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Toxic effects of BZP-based herbal party pills in humans: a prospective study in Christchurch, New Zealand

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Abstract

Aim This study describes patterns of human toxicity related to the use of 1-benzylpiperazine (BZP)-based 'herbal party pills'.

Methods From 1 April 2005 to 1 September 2005 all presentations associated with party pill use were captured on a prospective data collection form.

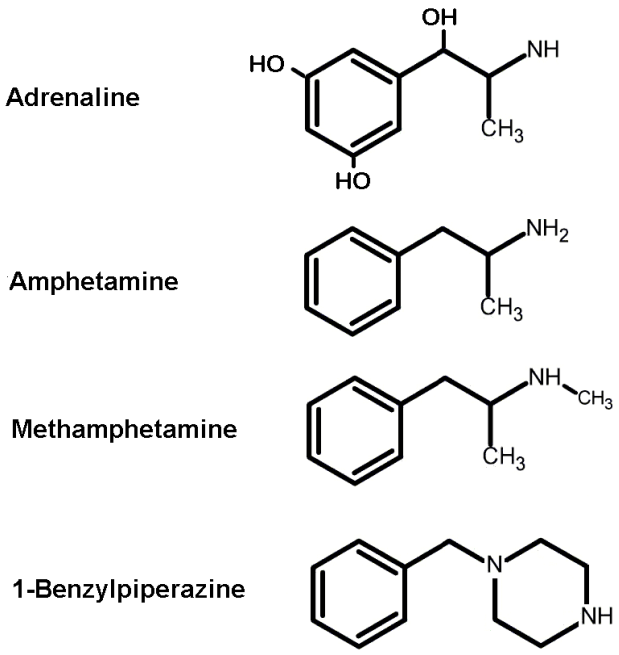
Results There were 61 patients who presented on 80 occasions to the Emergency Department of Christchurch Hospital, New Zealand. Patients with adverse effects took an average of 4.5 tablets/capsules. Patients with mild to moderate toxicity experienced symptoms such as insomnia, anxiety, nausea, vomiting, palpitations, dystonia, and urinary retention. Some adverse reactions persisted up to 24 hours after ingestion. Fifteen toxic seizures were recorded. Two patients suffered life-threatening toxicity with status epilepticus and severe respiratory and metabolic acidosis.

Conclusions Herbal party pills have been sold without regulation since 2000, and are now widely used by young New Zealanders. The principal ingredient of these pills is 1-benzylpiperazine (BZP). They appear to have a narrow safety margin when used recreationally by some humans, possibly because of intrinsic pharmacodynamic properties, self-dosing variability, or genetic polymorphism. Those with seizure disorders or coronary disease should avoid BZP as should those taking prescription sympathomimetics or anticholinergics. Coingestion with MDMA or amphetamine should also be cautioned against. The results of this study indicate that BZP can cause unpredictable and serious toxicity in some individuals. Furthermore, the results of this study should be carefully considered in any discussion on the legal status of piperazine-based party pills.

(Herbal) party pills have become widely available and are very commonly used amongst young New Zealanders during the past 18 months (since mid-2004). These pills have been marketed as 'herbal' and 'safe'. The accumulating evidence of toxicity challenges these claims, however.

Party pills are taken for their ability to increase alertness as well as elevate mood and energy. The main ingredient in most party pills in New Zealand (NZ) is 1-benzylpiperazine (BZP) which is predominantly a synthetic sympathomimetic of approximately one-tenth the potency of dexamphetamine[1] (see Figure 1 for structural comparison). BZP is one of a family of piperazine-based psychoactive compounds. It is sometimes mixed with a similar compound trifluormethylphenylpiperazine (TFMPP) in an attempt to mimic the psychoactive effects of methylenedioxymethamphetamine (MDMA or 'ecstasy').[2]

Figure 1. Structural comparisons of four related substances, including BZP



BZP is chemically synthesised and is not a naturally occurring substance. It is most commonly classified under the class of 'designer drugs'. Most BZP on the NZ market seems to be manufactured and imported from East Asia. The chemical process to manufacture BZP is straightforward and there are reports that it is being locally manufactured in kitchens.

BZP was originally synthesised by Wellcome Research Laboratories UK as a potential anthelmintic for livestock.[3] It was not used because it was relatively ineffective and caused adverse effects such as seizures in mammals. Decades later, it was found that BZP caused hyperactivity, involuntary head movements, and a reduction in reaction times in humans—reactions also associated with amphetamines.[1]

A cluster of human studies was done in the 1970s to investigate BZP as a potential antidepressant.drug.[1,4,5] Research was halted after it was found to have subjective and physiological effects very similar to dexamphetamine. One study showed that chronic amphetamine users could not distinguish between equipotent doses of BZP and dexamphetamine.[4] The researchers recommended that BZP be placed under the same statutory control as amphetamines. A BZP prodrug was investigated as an antidepressant in Hungary in the 1980s but abandoned in phase 2 trials because of adverse side effects.[6] BZP is a schedule 1 illegal stimulant in the USA[7] and is controlled in all states of Australia.

BZP has a complex action working directly and indirectly on central monoamine receptors. It can cause the stimulation independent release of noradrenaline as well as blocking synaptic reuptake.[8]

BZP also shows amphetamine like stimulation and reuptake inhibition of dopamine (DA) and serotonin. These neurotransmitters are responsible for the psychoactive properties of BZP.[9,10] The peripheral actions of BZP on alpha-2 adrenoceptors mediate reflex tachycardia and hypertension.

The pharmacokinetics and human metabolism of BZP are incompletely understood, although BZP is known to be poorly metabolised and is largely excreted unchanged by the kidneys. Staack et al have recently carried out studies on metabolic pathways and postulated several enzymatic steps.[11] The cytochrome P450 enzyme system CYP2D6 appears to be a central component in the degradation of BZP. This enzyme is known for its genetic polymorphism, which may explain the erratic distribution of adverse toxic effects, especially when coadministered with other drugs such as MDMA.[12] Another enzyme involved in the breakdown of BZP is catechol-*O*-methyl-transferase (COMT), which is also known to express genetically determined variations of activity. No information is available on interactions with other prescribed or recreational drugs, effects on carrier protein binding, or toxicity of metabolites. Additive effects are likely but more research is required in the area.

BZP is occasionally misrepresented to users as the illicit drug known as 'ecstasy'. For several years BZP has been sold free of any legal constraint. As of July 2005, BZP is legally available for sale only to adults over 18 years of age in New Zealand. It is available under at least 120 brand names/synonyms (including *Frenzy, Bliss, Charge, Herbal ecstasy, A2,* and *Legal X*). It is sold in capsules, pill, or powder form from an increasing number of retailers.

Patients presented to Christchurch Hospital's Emergency Department (ED) with BZP toxicity as early as 4 years ago. Presentations were very infrequent up till 2004, however, when a sudden escalation began. In 2005, four to five patients per weekend have been seen with adverse and toxic effects from these pills. This increase in presentations is consistent with the increasing number of outlets seen in Christchurch. There is almost no human toxicity research available that can help us manage these cases. Experimental research was based on much smaller "therapeutic" doses. There have been recent case reports of deaths associated with BZP in combination with other sympathomimetics though no deaths attributed to BZP alone.[13,14] There are no series describing BZP toxicity in humans.

Methods

Christchurch Hospital's Emergency Department has an annual census of 65,000 patients, and services a city population of 340,000. All ambulance and emergency self-referrals are seen in this facility.

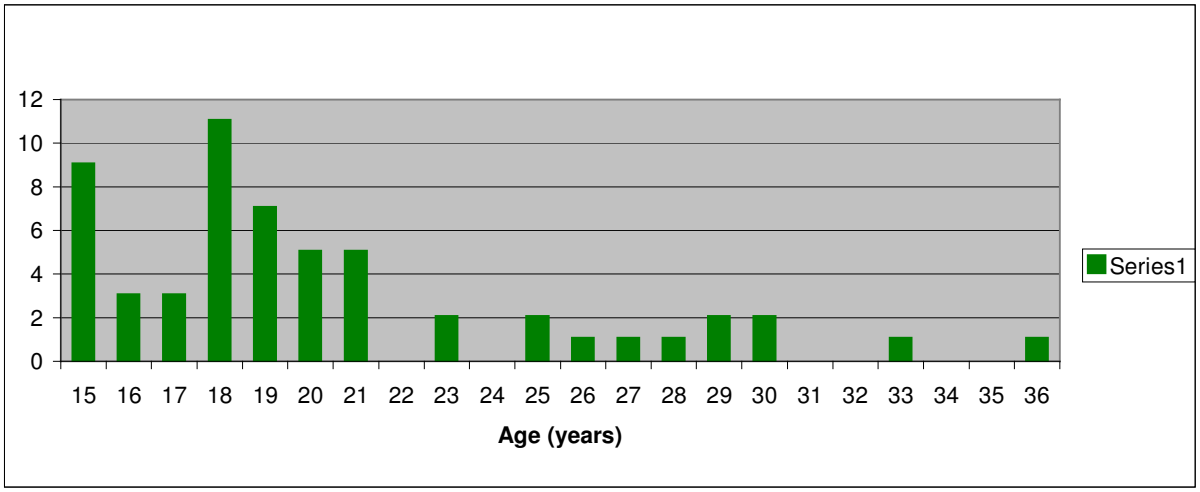
An increase in presentations was detected in late 2004 and a pilot retrospective audit of BZP presentations was undertaken to detect general patterns of toxicity. From this study, a standardised reporting form was developed. From 1 April 2005 to 1 September 2005 all presentations associated with party pill use were prospectively captured. Several representative cases had their hospital visits cost-analysed to estimate the financial impact of BZP patients on our institution. Selected cases with severe toxicity had urine or blood samples sent to confirm the presence of BZP or other illicit substances.

Results

During the 5 months of data collection (1 April 2005 to 1 September 2005), 61 patients attended a total of 80 occasions with adverse effects after ingestion of party pills. The

male to female ratio was 1:1.3. The age range was 15 to 36 years with a mean of 20.4 and a mode of 18 years (see Figure 2). Patients reported the number of pills they had taken in 61 instances (not known or unrecorded in 19 instances); the average was 4.5 tablets (range was 1 to 25). Alcohol was coingested on 39/80, marijuana in 12/80, and nitrous oxide used in 10/80 presentations respectively. Four patients used multiple illicit coningestants which included MDMA, LSD, and ritalin.

Figure 2. Age distribution of BZP users admitted to Christchurch Hospital's Emergency Department from April to September 2005 for adverse reactions



Patients experienced symptoms such as anxiety, vomiting, headache, palpitations, confusion, collapse, and seizures. Some symptoms had persisted for up to 24 hours after ingestion. Symptoms and their frequency are listed in Figure 3.

Vital signs showed expected sympathomimetic effects in patients with tachycardia and hypertension. Electrocardiograph recordings showed all patients were in sinus rhythm and most had a sinus tachycardia. A prolonged QTc was noted in 32% of patients. All other intervals were within normal limits and no supraventricular or ventricular arrhythmias were detected. Vital sign recordings and QTc are recorded in Figure 4.

One patient presented with minor symptoms of BZP toxicity and a plasma sodium of 118 mmol/L. Serum osmolality measured 242 mosmol/kg and other biochemical and haematological indices were normal. The measurement was repeated to rule out sampling error. The sodium returned to normal 5 hours later.

Seizures after BZP-use occurred in 14 patients, with one patient having had seizures on two occasions. Seizures when witnessed or described were of the grand mal type. Seizures occurred on average 3.9 hours after reported ingestion of party pills with a range between 30 minutes and 8 hours.

Figure 3. Symptoms of BZP ingestion noted in 80 admissions of 61 patients attending Christchurch Hospital's Emergency Department in mid-2005

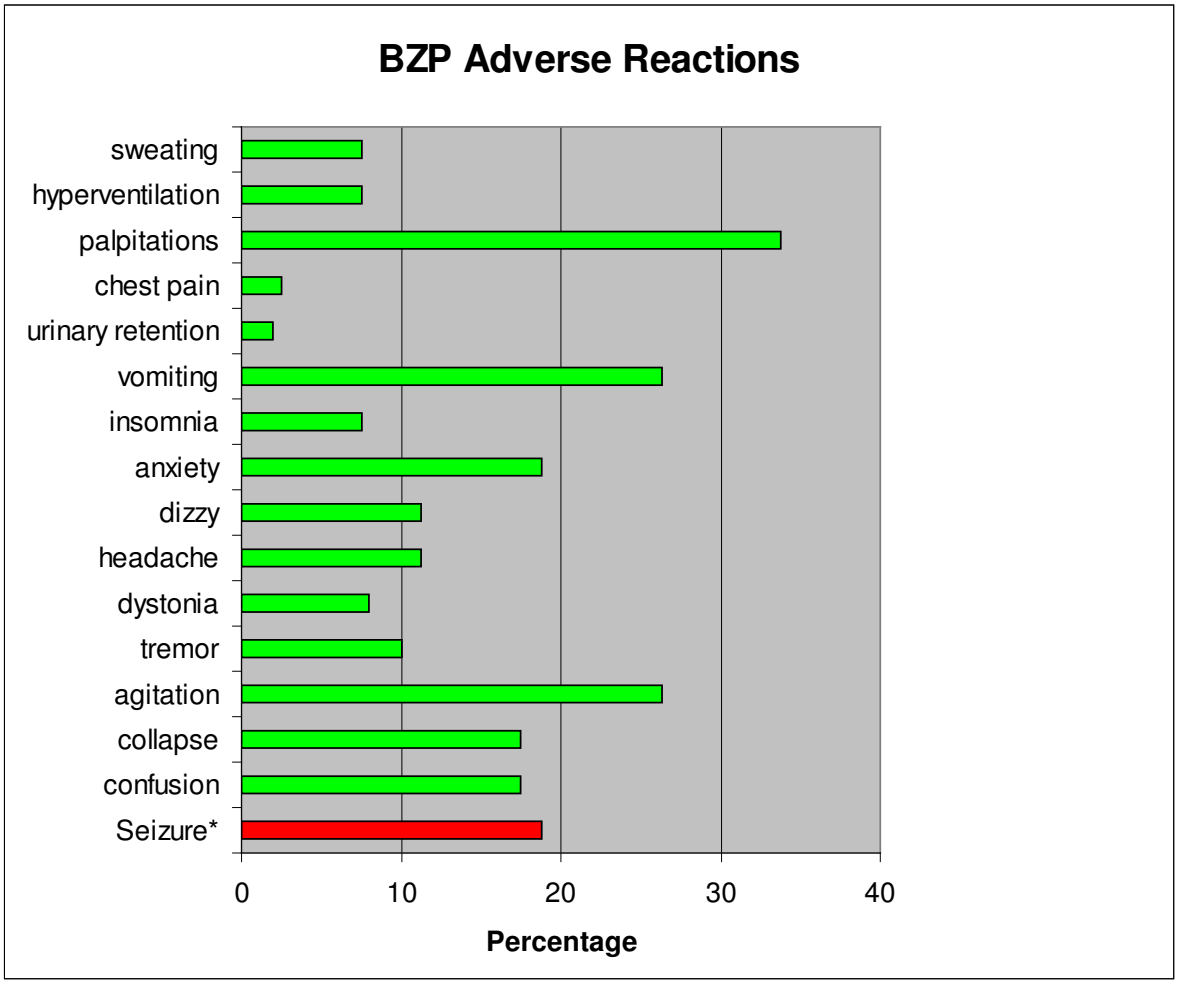


Figure 4. Vital signs of BZP-toxic patients, N=80

Temperature mean (°C)	**37.8 (range 34.3 to 38.6)**
Heart rate mean (bpm)	**119 (range 72–170)**
Systolic blood pressure mean (mmHg)	**140 (range 70–180)**
Diastolic blood pressure mean (mmHg)	**77 (range 70–109)**
ECG QTc mean 424mS (normal <430) 32% had a QTC between 430–490	

Patients who had seizures appeared not to have taken more tablets than non-seizing-patients (average taken 4.3 pills vs 4.55 in non-seizing patients p=0.75).

Following are details of three cases from the severe toxicity group.

Patient 1—A 16-year-old female was out at a sporting event with friends. She had taken three party pills at 1900 hours (7pm) and took one more pill at 2030 hours (8:30pm). No alcohol had been used. She had no suicidal or self-harm intent.

At 2300 hrs (11pm) she collapsed in a crowd and had a witnessed tonic clonic seizure. The ambulance arrived when the patient was postictal. Seizure activity started again and two doses of diazepam were required to stop the seizures. The patient was totally unresponsive, with a Glasgow Coma Score (GCS) of 3/15 and she was intubated for airway control then transferred to Christchurch Hospital. On arrival she had a heart rate of 149, a blood pressure of 70/55 mmHg, blood sugar level of 5.6 mmol/L, and a temperature of 36°C.

She had three further seizures in the Emergency Department and her first blood gas showed a severe combined metabolic and respiratory acidosis with a pH of 6.87, pCO_2 of 60 mmHg, pO_2 of 115 mmHg on supplemental oxygen, HCO_3 of 10.7 mmol/L (23.0–29.0), and base excess of –23 mmol/L (-3 to +3). The patient was transferred to Intensive Care Unit (ICU). She was extubated and 12 hours later she had a GCS of 15/15. This patient had no history of seizure disorders or drug abuse. A week later she reported that she " felt unwell but better" and appeared to have suffered no apparent long-term adverse effects. Subsequent toxicological analysis of urine revealed the presence of BZP and metabolites and no other identifiable illicit drugs or alcohol.

Patient 2—An 18-year-old female patient had a total of five seizures and had a recorded plasma pH of 6.64 (again a mixed metabolic and respiratory acidosis). This patient was intubated and transferred to the ICU. Urinalysis from this patient also confirmed the presence of BZP with no other toxic agents. Patient 2 was subsequently extubated and recovered with no apparent long-term effects.

Patient 3—A 25-year-old male patient took two party pills with alcohol in the evening, then he took two more the following morning. He then had a tonic seizure 3 hours later while driving a car. The front passenger took control to avert a head-on collision and was able to bring the vehicle to a halt. The seizure lasted approximately 3 minutes followed by a postictal phase. The patient had a pulse of 170 bpm, blood pressure of 148/75 mmHg, and blood sugar level of 5.4 mmol/L. On arrival to the ED he was drowsy but conversant with no focal neurological signs. He had no known seizure disorder or alcohol dependence. Plasma biochemistry was normal; and urine showed metabolites of BZP, ethanol, and no other drugs.

During the study period benzodiazepines were administered in 14/80 cases for general agitation, in 11/80 cases for panic attacks or palpitations, and for seizures in 3/80 cases (the remaining 12 seizure cases stopped fitting spontaneously). Antiemtics and intravenous fluids were required in 11/80 cases. Two patients required urinary catheterisation for retention.

Forty-nine patients were seen and treated in the ED with an average length of stay (LOS) of 4.2 hours. The average cost of these consultations was $NZ350 per visit which includes investigations, doctor time, staff nurse time, and fixed overhead expenses. Twenty-nine patients were admitted for a period of observation (average LOS 11 hours at an average cost of $NZ500 per visit). Two patients were admitted to

the ICU then stayed a further day on an inpatient ward (average cost of $NZ3500 per visit).

Discussion

This study group is the largest cohort with BZP toxicity recorded internationally. This study was possible because of the unrestricted availability and use of BZP in New Zealand.

Females presented with adverse effects more frequently than males. This may be because the BZP-containing party pills are not dosed per weight; therefore females being generally smaller may be taking a relatively higher dose than. BZP is available in dose packages ranging from 70 mg to 1000 mg in Christchurch so analysis of pill numbers taken bears no relation to actual dose taken. This is reflected in the average number of pills taken in seizure versus non-seizure patients of 4.3 and 4.5, respectively.

Many patients take multiple doses of BZP because the first dose does not produce the desired effects immediately. Previous research confirmed that the physiological effects of BZP are not felt for up to 2 hours after oral ingestion.[1] Slow onset of action and slow abatement of symptoms are characteristic for this drug when taken orally. Exceeding recommended package doses may result in increased toxicity with some patients experiencing palpitations and/or vomiting for up to 24 hours after ingestion. Furthermore, some users now inject BZP intravenously to experience a faster onset of action, although this is reported as being painful due to is alkalinity (raw BZP in solution has a pH≥12).

Most patients with minor toxicity present with palpitations, agitation, nausea, and vomiting. Other effects observed were intractable vomiting, confusion, and collapse. Some presented with insomnia or inability to pass urine. Most of these patients responded to reassurance, a period of observation, and very selective use of benzodiazepines. The number of patients who present to hospital for treatment probably represent a very small fraction of users in any particular weekend. Indeed, it has been estimated by the Social Tonics Association New Zealand (STANZ) that more than 8 million doses of BZP have been sold in NZ to date.[14]

Also observed (but not tallied) were patients with facial dystonia and trismus. One patient presented with minor symptoms and a plasma sodium measured at 118 mmol/L. Acute hyponatraemia has been well-described with MDMA and is possibly caused by the stimulated release of antidiuretic hormone. A similar mechanism may be responsible with BZP. There have also been reports of BZP causing either a toxic paranoid psychosis or exacerbations of existing mental illness.[15,16] Such events were not observed during the study period, however.

Of greatest concern are 14 patients who had seizures after the ingestion of party drugs. BZP appears to induce toxic seizures in neurologically normal subjects. Two displayed airway compromise and metabolic derangements that were potentially fatal. It is not clear whether this is a dose-related effect as yet—one patient reported taking 12 tablets before a seizure and one reported having only taken two tablets prior to having a seizure. In animal studies, 10 mg/kg of BZP is enough to induce seizures in most laboratory rats.[9] Genetic polymorphism in the cytochrome P450 or COMT system may possibly account for severe toxicity in some patients. One of the 14

patients had known epilepsy but the remainder had no past history of neurological disorders.

Based on this study's results, the authors make the following recommendations for the management of BZP toxicity. Patients with seizure disorders, psychiatric illness or coronary disease should avoid BZP as should those taking prescription sympathomimetics or anticholinergics (prescription antidepressants). Coingestion with MDMA or amphetamine should also be cautioned against, as this combination could lead to fatal toxicity.[12,13] And users should not drive for at least 8 hours after ingesting BZP.

When patients present to healthcare-facilities with BZP toxicity they should receive an electrocardiograph and an estimation of plasma sodium. Those with moderate to severe toxicity may require treatment with benzodiazepines, intravenous fluids, and antiemetics. These patients should be observed for 6–8 hours post-BZP ingestion in case of delayed seizure. Toxic seizures should be treated with benzodiazepines and airway management. Barbiturates may be required in status epilepticus.[17]

The World Anti-Doping Agency and the New Zealand Sports Drug Agency have banned BZP in competitive sport from 2005. The Misuse of Drugs (Amendment) No. 3 Bill has now been enacted creating a new category of controlled but not banned substances (Schedule D). BZP has been placed on this schedule and it is now illegal to sell BZP to minors. The Ministry of Health (MOH) in NZ has determined that there is inadequate information about BZP to put stronger controls on its distribution at present.[18] They have commissioned research into BZP toxicity and studies are under way at the National Poisons Centre and other centres.

More research is needed into the pharmacokinetics and dose response of BZP in humans, as is research to monitor the social impact of having designer drugs legally available in NZ. There are at least three other piperazine-based substances and other psychoactives that could potentially be marketed in NZ under Schedule D. These substances are not classified as foods, dietary supplements, or medicines so no evidence of safety in human consumption is required before they can be sold to the public.

Many users are currently taking BZP-based pills without significant adverse effects. However, the results of this study indicate that BZP can cause unpredictable and serious toxicity in some individuals. BZP is currently a legal stimulant in NZ and this status makes it available and attractive to a far wider market of users than if it were illicit. Moreover, it has propagated a culture of accepting pill use as a normal behaviour at parties. These factors should be carefully weighed in any consideration of the legal status of piperazine-based party pills.

In 2006, the Drug Policy Unit at the MOH plan to review the available evidence on the safety of BZP.

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References:

1. Bye C, Munro-Faure AD, Peck AW, Young PA. A comparison of the effects of 1-benzylpiperazine and dexamphetamine on human performance tests. Eur J Clin Pharmacol. 1973;6:163–9.
2. Baumann MH, Clark RD, Budzynski AG, et al. N-substituted piperazines abused by humans mimic the molecular mechanism of 3,4-methylenedioxymethamphetamine (MDMA, or 'Ecstasy'). Neuropsychopharmacology. 2005;30:550–60.
3. Staack RF, Maurer HH. Metabolism of designer drugs of abuse. Curr Drug Metab. 2005;6:259–74.
4. Campbell H, Cline W, Evans M, et al. Comparison of the effects of dexamphetamine and 1-benzylpiperazine in former addicts. Eur J Clin Pharmacol. 1973;6:170–6.
5. Connelly B. History of BZP. Grass Valley CA: The Vaults of Erowid; 2003. Available online. URL: http://www.erowid.org/chemicals/bzp/bzp_article2.shtml Accessed December 2005.
6. Personal communication with Professor Kalman Magyar, Semmelweis University, Budapest, Hungary; June 2005
7. Schedules of Controlled Substances; Placement of 2,5-Dimethoxy-4- (n)-propylthiophenethylamine and N-Benzylpiperazine Into Schedule I of the Controlled Substances Act . DEPARTMENT OF JUSTICE. Drug Enforcement Administration. FR Doc 04-6110 [Federal Register: March 18, 2004 (Volume 69, Number 53)] [Rules and Regulations] [Page 12794–7] From the Federal Register Online via GPO Access.
8. Magyar K, Fekete MI, Tekes K, Torok TL. The action of trelibet, a new antidepressive agent on [3H] noradrenaline release from rabbit pulmonary artery. Eur J Pharmacol. 1986;130:219–27.
9. Baumann MH, Clark RD, Budzynski AG, et al. Effects of "Legal X" piperazine analogs on dopamine and serotonin release in rat brain. Ann N Y Acad Sci. 2004;1025:189–97.
10. Malomvolgyi B, Tothfalusi L, Tekes K, Magyar K. Comparison of serotonin agonistic and antagonistic activities of a new antidepressant agent Trelibet (EGYT-475) and its metabolite EGYT-2760 on isolated rat fundus. Acta Physiol Hung. 1991;78:201–9.
11. Staack RF, Fritschi G, Maurer HH. Studies on the metabolism and toxicological detection of the new designer drug N-benzylpiperazine in urine using gas chromatography-mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2002;773:35–46.
12. Balmelli C, Kupferschmidt H, Rentsch K, Schneemann M. [Fatal brain edema after ingestion of ecstasy and benzylpiperazine]. Dtsch Med Wochenschr. 2001;126:809–11. In German.
13. Wikstrom M, Holmgren P, Ahlner J. A2 (N-benzylpiperazine) a new drug of abuse in Sweden. J Anal Toxicol. 2004;28:67–70.
14. Submission of Social Tonics Association of New Zealand to the Health Select Committee on the matter of Misuse of Drugs Amendment Bill (No3); 2005 Jan. Available online. URL: http://www.stanz.org.nz/SOP%20Submission%20for%20STANZ%20%20-%20Jan%2020052.pdf Accessed December 2005.
15. Austin H, Monasterio E. Acute psychosis following ingestion of 'Rapture'. Australas Psychiatry. 2004;12:406–8.
16. Personal communication with Dr Erik Monasterio, Forensic Psychiatrist, Hillmorton Hospital, Christchurch, Sept 2005
17. The National Poisons Centre NZ, Dunedin. Toxic seizures. URL: http://www.toxinz.com/

18. The Expert Advisory Committee on Drugs (EACD) Advice to the Minister on: Benzylpiperazine (BZP); 2004 April. Available online. URL: http://www.ndp.govt.nz/committees/eacd/BZPpaper20045663.pdf Accessed December 2005.