS) and Profile of Mood States (POMS; Foltin and Fischman 1991).

A shortened version of the ARCI form was used to determine drug-induced effects. The original ARCI form consisted of 550 true or false questions, however the form used in this study consisted of 49 questions. The questions were categorised into five empirically derived scales that have proved sensitive for psychoactive drugs (Foltin and Fischman 1991). 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. (2003), is used to clinically evaluate mood states. The form was composed of 65 separate items, which assessed the tension/anxiety (T), depression/dejection (D), anger/hostility (A), fatigue/inertia (F), vigour/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 above-mentioned categories.

Visual Analogue 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). A 0 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.

Analyses

Data were analysed using Statistica Version 9. A 2×2 repeated-measures analysis of variance (ANOVA) was performed, using one within-subjects factor (time, pre- and post-drug) and one between-subjects factor (drug group, BZP/TFMPP and placebo). As previous studies have investigated the subjective effects of BZP and TFMPP alone in humans (Jan et al. 2010; Lin et al. 2009), planned comparisons were performed on the subjective effects that were known to be significantly affected following administration of each drug alone. Univariate tests were conducted in order to determine differences between pre- and post-drug scores within each group, as well as differences between the two groups pre- and post-drug administration. Results were considered significant if $p<0.05$.

Results

Physiological measures

BZP/TFMPP administration produced significant increases in systolic and diastolic blood pressure and heart rate relative to placebo. There were significant effects of time for all three measures [$F(1, 34)=6.5$, 10.5 and 6.1; partial $\eta^2=0.16$, 0.24 and 0.15; $p=0.016$, 0.003 and 0.019 respectively]; significant time×drug interactions were also seen. Further analysis using univariate tests showed significant increases in systolic and diastolic blood pressure as well as heart rate in the BZP/TFMPP-treated group, and there was a significant difference in heart rate between the BZP/TFMPP- and placebo-treated groups post-administration (Table 1). No significant changes in body temperature were observed in either group.

Subjective effects

Addiction research centre inventory

Of the five scales in the ARCI, only MBG, LSD and A were known to be significantly affected by administration

Table 1 Summary of physiological and subjective effects showing significant time×drug interactions and univariate tests for planned comparisons

Effect	Time×drug interaction [F, p value, partial η^2 (df 1, 34)]	Planned comparisons [F, p value (df 1, 34)]	
		Post-BZP/TFMPP vs pre-BZP/TFMPP	Post-BZP/TFMPP vs post-placebo
Physiological			
Systolic	4.3, 0.046, 0.11	12.0, 0.001	–
Diastolic	4.8, 0.036, 0.12	16.5, <0.001	–
Heart rate	10.4, 0.003, 0.23	18.3, <0.001	6.3, 0.02
ARCI			
LSD	3.6, 0.065, 0.097	20.0, <0.001	–
A	2.6, 0.12, 0.071	13.1, 0.001	5.2, 0.03
POMS			
V	4.8, 0.035, 0.12	13.1, 0.001	–
VAS			
Drug effect	7.0, 0.012, 0.17	41.6, <0.001	7.0, 0.012
Good drug effect	6.4, 0.016, 0.16	44.9, <0.001	6.5, 0.016
Drug liking	7.9, 0.008, 0.19	33.9, <0.001	8.0, 0.008
Stimulated	7.3, 0.011, 0.18	30.7, <0.001	5.8, 0.021
Self-confident	5.9, 0.020, 0.15	4.3, 0.046	–

of BZP or TFMPP alone (Jan et al. 2010; Lin et al. 2009). BZP/TFMPP administration caused significant increases in two of the three abovementioned scales, relative to placebo—LSD and A. Both scales were associated with significant effects of time [F(1, 34)=16.5 and 10.3; partial η^2=0.33 and 0.23; p=0.000 and 0.003 respectively], as well as time×drug interactions. Univariate tests showed significantly increased LSD and A scores of participants in the post-BZP/TFMPP group, with a significant difference in the A score between the two groups post-administration (Table 1). The placebo group reported significantly higher LSD scores than the BZP/TFMPP group at baseline, before drug/placebo administration [F(1, 34)=4.3; p=0.046], however no significant difference was seen pre- and post-placebo administration.

Profile of mood states

BZP administration significantly changed a number of POMS scales—D, F, C, V and TMD—and TFMPP administration increased T (Jan et al. 2010; Lin et al. 2009). In comparison, BZP/TFMPP administration only significantly increased V, relative to placebo. A significant time effect was seen [F(1, 34)=6.9, partial η^2=0.17; p=0.013], along with a significant time×drug interaction. Upon univariate testing, a significant increase in V was seen between the pre- and post-BZP/TFMPP group, with no difference between the BZP/TFMPP and placebo groups post-administration (Table 1). No differences were found in the other scales.

Visual analogue scales

Administration of BZP or TFMPP alone has been associated with changes in 11 of the 22 VAS scales—drug effect, good drug effect, drug liking, stimulated, high, anxious, hungry, talkative, self-confident and social (Jan et al. 2010; Lin et al. 2009). The combination of BZP/TFMPP produced significant changes in only five—increased drug effect, good drug effect, drug liking, stimulated and self-confident. Significant effects of time were seen in all except the self-confident scale [F(1, 34)= 35.4, 41.1, 24.4 and 22.0; partial η^2=0.51, 0.55, 0.42 and 0.39 respectively; all p<0.001], and significant effects of drug were seen in all except the stimulated and self-confident scales [F(1, 34)=6.9, 6.5 and 5.4; partial η^2=0.17, 0.16 and 0.14; p=0.013, 0.016 and 0.026 respectively]. However, all five scales were associated with significant time×drug interactions. Univariate tests showed significant changes in all five scales between pre- and post-BZP/TFMPP group, as well as significant differences between the post-BZP/TFMPP and post-placebo group in all scales with the exception of self-confident (Table 1). The placebo group also reported a significant drug effect and good drug effect pre- and post-dosing [F(1, 34)=4.9 and 6.8; p=0.033 and0.014 respectively], however the effect was much larger in the pre- and post-BZP/TFMPP group (Figs. 2 and 3).

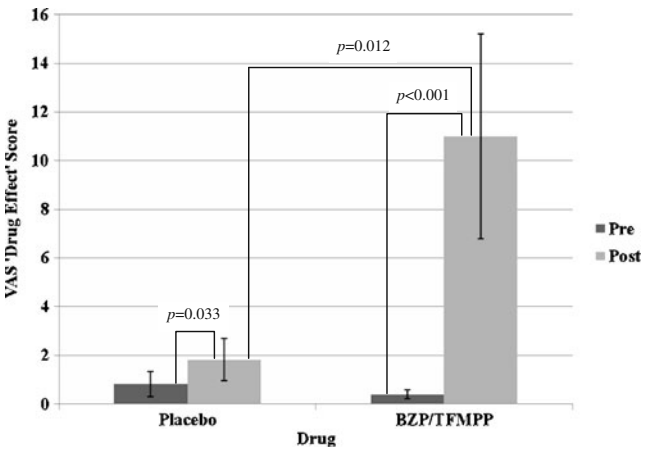

Fig. 2 Graph illustrating changes in mean ± SE VAS scores for the 'Drug Effect' scale before and after placebo and BZP/TFMPP administration

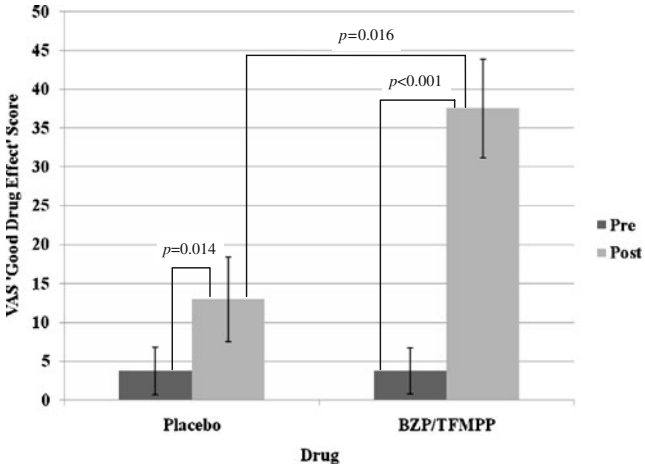

Fig. 3 Graph illustrating changes in mean ± SE VAS scores for the 'Good Drug Effect' scale before and after placebo and BZP/TFMPP administration

No adverse effects outside the study measures were reported by participants.

Discussion

Physiological measures

Administration of a combination of BZP and TFMPP significantly increased blood pressure and heart rate; these physiological effects are similar to those seen 120 min after administration of BZP alone (Lin et al. 2009). These effects can be attributed to postsynaptic α_1- and α_2-adrenoceptor activation by increased NA release. However, there is also evidence that central serotonergic neurons are involved in the regulation of sympathetic nerve discharge (SND), and therefore blood pressure (McCall et al. 1987). McCall et al. (1987) showed that TFMPP, as a 5-HT_{1B} agonist, has variable effects on SND. Enhancement of SND results in excitatory effects, which is accompanied by hypertension and tachycardia. The increase in blood pressure and heart rate, therefore, was not surprising and can be likened to amphetamines as they are known releasers of NA in the periphery and have been shown to affect blood pressure in humans (Trendelenburg et al. 2001).

The combination of these drugs at this dose had no effect on body temperature. The effect of stimulants on thermoregulation are known to be dependent on dose and ambient temperature (Bushnell and Gordon 1987), so it might be that changes in body temperature could be observed using either a higher dose of BZP/TFMPP or a higher ambient temperature. In order to make conclusive statements, further research into the role of ambient temperature and the potential development of BZP/TFMPP-induced hyper- or hypothermia needs to be carried out. The relationship between dance music events and recreational drugs has been well established and the adverse effects of such drugs are strongly associated with the environment in which they are used, and not exclusively from the toxic properties of the drugs themselves. For example, many MDMA-related deaths relate to the temperature of the environment—high ambient temperatures and lack of facilities to balance the effects of dancing, including a lack of water (Bellis et al. 2002). This may also have implications for the settings in which party pills are used.

Subjective effects

Addiction research centre inventory

In previous studies, increases in the 'dysphoria' (LSD) and 'dexamphetamine-like effects' (A) scales were seen following administration of both BZP and TFMPP alone (Jan et al. 2010; Lin et al. 2009). Administration of these two drugs in combination induces similar dexamphetamine-like effects, as well as dysphoria—an effect that can be caused by stimulants such as dexamphetamine and MDMA. Evidence has shown that dexamphetamine-induced dysphoria is variable and dose-dependent (Chait et al. 1985; Martin et al. 1971; Tancer and Johanson 2003) and this may also be the case with BZP/TFMPP. Alternatively, it may be due to a time-dependent rebound effect, as seen when BZP is administered alone (Lin et al. 2009).

Although the placebo group reported significantly higher LSD scores than the BZP/TFMPP group at baseline, no significant changes were seen between pre- and post-placebo administration LSD scores. This initial difference may be attributed to the wide variation observed in data of a subjective nature.

Profile of mood states

BZP/TFMPP was associated with a significant increase in the vigour/activity (V) scale. This is one of a number of well-characterised effects seen following administration of dexamphetamine (Chait et al. 1985; Foltin and Fischman 1991). The lack of changes in other POMS scales may be due to a dose effect—200 mg of BZP and 60 mg of TFMPP were given to participants in previous studies (Jan et al. 2010; Lin et al. 2009), only half of each was given in this combination (100 mg of BZP with 30 mg of TFMPP). It is possible that the synergistic effect suggested by Baumann et al. (2005) on DA transmission as observed in rats when BZP and TFMPP are co-administered, also occurs in humans so halving the dose may have reduced the risk of adverse effects. It may also be that changes in other scales, similar to those seen with dexamphetamine and MDMA—decreased depression/deject (D) and fatigue/inertia (F) and/or increased tension/

anxiety (T) and confusion/bewilderment (C)—may be seen with higher doses of one or both of the drug combination.

Visual analogue scale

The changes induced by BZP/TFMPP using the VAS are among some of the well-characterised stimulant effects also observed following administration of MDMA and dexamphetamine (Chait and Johanson 1988; Tancer and Johanson 2003).

Of the five scales significantly changed by BZP/TFMPP, significant changes were also observed following placebo in two scales i.e. drug effect and good drug effect. This was likely due to the placebo effect or the effect of expectation on mood following the administration of central nervous system stimulants (Volkow et al. 2006). However, this might also be due to the standard deviations of the data reflecting the large variation in response which is often observed when measuring the subjective nature of drug effects.

Many of these physiological and subjective effects overlap with those described by participants in previous work carried out in our laboratory following an oral dose of BZP and TFMPP alone. These changes were particularly prominent in the ARCI and VAS, despite the lower doses given in combination. However, exclusive reliance on the subjective effects of stimulants does not take into consideration external factors such as the social environment, physical setting, user history and personality traits. These variables must be taken into account when assessing similarity of effects and whether or not a drug is likely to induce addiction (Foltin and Fischman 1991).

The combination of BZP and TFMPP at these doses clearly induces similar subjective effects to dexamphetamine and MDMA. The former is well known to induce addiction if used on a recreational basis. The effects of BZP/TFMPP are anecdotally reported as more similar to MDMA, so perhaps MDMA could also have been used as a positive comparator. However, difficulties in both prescribing and obtaining a reliable source of MDMA prevented us from undertaking this comparison.

It has been claimed that, unlike dexamphetamine, dependence on MDMA is unlikely to be a serious problem because the pleasurable effects of the drug decrease if used too frequently and the increase in unpleasant effects would reduce the incentive to continue using the drug in a manner likely to induce dependence—a phenomenon classically observed following the use of hallucinogens (Kalant 2001). This may also be true of BZP/TFMPP as hallucinogenic effects have been reported anecdotally following the use of TFMPP (Erowid 2010). However, this might also be due to the relative amounts or ratios of BZP taken in combination with TFMPP.

BZP has been shown to induce place preference in rats—a phenomenon unique to drugs with rewarding effects (Meririnne et al. 2006), as well as self-administration by monkeys (Fantegrossi et al. 2005), suggesting that BZP might produce similar neuro-adaptations as those seen following methamphetamine administration (Johnstone et al. 2007). In contrast, TFMPP was not self-administered by monkeys, and its discriminative stimulus properties did not generalise to amphetamine (Fantegrossi et al. 2005).

In humans, adverse effects have been associated with high plasma levels of BZP-based party pills upon emergency department admission, with co-administration of ethanol increasing the likelihood of common and distressing symptoms (Gee et al. 2008). Adverse effects have also been reported in humans following combined BZP/TFMPP administration; however, these were seen following administration of very high doses of each drug (300/74 mg) in addition to six standard units of ethanol—the recommended safe upper limit of alcohol use in one session (Thompson et al. 2010).

There have been anecdotal reports of dependence on party pills from a telephone-based survey undertaken by Wilkins et al. (2006); however, due to the lack of specific measures of dependency for a wide range of party pill drugs, the Short Dependence Scale (SDS) was used, with a cut-off point validated for amphetamine dependency only. There have been no other published cases of dependence reported worldwide despite the large number of users, and estimates of over 20 million doses sold in New Zealand alone and the increasing number of seizures within the USA (DEA 2010). This may be due to the unpleasant effects described by some users, which may limit the extent to which BZP is abused (Johnstone et al. 2007), or the slow absorption of BZP/TFMPP when taken orally, which is in turn thought to affect the speed with which drug dependence is induced. However, the long-term effects of regular party pill consumption remain largely unknown and further research is required.

Acknowledgements This study was funded by the Health Research Council of New Zealand. The authors would like to acknowledge Dr. John Sollers III for his statistical advice, and Ricky Wan, Wony Koak, Kate Kim and Salouni Govan for their assistance with data collection.

Conflict of interest The authors have no conflict of interest to declare.

References

Antia U, Lee HS, Kydd RR, Tingle MD, Russell BR (2009a) Pharmacokinetics of 'party pill' drug N-benzylpiperazine (BZP) in healthy human participants. Forensic Sci Int 186:63–67

Antia U, Tingle MD, Russell BR (2009b) In vivo interactions between BZP and TFMPP (party pill drugs). NZ Med J 122:29–38

Antia U, Tingle MD, Russell BR (2009c) Metabolic interactions with piperazine-based 'party pill' drugs. J Pharm Pharmacol 61:877–882

Antia U, Tingle MD, Russell BR (2010) Validation of an LC–MS method for the detection and quantification of bzp and tfmpp and their hydroxylated metabolites in human plasma and its application to the pharmacokinetic study of TFMPP in Humans*. J Forensic Sci 55:1311–1318

Appel JB, Callahan PM (1989) Involvement of 5-HT receptor subtypes in the discriminative stimulus properties of mescaline. Eur J Pharmacol 159:41–46

Auerbach SB, Rutter JJ, Juliano PJ (1991) Substituted piperazine and indole compounds increase extracellular serotonin in rat diencephalon as determined by in vivo microdialysis. Neuropharmacology 30:307–311

Baumann MH, Clark RD, Budzynski AG, Partilla JS, Blough BE, Rothman RB (2005) N-substituted piperazines abused by humans mimic the molecular mechanism of 3,4-methylenedioxymethamphetamine (MDMA, or 'Ecstasy'). Neuropsychopharmacology 30:550–560

Bellis MA, Hughes K, Lowey H (2002) Healthy nightclubs and recreational substance use: from a harm minimisation to a healthy settings approach. Addict Behav 27:1025–1035

Bushnell PJ, Gordon CJ (1987) Effects of d-amphetamine on behavioral and autonomic thermoregulation in mice. Pharmacol Biochem Behav 27:431–435

Bye C, Munro-Faure AD, Peck AW, Young PA (1973) A Comparison of the effects of 1-benzylpiperazine and dexamphetamine on human performance tests. Eur J Clin Pharmacol 6:163–169

Campbell H, Cline W, Evans M, Lloyd J, Peck AW (1973) Comparison of the effects of dexamphetamine and 1-benzylpiperazine in former addicts. Eur J Clin Pharmacol 6:170–176

Chait LD, Johanson C-E (1988) Discriminative stimulus effects of caffeine and benzphetamine in amphetamine-trained volunteers. Psychopharmacology 96:302–308

Chait LD, Uhlenhuth EH, Johanson C-E (1985) The discriminative stimulus and subjective effects of d-amphetmine in humans. Psychopharmacology 86:307–312

Christensen L (1993) Effects of eating behavior on mood: a review of literature. Int J Eat Disord 14:171–183

Cloëz-Tayarani I, Harel-Dupas C, Fillion G (1992) Inhibition of [3 H] gamma-aminobutyric acid release from guinea-pig hippocampal synaptosomes by serotonergic agents. Fundam Clin Pharmacol 6:333–341

DEA (2010) Drug Enforcement Administration - Drugs and Chemicals of Concern: N-benzylpiperazine, http://www.deadiversion.usdoj.gov/drugs_concern/bzp_tmp/bzp_tmp.htm

Erowid (2010) Erowid Experience Vaults: Piperazine Reports, http://www.erowid.org/chemicals/piperazines

Fantegrossi WE, Winger G, Woods JH, Woolverton WL, Coop A (2005) Reinforcing and discriminative stimulus effects of 1-benzylpiperazine and trifluoromethylphenylpiperazine in rhesus monkeys. Drug Alcohol Depend 77:161–168

FDA (2008) U.S. Food and Drug Administration, http://www.fda.gov

Foltin RW, Fischman MW (1991) Assessment of abuse liability of stimulant drugs in humans: a methodological survey. Drug Alcohol Depend 28:3–48

Gee P, Gilbert M, Richardson S, Moore G, Paterson S, Graham P (2008) Toxicity from the recreational use of 1-benzylpiperazine. Clin Toxicol 46:802–807

Jan RK, Lin JC, Lee H, Sheridan JL, Kydd RR, Kirk IJ, Russell BR (2010) Determining the subjective effects of TFMPP in human males. Psychopharmacol Berl 211:347–353

Johnstone AC, Lea RA, Brennan KA, Schenk S, Kennedy MA, Fitzmaurice PS (2007) Benzylpiperazine: a drug of abuse? J Psychopharmacol 21:888–894

Kalant H (2001) The pharmacology and toxicology of 'ecstasy' (MDMA) and related drugs. CMAJ 165:917–928

Klodzinska A, Chojnacka-Wojcik E (1992) Hyperthermia induced by m-trifluoromethylphenylpiperazine (TFMPP) or m-chlorophenylpiperazine (m-CPP) in heat-adapted rats. Psychopharmacology 109:466–472

Lin JC, Bangs N, Lee H, Kydd RR, Russell BR (2009) Determining the subjective and physiological effects of BZP on human females. Psychopharmacol Berl 207:439–446

Magyar K, Fekete MI, Tekes K, Torok T (1986) The action of trelibet, a new antidepressive agent on [3 H]noradrenaline release from rabbit pulmonary artery. Eur J Pharmacol 130:219–227

Martin WR, Sloan JW, Sapira JD, Jasinski DR (1971) Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin Pharmacol Ther 12:245–258

McCall RB, Patel BN, Harris LT (1987) Effects of serotonin$_1$ and serotonin$_2$ receptor agonists and antagonists on blood pressure, heart rate and sympathetic nerve activity. J Pharmacol Exp Ther 242:1152–1159

McNair DM, Heuchert JWP, Shilony E (2003) Research with the Profile of Mood States (POMS) 1964–2002: A comprehensive bibliography. MHC Inc.: 7–8

Meririnne E, Kajos M, Kankaanpaa A, Seppala T (2006) Rewarding properties of 1-benzylpiperazine, a new drug of abuse, in rats. Basic Clin Pharmacol Toxicol 98:346–350

Millan MJ, Dekeyne A, Gobert A (1998) Serotonin (5-HT)2 C receptors inhibit dopamine (DA) and noradrenaline (NA) exact mechanism, but not 5-HT, release in the frontal cortex in vivo. Neuropharmacology 37:953–955

Miranda F, Orozco G, Velazquez-Martinez DN (2002) Full substitution of the discriminative cue of a 5-HT(1A/1B/2 C) agonist with the combined administration of a 5-HT(1B/2 C) and a 5-HT(1A) agonist. Behav Pharmacol 13:303–311

Nissbrandt H, Waters N, Hjorth S (1992) The influence of serotoninergic drugs on dopaminergic neurotransmission in rat substantia nigra, striatum and limbic forebrain in vivo. Naunyn Schmiedebergs Arch Pharmacol 346:12–19

Saudou F, Amara DA, Dierich A, LeMeur M, Ramboz S, Segu L, Buhot M-C, Hen R (1994) Enhanced aggressive behavior in mice lacking 5-HT$_{1B}$ receptor. Science 265:1875–1878

Sawynok J, Reid A (1992) Noradrenergic mediation of spinal antinociception by 5-hydroxytryptamine characterization of receptor subtypes. Eur J Pharmacol 223:49–56

Tancer M, Johanson C-E (2003) Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP. Drug Alcohol Depend 72:33–44

Thompson I, Williams G, Caldwell B, Aldington S, Dickson S, Lucas N, McDowall J, Weatherall M, Robinson G, Beasley R (2010) Randomised double-blind, placebo-controlled trial of the effects of the 'party pills' BZP/TFMPP alone and in combination with alcohol. J Psychopharmacol 24:1299–1308

Trendelenburg U, Holdstock L, de Wit H (2001) Individual differences in responses to ethanol and d-amphetamine: a within-subject study. Alcohol Clin Exp Res 25:540–548

Volkow ND, Wang G-J, Ma Y, Fowler JS, Wong C, Jayne M, Telang F, Swanson JM (2006) Effects of expectation on the brain metabolic responses to methylphenidate and to its placebo in non-drug abusing subjects. Neuroimage 32:1782–1792

White R, Standen O (1953) Piperazine in the treatment of threadworms in children; report on a clinical trial. BMJ 4:755–757

Wilkins C, Girling M, Sweetsur P, Huckle T, Huakau J (2006) 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