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The benzylpiperazine (BZP) / trifluoromethylphenylpiperazine (TFMPP) and alcohol safety study

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Abstract

Party pills containing benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) are used as recreational drugs for their stimulant effects. An estimated 20 million doses of these party pills have been sold legally in New Zealand over the past six years. There is a significant gap in the research on the clinical effects of BZP and TFMPP, with only two small clinical trials on BZP published in the 1970s, and no clinical trials on TFMPP. This situation led to the Expert Advisory Committee on Drugs (EACD) recommendation that more information on the effects of BZP and TFMPP should be obtained. We conducted a randomised double blind placebo controlled trial which assessed the effects of BZP/TFMPP alone and in combination with alcohol (six standard units). The doses of BZP/TFMPP (300mg/74mg over a two hour period) were based on those recommended by the party pill industry. The six units of alcohol given was the maximum dose recommended by ALAC to be taken in a session. Cardiovascular parameters, psychological functioning, driving performance and delayed effects on sleep and mood were assessed. The study was stopped after 35 of the planned 64 subjects had undertaken testing due to concerns regarding adverse events. Severe adverse events were experienced in 0/6 (0%) in the placebo group, 0/12 (0%) in the alcohol group, 4/10 (40%) in the party pill group and 3/7 (43%) in the combined party pill and alcohol group. The severe adverse events included agitation, anxiety, hallucinations, vomiting and migraine. Party pills, alone and in combination with alcohol, markedly increased blood pressure, although had no significant effect on QTc interval or body temperature. Party pills alone improved driving performance at 6.5 hours after dosing. We conclude that party pills commonly cause severe adverse reactions and have marked cardiovascular effects when taken in similar doses to those recommended by manufacturers.

Background

Party pills, also known as "herbal highs" or "social tonics", have become increasingly popular in New Zealand since their introduction in 1999, with more than 20 million doses reportedly sold in the past six years.[1] These pills, which contain BZP often in combination with TFMPP as their main active ingredients, are used for their stimulant and euphoric effects.[2] They remain legal in New Zealand because the Expert Advisory Committee on Drugs (EACD) found there was insufficient evidence to make a recommendation on how BZP should be classified under the Misuse of Drugs Act.[3] In 2004, the EACD stressed the need for research into the effects of BZP and related substances.[3] In June 2005, Parliament imposed an age restriction of 18 years for the purchase of BZP by placing BZP in a new category of restricted but not illegal substances, known as Schedule 4 in The Misuse of Drugs Amendment Act 2005.[4,5] In contrast, the United States Drug Enforcement Administration (DEA) placed BZP in Schedule 1 of the Controlled Substances Act (CSA) along with substances such as lysergic acid diethylamide (LSD) and heroin,[6] due to its abuse potential and lack of accepted medical use or safety.

BZP and TFMPP are members of the piperazine group of chemically synthesized compounds, along with other well-known examples such as cyclizine and sildenafil.[7] BZP was originally synthesized in 1944 as a potential antiparasitic agent,[6] and subsequently found to reverse the effects of tetrabenazine (a dopamine depleting drug) in rats and mice, indicating potential antidepressant activity.[8] Two clinical trials were conducted in the 1970s to establish the clinical effects of BZP in humans prior to proceeding with clinical trials in depressed patients.[9] These trials found that BZP has cardiovascular and central nervous system effects similar to dexamphetamine.[9,10] Bye et al reported that BZP has psychomotor stimulant activity similar to dexamphetamine,

most reliably tested by using a prolonged signal detection test, and cardiovascular effects including tachycardia and increased blood pressure[10]. Campbell et al showed that former amphetamine addicts expressed a similar liking for equipotent doses of BZP and dexamphetamine.[9] Doses of 100mg 1-benzylpiperazine and 10mg dexamphetamine were used, suggesting that the effective potency of the two drugs was approximately 10:1[9]. Campbell et al concluded that BZP is liable to abuse by an addict population and recommended against further clinical studies.[9]

Hungarian drug trials conducted in the 1980s by EGIS Research on Trelibet (N-benzyl-piperazine-piconyl fumarate or EGYT-475) as a potential antidepressant provide the original pharmacological information on BZP. N-benzylpiperazine (EGYT-2760) was shown to be the active metabolite of Trelibet.[11] BZP caused resting and nerve-evoked release of noradrenaline as well as inhibiting synaptic reuptake in peripheral sympathetic nerve fibres.[12] BZP has also been shown to have central serotoninomimetic action which involved 5-HT uptake-inhibition and 5-HT1 receptor agonistic effect in rats.[13] EGIS Research stopped investigating the BZP pro-drug Trelibet during the Phase II studies when it became clear that the compound was toxic and produced amphetamine-like side effects.[14]

In the online library of information about psychoactive plants, chemicals and related topics, Erowid.org, BZP's action has been described as like both amphetamine and 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy").[15] TFMPP has been shown to act as an agonist at postsynaptic receptors for serotonin and inhibit serotonin uptake and oxidation in rats.[16] It has the reputation of producing moderate psychedelic actions of its own in man.[17,18] The combination of BZP and TFMPP has gained popularity as rave drugs which produce feelings of euphoria and energy and a desire to socialize.[19] The

BZP and TFMPP combination releases dopamine and serotonin from neurons via mechanisms dependent on dopamine transporters and serotonin transporters, mimicking the molecular mechanism of MDMA.[20] The findings of Baumann et al provide the basis for the recreational use of the BZP/TFMPP combination in mimicking the effects of MDMA.[21] Baumann et al also showed that high doses of BZP/TFMPP caused seizures in rats, indicating a narrow window of safety and recommended caution in ingesting BZP and TFMPP in combination.[20]

BZP and TFMPP in ratios ranging from 2:1 to 10:1 are commonly used and reportedly cause entactogenic body effects similar to MDMA.[22,23] However, the differing clinical effects of the various ratios have not been investigated. It has been postulated that BZP produces an energy rush like that of metamphetamine, although considerably milder, and when combined with TFMPP produces a euphoric feeling similar to MDMA.[2]

There has been a published case report of acute psychosis following the use of BZP in combination with cannabis and nitrous oxide[24] and two deaths, following ingestion of BZP with amphetamine or MDMA.[25,26] There have been no fatalities reported with BZP or BZP/TFMPP use alone. A case series of 61 patients who presented on 80 occasions to Christchurch Hospital's Emergency Department in 2005 with adverse events after the ingestion of party pills shows patterns of toxicity relating to their use.[27] Severe toxic reactions included fifteen seizures, prolonged QTc interval in 32% of patients, hyponatraemia, urinary retention, agitation, palpitations and panic attacks. Two patients required intensive care treatment. The seizures occurred in patients without underlying neurological disorders and did not appear to be dose-related.

A cross-sectional survey of presenters to the Waikato Hospital Emergency Department revealed 12% of the 1043 people surveyed had used legal party pills, the most prevalent group (30%) being 14-25 year olds.[28] About two thirds of those surveyed were drinking alcohol when the pills were first tried, and over one third had, at some stage, taken more pills than recommended. A Massey University phone survey of 2010 people aged 13-45 years old also showed that co-ingestion of alcohol with party pills and that taking more than the recommended number of tablets is common.[29] This survey found that 20% of the sample had ever tried legal party pills, and 15% had used them in the preceding 12 months. When asked the greatest number of pills used in a single occasion, 42% of users reported having taken four or more pills, 20% said six or more pills and 11% said eight or more pills.

The dose of BZP products is reported to have steadily increased since their introduction in New Zealand, from a standard dose of 70-80mg to 250mg per session.[29,30] The industry recommends doses of party pills typically in the range of 75-500mg BZP.[17,23,31,32] Industry sources have reported that recreational doses up to 2500mg have been taken with no adverse effects other than nausea and hyperthermia, which were not severe enough to require treatment.[31] However there have been no clinical trials in humans on the combination of BZP and TFMPP or TFMPP alone, and no pharmacokinetic studies on either BZP or TFMPP. The interaction between BZP/TFMPP and alcohol has not been previously investigated. The aim of this study was to assess the safety effects of the combination, in particular related to physiological, driving and psychological function.

Method

The study was a randomised double blind placebo-controlled trial. It was approved by the Central Regional Ethics Committee. Recruitment was through newspaper advertising, posters at the local university campus and Cosmic Corner party pill retail outlet and through word of mouth. Study volunteers gave written informed consent before undergoing any tests and were reimbursed for their involvement in the study.

Subjects

Inclusion criteria: All subjects were 20 years of age or older. They had previously taken party pill containing BZP and/or TFMPP on three or more occasions without serious adverse reactions such as seizures or other toxic effects requiring medical attention. They had a valid New Zealand drivers licence. Use of alcohol was also a pre-requisite.

Exclusion criteria: Subjects with a history of diagnosed psychiatric conditions, epilepsy, moderate to severe asthma, hypertension (BP >150/95 at first hospital visit), glaucoma, thyroid disorders, diabetes, urinary difficulties, cardiovascular disease or lactose intolerance were excluded. Those using any medication with an effect on serotonin or dopamine were excluded.

Doses and administration

The BZP/TFMPP study capsules were derived from the contents of two Jet and two Bliss capsules, repacked by equal weight into four two-tone green gelatine capsules. Each study capsule contained 75.0mg BZP.2HCl and 18.4mg TFMPP.2HCl. The placebo capsules comprised a homogenous mixture of lactose powder and thiamine packed into two-tone green gelatine capsules. Approximately 114mg of thiamine was added to each placebo capsule in order to assist blinding by replicating the characteristic

smell of the Vitamin B complex contained in the Jet and Bliss party pills. As per industry recommended guidelines for party pill consumption, two capsules were given to each subject at time zero and two further capsules two hours later (time 2h or 120min). The total intervention dose given was thus equivalent to 300mg BZP.2HCl and 74mg TFMPP.2HCl.

Subjects were randomly allocated to receive the active BZP/TFMPP or placebo capsules with six 320ml drinks given over a three hour period. Drinks consisted of freshly squeezed orange juice containing 30ml of Absolut™ vodka (1 standard unit of alcohol) or water per drink. Six standard units of alcohol were chosen as this represents the recommended safe upper limit of alcohol use in a session.[33] The vodka was given in a dose diluted by the orange juice so that subjects could not tell if alcohol was present or not. Drinks were given at the standardised times of 0, 54, 96, 120, 138 and 156 minutes. Subjects were fasted prior to and during medication dosing.

Study procedures

A preliminary visit to the hospital-based research unit took place, at which time full explanation of the study was provided. Informed consent was gained as were details of a responsible adult aged over 20 years who would act as a support person for the subject on their test day. A computer-based questionnaire on previous party pill and alcohol use, driving history and sensation seeking tendencies was performed. The DSM-IV criteria for substance dependence was used in a computerised format to determine which subjects displayed signs of a substance use disorder.[34] Subjects undertook the practice test component of the Conners' Continuous Performance Test.[35] They then received training on the driving simulator (STISIM™ Drive Systems Technology Inc, Hawthorne, California, USA) which presents a realistic PC-based driving performance

test.[36] Three training runs were completed to familiarise subjects with the simulator controls and tasks, namely the divided attention and car following tasks, and then the twelve minute driving test was performed with standardised instructions.

The clinical investigator contacted the nominated support person, explained the study in detail to them, and gained their written undertaking to act as support person for the subject on his or her test day. The role of the support person was to be aware of potential risks or side effects of the study and to support and monitor the subject for the presence of side effects as necessary. Both the subject and the support person were provided with written information regarding who to contact should any medical emergency or complications occur.

Subjects were advised to avoid the use of any recreational drugs from one week before until one week after the test day, to avoid the use of alcohol from 8pm the night before the test day, and to fast from food for a minimum of six hours before the start of their test day.

Subjects attended the research unit for a twelve hour test day, during which time caffeine and nicotine use was not permitted. Compliance and consent were reviewed at the start of the day, and weight and height measured. Urine was tested using the One Step Multi-Drug Multi-Line Screen Test for the presence of amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, MDMA, opiates, phencyclidine, and tricyclic antidepressants. An indwelling intravenous cannula was inserted and blood samples taken.

Measures

Driving performance was assessed using a twelve-minute test on the STISIM driving simulator. The simulator displays a realistic driving scenario similar to driving along a straight piece of open road. The three training scenarios were repeated on the test day, prior to the baseline driving test. The driving test comprised three sections:

1) accelerating up to and following a car at a consistent distance (taught in the training scenarios)
2) completing divided attention tasks (use of indicators and horn according to symbols displayed on screen) while following another car
3) continuing to complete divided attention tasks while maintaining the speed limit

Subjects were given standardised instructions. They were asked to drive at the correct speed limit (unless following a car which should be done at the correct distance), indicate or press the horn immediately when the divided attention prompt appeared, and try to stay in the middle of the left lane. The primary outcome variable was the Standard Deviation of Lateral Position (SDLP) from the third section of the driving test (road tracking). SDLP measures the ability of the driver to control weaving of the car and has been shown to be a sensitive indicator of drug-induced driving impairment.[37]

A self-reported evaluation of intoxication, driving safety and degree of sleepiness was made before and after each driving test. A standardised clinical sobriety test was performed after the first three driving tests.

The vital signs including heart rate, systolic and diastolic blood pressure and temperature were recorded two hourly for ten hours. An electrocardiograph (ECG) was taken just prior to the 3.5 hour and 6.5 hour blood test. The QTc interval was chosen as the key electrophysiological outcome variable.

Psychological tests included the Digit Symbol Substitution Test (DSST), the Profile of Mood States (POMS), and the Conners' Continuous Performance Test (CPT). The DSST measures psychomotor performance involving attention, motor speed, and visuo-motor coordination and is a subset of the Weschler Adult Intelligence Scale-Revised.[38] The written 90-second test requires subjects to match symbols to digits based on a digit-symbol code. The CPT is a computer delivered neuropsychological test designed to measure sustained attention and vigilance requiring speed and accuracy on a sustained reaction time task.[35,39] The POMS is a self-report measure which identifies and assesses transient, fluctuating affective mood states.[40] We used the 65-item questionnaire which identifies six clearly defined mood states: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigour-Activity, Fatigue-Inertia and Confusion-Bewilderment.

Subjects reported whether acute side effects had occurred with previous party pill use in a computerised questionnaire. A list of 32 previously reported adverse effects from party pill use was displayed, and subjects asked to state whether these effects had occurred previously or never.

Information on adverse effects relating to the study intervention was collected in two ways. Ten hours after dose ingestion, subjects reported whether they had experienced any of a shown computerised list of acute side effects on the test day, and if so, if they rated the symptom as severe or not. They reported delayed side effects during a structured interview at a follow-up visit one week after the test day. The severity of adverse events was rated according to the standardised definitions of Clinical Research Adverse Events,[41-43] with the modification that any event rated by the subject as "severe" was included as a severe event:

Mild – awareness of sign or symptom, but easily tolerated

Moderate – marked symptoms, discomfort enough to cause interference with usual activity

Severe – incapacitating with inability to work or perform usual activity; rated by subject as severe.

Sleep diaries were given to each subject at the end of the test day for completion over the following seven days. Each subject was asked to report the hours and times slept each night for seven nights, the number of minutes taken to fall asleep, and to rate their degree of sleepiness (Stanford Sleepiness Scale) and perceived quality of sleep (Leeds Sleep Evaluation Questionnaire) at about the same time each day (the time recommended was 24 hours after the second intervention dose on the test day). The Leeds Sleep Evaluation Questionnaire comprises ten self-rating 100-mm-line analogue questions pertaining to four consecutive aspects of sleep: getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS) and behaviour following wakefulness (BFW).[44] It has been used to monitor subjectively perceived changes in sleep during psychopharmacological investigations involving a variety of psychoactive agents, including CNS stimulants.[44] The GTS parameter was chosen as the key outcome variable.

Sleep diaries and questionnaires were returned at the follow-up meeting seven days after the test day. At this time, a repeat Profile of Mood States for the previous week was performed, and the subjects gave feedback regarding any problems experienced since the test day.

The sequence of testing performed on the test day is shown in Table 1, with the time in hours after dose administration shown for each test. Meals were provided at four and seven hours after drug administration.

Table 1 – Sequence of testing

	Pre-dose	2h	3h	3.5h	4h	6h	6.5h	8h	10h
Urine drug screen	X								
Vital signs	X	X			X	X		X	X
DSST	X		X			X			
POMS	X		X			X			
CPT	X		X			X			
ECG	X			X			X		
Bloods for BZP, TFMPP, and ethanol levels	X			X			X		
Driving test	X			X			X		
Self-reported evaluation of intoxication, sleepiness, and driving performance	X			X			X		
Sobriety test	X			X			X		
Adverse events questionnaire									X

Analytical assays

Blood samples (5ml EDTA tubes) were obtained for analytical analysis of BZP, TFMPP and alcohol levels at baseline and directly before each driving test. BZP and TFMPP were extracted from 0.2mL blood by solid phase extraction and LC-MS/MS (liquid chromatography tandem mass spectrometry). The MS was carried out in mass reaction monitoring (MRM) mode. The method was validated on three different days using a range of 30-1495ng/mL of BZP and 4-207ng/mL of TFMPP. Calibration curves established were linear and had correlation coefficients of $\geq$0.999. Alcohol levels were determined by gas chromatography with flame ionisation detection (GC-FID).

Statistical analysis

The trial utilised a randomised factorial design. Analysis was by a general linear model. An interaction term was tested and if not statistically significant for a response variable it was omitted from the model and main effects only fitted for alcohol and BZP/TFMPP. For the driving variable a baseline effect was also fitted. Although descriptive statistics are presented for each factorial combination of treatments this is for illustrative purposes only.

When the interaction term was not significant it is not statistically valid to test, for example, a particular factorial combination such as BZP/TFMPP alone versus placebo alone, or alcohol alone versus BZP/TFMPP alone. In the case where the interaction term was not statistically significant then the main effects are independent and represent alcohol versus not using alcohol and BZP/TFMPP versus not using BZP/TFMPP.

Normality assumptions were met for analyses.

SAS version 9.1 was used for the analysis.

Results

Pill composition and dose selection

The dose of BZP and TFMPP included in the commercial and study capsules is shown in Table 2. The labelled doses of BZP or TFMPP stated by the manufacturer are likely to refer to the dihydrochloride (.2HCl) form of the active chemical. The doses of various amino acids, antioxidants, minerals and vitamins contained in the capsules were not formally analysed for this study. The dose variability between capsules was greater in the commercially available preparation than those prepared by the hospital pharmacist for the study.

Table 2 – The mean (SD) dose of BZP and TFMPP included in capsules (mg)†

Capsule	Labelled dose of BZP	Labelled dose of TFMPP	BZP Mean (SD)	BZP.2HCl Mean (SD)	BZP.HCl Mean (SD)	TFMPP Mean (SD)	TFMPP.2HCl Mean (SD)	TFMPP.HCl Mean (SD)
Jet	85	10	64.5 (5.8)	91.2 (8.2)	77.8 (7.0)	7.3 (0.8)	9.6 (1.1)	8.5 (1.0)
Bliss	50	25	38.9 (4.8)	55.0 (6.8)	46.9 (5.8)	19.3 (2.5)	25.4 (3.3)	22.3 (2.9)
Study capsule	N/A	N/A	53.0 (2.2)	75.0 (3.1)	64.0 (2.7)	13.9 (0.7)	18.4 (1.0)	16.2 (0.8)

† Ten capsules were analysed for each of these analyses

Baseline characteristics

The characteristics of the 35 subjects who completed the study are shown in Table 3. Most subjects were male, aged between 20 and 30 years, in paid employment and identified as being New Zealand Europeans. Their average Body Mass Index (BMI) of 26.4 kg/m^2 lies just above the normal healthy range for adults (18.5-24.9 kg/m^2).[45]

Results from baseline urine drug screening on the test day confirmed that 32 of the 35 subjects tested negative for the presence of recreational drugs. Three subjects were positive for cannabis, and were included in the trial because they reported there had

been no cannabis use in the week prior to the test day, recognising that cannabinoid urinary metabolites can be detected up to 77 days after chronic use.[46]

Table 3 – The characteristics of the subjects

	All subjects n=35
Age in years, median (range)	24(20-38)
Male gender, n (%)	22 (62.9)
Occupation, n (%)	
Student	6 (17.1)
Paid employment	29 (82.9)
Ethnicity *(more than one response allowed),* n (%)	
NZ European	30 (85.7)
Maori	4 (11.4)
Samoan	1 (2.9)
Indian	1 (2.9)
European - other	3 (8.6)
BMI in kg/m^2, mean (SD)	26.4 (4.2)
Weight in kg, mean (SD)	79.5 (15.5)
Urine drug test, n (%)	
Negative	32 (91.4)
Positive for cannabis	3 (8.6)

Party pill use

The patterns of party pill use by the subjects included in the study are shown in Table 4. Most subjects had used party pills five or more times prior to the study. Most did not know the active ingredients of the party pills typically taken. Of those who did know what ingredients were contained in party pills, most used a BZP/TFMPP combination pill (9 out of 11). Using the standard DSM-IV criteria, about a fifth of the subjects showed patterns of psychological dependence on party pills. Physiological dependence, as determined by the presence of tolerance or withdrawal symptoms, was present in six out of the group of 35.

Table 4 – Party pill use

	All subjects, n = 35 n (%)
Lifetime party pill use, n=34 †	
3-5 times	10 (29.4)
5-10 times	11 (32.4)
10-50 times	12 (35.3)
More than 50 times	1 (2.9)
Type of party pill typically used	
BZP only	2 (5.9)
BZP/TFMPP combination	9 (26.5)
Unsure	23 (67.6)
Frequency of driving within 10 hours of party pill use	
Always	2 (5.7)
Most of the time	9 (25.7)
Some of the time	11 (31.4)
Never	13 (37.1)
Frequency of driving within 10 hours of party pill and alcohol use	
Always	1 (2.9)
Most of the time	3 (8.6)
Some of the time	12 (34.3)
Never	19 (54.3)
DSM-IV criteria:	
Party pill psychological dependence, n=33 ‡	6 (18.2)
Party pill physiological dependence (i.e. tolerance or withdrawal present)	6 (17.1)

† Data on this parameter was missing for one subject

‡ Data on this parameter was missing for two subjects

In terms of previous use, subjects took up to five party pills on a typical occasion. A maximum of 14 pills were taken on a single occasion (Table 5).

Table 5 – Number of party pills taken by subjects

	Median	Min	Max
Number of party pills used on a typical occasion	2	1	5
Largest number of pills taken on one occasion	5	2	14

The most popular party pills reportedly used by our subjects were Charge, Jet, Bliss, Kandi, Rapture, Frenzy and the Grunter. Recommended consumption and maximum doses of these varieties are summarised in Table 6. The recommended maximum dose of BZP in this group of party pills ranged from 100 to 360mg combined with TFMPP doses ranging from 0 to 100mg.

Table 6 – Industry recommended doses of popular party pills

	BZP/tab	TFMPP/tab	Recommended consumption	Maximum recommended dose
Charge	75mg	5mg TFMPP	2 then a further 2 in 2-3 hours if tolerated	300mg BZP 20mg TFMPP
Jet	85mg	10mg	2	170mg BZP 20mg TFMPP
Bliss	50mg	25mg	2	100mg BZP 50mg TFMPP
Jet+Bliss mix	2 Bliss and 1 Jet capsules, doses above		3	185mg BZP 60mg TFMPP
Kandi	90mg	Not specified	2, wait 2h, then another 2 if tolerated	360mg BZP
Rapture	75mg	25mg	2, wait 2h, then another 2 if tolerated	300mg BZP 100mg TFMPP
Frenzy	75mg	Nil	2, wait 2h, then another 2 if tolerated	300mg BZP
The Grunter	200mg	20mg	1	200mg BZP 20mg TFMPP

Alcohol use

The patterns of alcohol use by the subjects included in the study are shown in Table 7. Most subjects were drinking alcohol when they first tried party pills. The vast majority reported using party pills with alcohol some, most or all of the time. About two in three

subjects had a pattern of high risk drinking as defined by ALAC.[33] About one in four subjects had alcohol dependency by DSM-IV criteria.

Table 7 – Alcohol use by subjects

	All subjects, n = 35 n (%)
History of alcohol use when first tried party pills	30 (85.7)
Frequency party pills and alcohol are combined	
Always	17 (48.6)
Most of the time	3 (8.6)
Some of the time	13 (37.1)
Never	2 (5.7)
Frequency of alcohol consumption, n=34 †	
Daily	3 (8.8)
1-6 times a week	23 (67.6)
2-4 times a month	8 (23.5)
Less than once a month	0 (0)
Number of standard drinks consumed on a typical occasion, n=34	
One	1 (2.9)
2-4	9 (25.5)
4-6	10 (29.5)
More than 6	14 (41.2)
Number of standard drinks consumed in typical week, n=34 †	
Less than 7	9 (26.5)
7-14	12 (35.3)
14-21	10 (29.4)
More than 21	3 (8.8)
DSM-IV criteria:	
Alcohol psychological dependence (n=33) ‡	8 (24.2)
Alcohol physiological dependence (i.e. tolerance or withdrawal present)	13 (37.1)

† Data on these parameters was missing for one subject

‡ Data on this parameter was missing for two subjects

Blood concentrations of BZP, TFMPP and alcohol

The blood levels of BZP, TFMPP and alcohol are shown in Figures 1, 2 and 3 respectively. The levels of BZP and TFMPP peaked at 6.5 hours at mean values of

585ng/ml and 41ng/ml respectively. Alcohol levels dropped sharply after reaching their peak mean value of 36mg/100ml at 3.5 hours.

Figure 1 – Mean (±SEM) blood concentration of BZP: A total of 300mg BZP was administered with 150mg taken at time 0 and at 2 hours

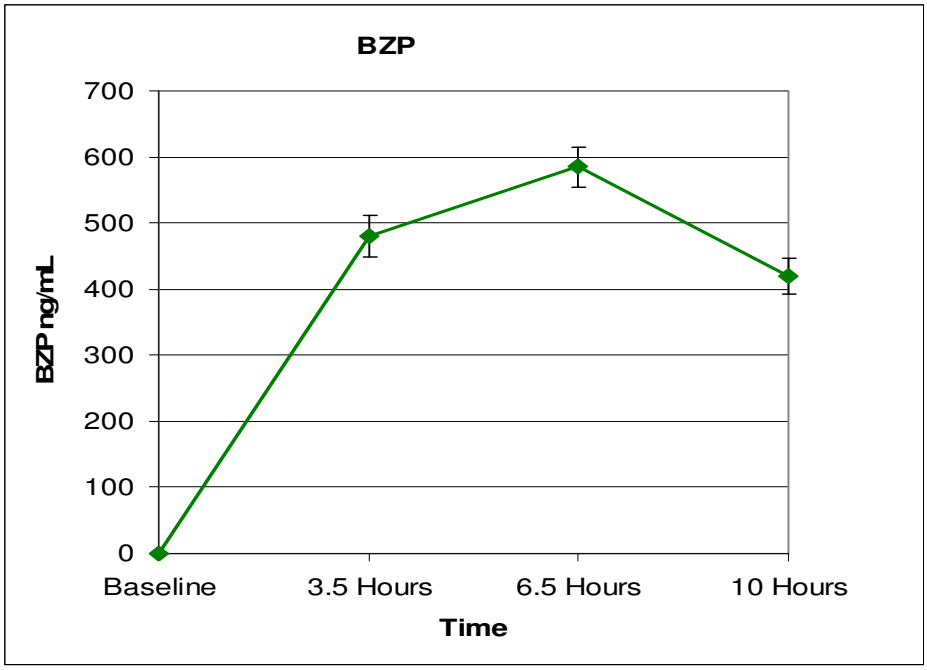


Figure 2 – Mean(±SEM) blood concentration of TFMPP: A total of 74mg TFMPP was administered with 37mg taken at time 0 and at 2 hours

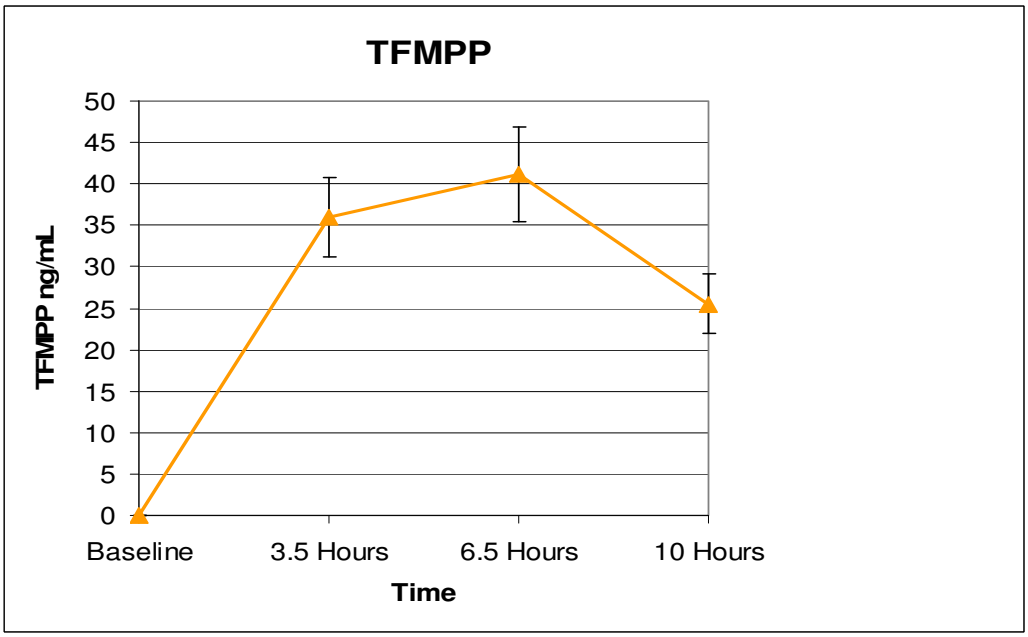
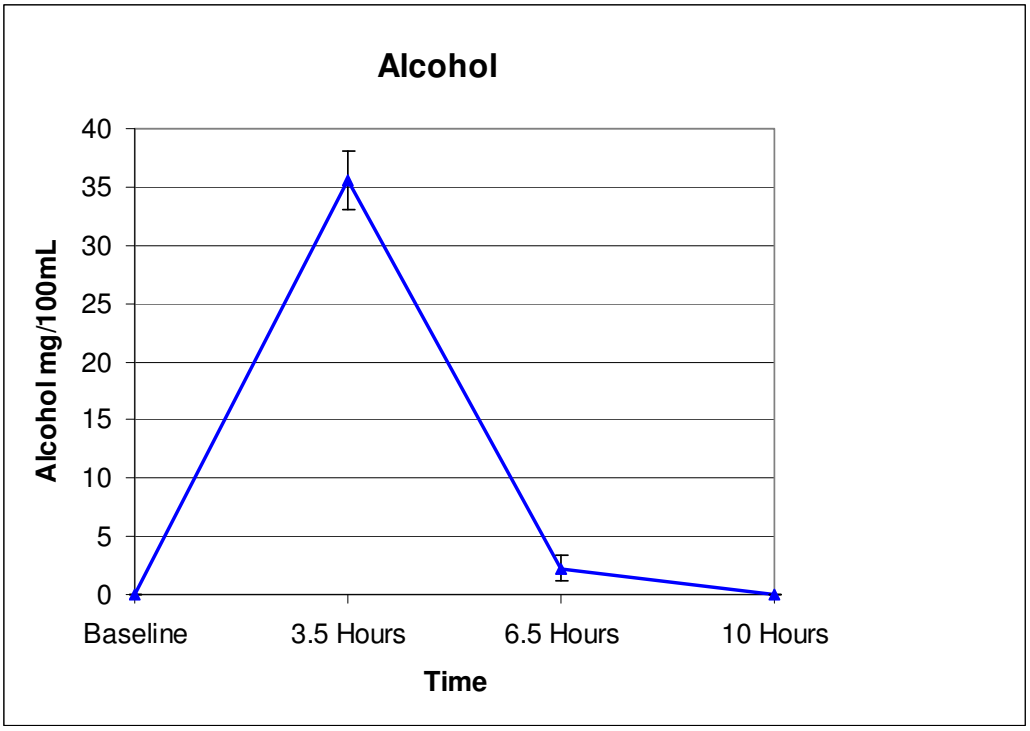


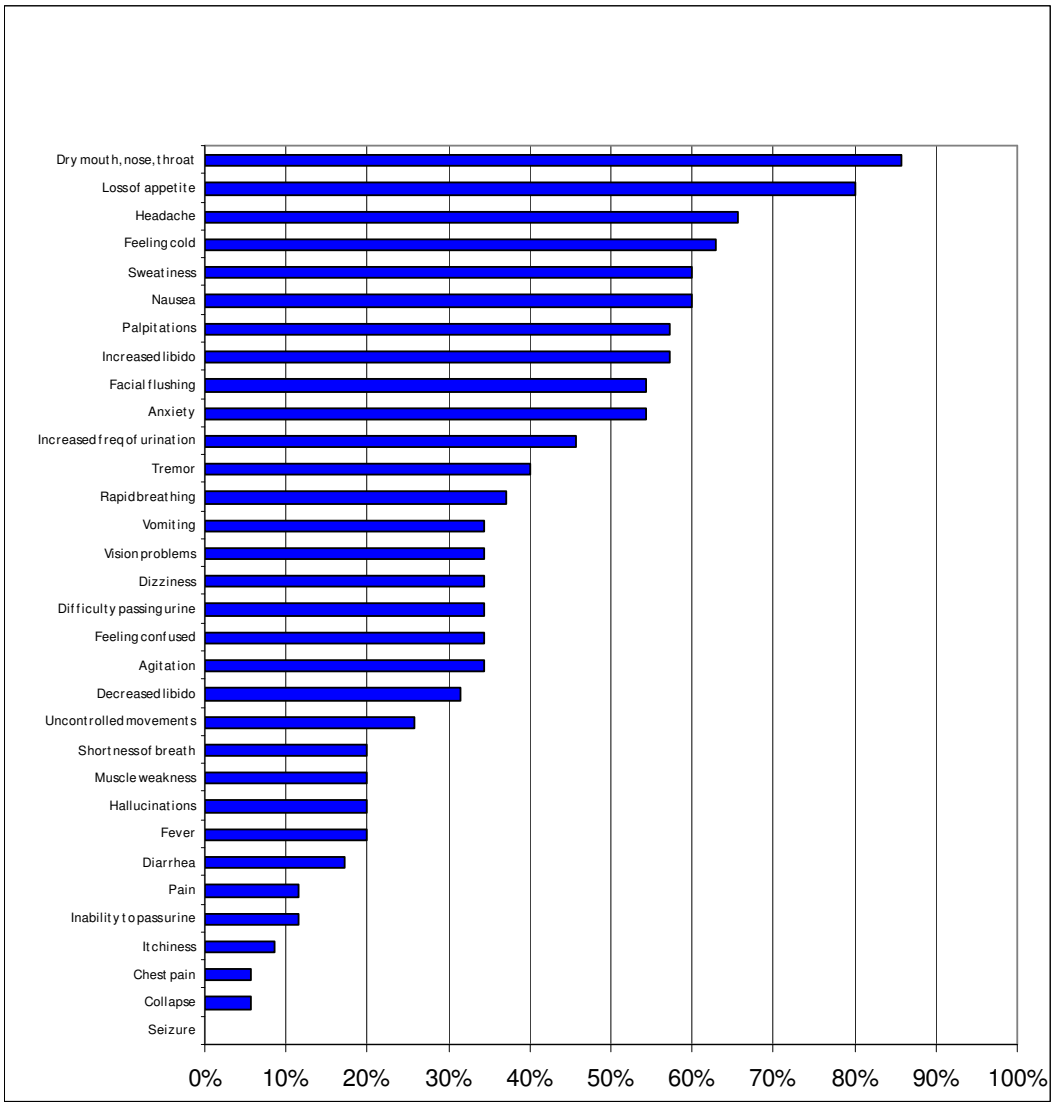
Figure 3 – Mean(±SEM) blood concentration of alcohol: A total of 6 units of alcohol was taken between 0 and 3 hours



Previous adverse events

The proportion of subjects reporting specific acute adverse events with previous party pill use is shown in Figure 4. The most commonly reported side effects from previous party pill use were dry mouth, nose and throat, loss of appetite, headache, feeling cold, sweatiness and nausea – all experienced by over half of the group. Palpitations, increased libido, facial flushing and anxiety were the next most commonly reported effects.

Figure 4 – Proportion of subjects reporting specific acute adverse effects with previous party pill use



Study adverse events

An interim safety analysis was undertaken after 35 subjects had completed the investigative modules, due to concerns about the frequency, nature and severity of the acute (test day) and delayed (one week) side effects that were being reported. The nature and intensity of the adverse events is shown in Table 8. At this stage, the treatment allocation was placebo (n=6), alcohol (n=12), BZP/TFMPP (n=10), and alcohol and BZP/TFMPP (n=7). There were 4/10 and 3/7 severe adverse events reported in the BZP/TFMPP and BZP/TFMPP & Alcohol groups; no severe events were

reported in the Placebo or Alcohol only groups. Together there were 7/17 (41%) severe adverse reactions in the BZP/TFMPP groups (with and without alcohol) and 0/18 (0%) severe adverse reactions in the non-BZP/TFMPP groups. Of those who had severe reactions, the mean (±SD) 6.5 hour blood levels of BZP and TFMPP were 570 (± 117) ng/ml and 43 (±31) ng/ml respectively compared with 593 (± 134) ng/ml and 40 (±18) ng/ml respectively in the subjects receiving BZP and TFMPP who had mild or no adverse reactions.

Due to the frequency and nature (agitation, anxiety, hallucinations, confusion, vomiting, insomnia, headaches and migraine) of the severe reactions, a decision was made to stop the study after 35 subjects had completed the testing.

Table 8 – Adverse Events

Intensity of AE	Treatment Group	Adverse Event
Severe	BZP/TFMPP	Severe agitation, anxiety
Severe	BZP/TFMPP	Severe headache, fatigue
Severe	BZP/TFMPP	Severe anxiety, panic attack (required treatment)
Severe	BZP/TFMPP	Hallucinations, agitation & anxiety
Severe	BZP/TFMPP & Alcohol	Severe vomiting , confusion
Severe	BZP/TFMPP & Alcohol	Severe migraine (worst ever)
Severe	BZP/TFMPP & Alcohol	Severe vomiting, insomnia (37 hours)
Mild	BZP/TFMPP	Exhaustion
Mild	Alcohol	Headache
Mild	BZP/TFMPP & Alcohol	Fatigue

Driving performance

In the model without baseline BZP/TFMPP use was associated with a significantly smaller SDLP (BZP/TFMPP versus no BZP/TFMPP −5.1 (−9.4 to –0.8), P=0.01) indicating better driving performance. There was no effect of alcohol on SDLP (alcohol versus no alcohol −0.9 (−5.1 to 3.1), P=0.68). There was no statistically significant interaction term between alcohol and BZP/TFMPP.

In the model with baseline, BZP/TFMPP was associated with a significantly smaller SDLP (BZP/TFMPP versus no BZP/TFMPP −4.2 (−6.8 to –1.6), P=0.002) indicating better driving performance. There was a weak effect of alcohol on SDLP (alcohol versus no alcohol 2.3 (−0.3 to 4.9), P=0.08). There was no statistically significant interaction term between alcohol and BZP/TFMPP.

Table 9 – The treatment effects on standard deviation of lateral position (SDLP, in centimetres) at 6.5 hours

Treatment	N	Mean (SD)	Median (Inter-quartile range)	Range
Alcohol/Placebo	12	30.8 (4.4)	32.6 (27.3 to 34.0)	22.9 to 35.7
Placebo/Placebo	6	28.9 (9.1)	26.5 (22.3 to 31.5)	30.0 to 45.9
Alcohol/BZP/TFMPP	7	24.8 (6.4)	26.0 (19.3 to 30.1)	15.8 to 34.0
Placebo/BZP/TFMPP	9	24.9 (5.1)	25.1 (22.5 to 29.1)	16.8 to 31.6

Physiological parameters

The effect of the different treatments on cardiovascular measures and body temperature is shown in Table 10 with the statistical significance of the differences shown in Table 11. BZP/TFMPP significantly raised the systolic and diastolic blood pressure.

BZP/TFMPP was weakly associated with a faster heart rate and higher body temperature. Alcohol had no detectable effect on blood pressure or heart rate but was associated with a lower body temperature. There was no significant effect of any treatment on the QTc interval.

Table 10 – The treatment effects on cardiovascular function and body temperature at 6.5 hours

Variable	Treatment	Mean (SD)
Systolic blood pressure (mmHg)	Alcohol/Placebo (N=12)	129.8 (11.7)
	Placebo/Placebo (N=6)	120.8 (14.9)
	Alcohol/BZP/TFMPP (N=7)	135.6 (19.5)
	Placebo/BZP/TFMPP (N=10)	141.6 (11.7)
Diastolic blood pressure (mmHg)	Alcohol/Placebo (N=12)	70.0 (7.9)
	Placebo/Placebo (N=6)	75.7 (11.3)
	Alcohol/BZP/TFMPP (N=7)	81.7 (13.2)
	Placebo/BZP/TFMPP (N=10)	84.8 (7.4)
Heart rate (bpm)	Alcohol/Placebo (N=12)	73.8 (14.7)
	Placebo/Placebo (N=6)	73.0 (10.9)
	Alcohol/BZP/TFMPP (N=7)	84.1 (13.2)
	Placebo/BZP/TFMPP (N=10)	80.3 (14.8)
Temperature (^{o}C)	Alcohol/Placebo (N=12)	36.5 (0.3)
	Placebo/Placebo (N=6)	36.8 (0.3)
	Alcohol/BZP/TFMPP (N=7)	36.8 (0.6)
	Placebo/BZP/TFMPP (N=10)	37.1 (0.4)
QTc interval	Alcohol/Placebo (N=12)	367.5 (13.3)
	Placebo/Placebo (N=6)	369.3 (13.2)
	Alcohol/BZP/TFMPP (N=7)	369.4 (18.2)
	Placebo/BZP/TFMPP (N=10)	373.3 (13.0)

Table 11 – The statistical significance of treatment differences in cardiovascular function and body temperature at 6.5 hours

Variable	Main effect	Estimate (95% CI)	P Value
Systolic blood pressure (mmHg)	Alcohol use versus none	1.3 (–8.9 to 11.6)	0.79
	BZP/TFMPP use versus none	12.0 (2.5 to 22.9)	0.02
Diastolic blood pressure (mmHg)	Alcohol use versus none	–4.4 (–11.1 to 2.4)	0.20
	BZP/TFMPP use versus none	10.5 (3.8 to 17.3)	0.003
Heart rate (bpm)	Alcohol use versus none	2.4 (–7.4 to 12.2)	0.63
	BZP/TFMPP use versus none	8.9 (–0.8 to 18.7)	0.07
Temperature (^{o}C)	Alcohol use versus none	–0.3(–0.6 to –0.03)	0.03
	BZP/TFMPP use versus none	0.3 (–0.02 to 0.5)	0.07

For none of the variables was the interaction term between alcohol and BZP/TFMPP statistically significant. The QTc measurement had no statistically significant effects (P>0.5) for either alcohol or BZP/TFMPP.

Sleep diary

BZP/TFMPP use was associated with a lower GTS score on the night of the test day indicating greater difficulty in getting to sleep (BZP/TFMPP versus no BZP/TFMPP -19.0 (-36.9 to -1.0), P=0.04). There was no effect of alcohol on this outcome variable (alcohol versus no alcohol -2.3 (-20.4 to 15.7), P=0.80). There was no statistically significant interaction between alcohol and BZP/TFMPP.

Table 12 – The treatment effects on getting to sleep (GTS, in millimetres) on the night of the test day

Treatment	N	Mean (SD)	Median (Interquartile range)	Range
Alcohol/Placebo	11	52.0 (18.2)	49.3 (43 to 63)	19.7 to 91.7
Placebo/Placebo	6	71.1 (16.1)	77.1 (66.7 to 79.0)	40.7 to 85.7
Alcohol/BZP/TFMPP	7	48.2 (28.7)	33.3 (25.7 to 68.7)	20.7 to 97
Placebo/BZP/TFMPP	9	34.1 (28.8)	33 (9.7 to 54.0)	0 to 86.3

Across the physiological variables including driving performance, cardiovascular function, body temperature and sleep, there was no interaction between alcohol and BZP/TFMPP suggesting that the physiological effects of the two treatments are independent. As the trial was stopped early there was likely to be low statistical power for comparisons, as shown with the wide confidence intervals for the comparisons that were performed. Some caution must be exercised in interpretation of statistically significant P values as multiple statistical testing has been carried out and this raises the possibility that some of the 'significant' tests are significant by chance alone.

Comment

The study has shown that BZP/TFMPP combination party pills, taken both alone and/or with alcohol, result in a high rate of severe adverse reactions. The nature, frequency and severity of the adverse reactions due to BZP/TFMPP were sufficient to require the premature cessation of the study. The adverse reactions occurred when BZP and

TFMPP were given in quantities recommended and frequently consumed in the community as recreational drugs.

There are a number of methodological issues relevant to the interpretation of this study's findings. Firstly, the study utilized a randomised double-blind placebo controlled design, and as a result the findings provide Level A evidence. Importantly, the reporting and documentation of the side effects was undertaken blind, by both the subject and investigator.

The cumulative dose of the dihydrochloride forms of BZP and TFMPP was 300mg and 74mg respectively. These doses were based on the recommended doses of BZP and TFMPP stated on the labels of the commercially available products of between 100mg and 360mg, and 20mg and 100mg respectively. The dose administered was also well within the range of doses normally taken. For example, our subjects took up to five pills on a typical occasion and up to 14 pills as a maximum. This is similar to that reported in other New Zealand surveys, in which 4 out of 10 users took four or more pills on one occasion and the maximum taken was up to 19.[28,29] As a result the findings of major side effects relate to doses typically taken by users of party pills.

Similarly the amount of alcohol administered was that recommended by ALAC as the maximum to be consumed on one occasion.[33] A total of six units of vodka (mixed in orange juice) taken over a three hour period, was designed to achieve a blood alcohol level between the legal level for a driver under 20 years (30mg/dl) but below the drink drive level for adults of 80mg/dl.[47] This was achieved, with a mean alcohol level of 36mg/dl in subjects randomised to alcohol.

The study drugs were administered in the morning, rather than in the evening when they are usually taken recreationally. This regime was followed to allow 10 hours of detailed investigations and observation, but probably meant that the recognized effects of party pills in causing insomnia were less marked than if the pills were taken in the evening.

The adverse effects resulting from BZP/TFMPP use were severe and posed a significant potential risk to subjects. In one case, the anxiety which occurred on the test day prevented the subject from completing the driving or blood tests. The potential risk associated with the insomnia caused by party pills was illustrated in one of our subjects who drove the day after dose administration having had no sleep whatsoever the night before. The severe acute effects included anxiety, agitation, and hallucinations whereas the delayed effects refer to the insomnia, headache, fatigue and malaise which occurred in the day or two after dose ingestion. The latter are commonly referred to as a "bad hangover" which causes many people to limit their use of party pills.[48]

These adverse effects are similar to those described in the recent Christchurch case series[27] and suggest party pills have a narrow safety margin in some users. This study adds the knowledge that BZP/TFMPP related products can cause serious toxicity including seizures, in doses used and recommended in the community, even in regular party pill users. Interestingly the combination of alcohol with party pills appeared to induce vomiting which was not observed with party pills alone. The vomiting occurred after the completion of the ten-hour period of observation.

The EACD reported in 2004 that there has previously been no evidence of physical dependence on BZP or similar substances.[3] However, our survey showed evidence of tolerance or withdrawal symptoms in about a fifth of subjects. BZP's "non-

addictiveness" has also been called into question by a recent study showing BZP has an abuse liability similar to amphetamines and cocaine in rhesus monkeys.[49] It is possible that BZP could exert an addictive effect by increasing the endogenous release of dopamine and/or serotonin, the mechanism seen with other similar drugs of misuse such as cocaine, amphetamine and MDMA.[50]

The study included detailed investigation of driving performance, cardiovascular effects, and psychological function as well as sleep quality and patterns during the week following the test day. While the detailed statistical analysis is awaited, a preliminary analysis on the study's primary outcome variables provided important information on these effects.

Party pills caused a marked increase in blood pressure which could increase risk in predisposed individuals. Following BZP/TFMPP, the mean blood pressure increased to 142/85 compared with 121/76 after placebo. The likely mechanism by which BZP and TFMPP cause an increase in blood pressure, and to a lesser extent heart rate, is via noradrenaline release which produces sympathomimetic effects.[9,10,12,13] Other amphetamines, for example methamphethamine and MDMA, have been shown to have similar effects.[51,52] Gee et al[27] found evidence of a prolonged QTc in 32% of subjects whereas in our study the doses of BZP/TFMPP given did not cause a prolongation of QTc.

The use of BZP/TFMPP improved driving performance is the acute setting. This finding is consistent with previous work on amphetamine, which can improve psychomotor skills, even in combination with alcohol.[53,54] The fatigue which follows this period of stimulation could however negatively affect driving ability, given that

fatigue and sleepiness have been associated with driving impairment.[55,56] Alcohol had a weak effect on SDLP, an observation which probably relates to the low alcohol level at the time of the 6.5 hour driving assessment.

Despite giving the dose early in the morning in this study, we found that party pills caused greater difficulty in getting to sleep, as shown by a significant decrease in the GTS score. This is comparable to the effect of amphetamine in reducing the GTS score.[44] The clinical relevance of such an effect is that hypersomnolence and fatigue following party pill use could impair quality of life, and worsen normal functioning, such as driving. It is known that amphetamine-like stimulants increase wakefulness by blocking dopamine reuptake, by stimulating dopamine release, or by both mechanisms.[57] It is likely that a BZP/TFMPP combination increases wakefulness by stimulating dopamine release.

Conclusion

In conclusion the study has demonstrated that the consumption of the party pills containing BZP/TFMPP either alone or in combination with alcohol in the recommended doses carries the risk of severe adverse effects. A BZP/TFMPP combination may have marked effects on cardiovascular function and sleep. These effects, which are similar to those of MDMA and amphetamine, are likely to be due to neurobiological changes in the central nervous system, particularly linked to dopamine, catecholamine and serotonin transmission. The study findings have personal, community, public health and regulatory implications.

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