Party pills
– how little is known?

Bruce Russell PhD

Correspondence to: b.russell@auckland.ac.nz

***Bruce Russell** gained his PhD at Otago University in Neuropharmacology and has extensive experience investigating the effects of drug misuse both as an academic scientist and as a Clinical Pharmacist. Currently he is employed as a Senior Lecturer in Pharmacotherapy at Auckland University and is establishing a clinical research programme to investigate the effects of acute and chronic use of BZP/TFMPP.*

Introduction

In New Zealand there is currently a range of products generically known as Party Pills, Legal Herbal Highs, Legal Party Drugs or Social Tonics that are available for recreational use to those over 18 years of age. There are in excess of 100 of these products which can be purchased from a wide variety of sources such as the Internet,[1] specialised stores or the more traditional corner dairy. Benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) are amphetamine-like compounds and the active ingredients of these products which are marketed as safe alternatives to illegal drugs such as 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) and methamphetamine (MA or P). Conservative reports from industry sources estimate that 150 000 'doses'/month of Party Pills are sold within New Zealand,[2] which is an indication of their widespread use.

All of these products currently fall outside medicines regulations and regulatory control, consequently their quality is not subject to scrutiny. However, there is a voluntary code of practice that was developed by industry representatives from the 'Social Tonics Association of New Zealand' or STANZ.[3]

BZP has been made illegal in a number countries such as the USA[4] on the grounds that it has a significant potential for abuse and there is no currently accepted medical use. Initially TFMPP was emergency scheduled under the Controlled Substances Act by the Drug Enforcement Agency in the USA due to safety concerns. Controversially, it was later removed from the schedule due to a lack of evidence, making it the first compound removed rather than permanently scheduled.

In April of 2004 the New Zealand Expert Advisory Committee on Drugs advised the Ministry of Health secretariat that there was insufficient information available on which to base a recommendation for classifying BZP and related substances within the schedules of the Misuse of Drugs Act 1975.[5] The committee suggested that more information about the health effects of BZP and similar substances should be obtained, that the prevalence of their use should be investigated and that BZP should not be marketed as a dietary supplement. The committee also raised the issue of potential drug interactions with prescription medicines, such as the Selective Serotonin Re-uptake Inhibitors.

Contents

BZP and TFMPP are members of a group of compounds known as piperazines. Well known clinical examples include cyclizine (1-diphenylmethyl-4-methylpiperazine) and sildenafil (1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazole [4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate) which belong to different pharmacological classes. BZP was originally developed as a potential anti-helminthic agent by Wellcome Research Laboratories and was subsequently found to reverse the sedative effects of tetrabenazine in rats and mice.[6] A BZP analogue, N-benzyl-piperazine-picolinyl fumarate (Trelibet) was briefly marketed as an antidepressant in Europe.[7]

Party Pills, in addition to BZP and/or TFMPP, often contain a wide variety of compounds, which are said to reduce the after effects and change the nature of the 'experience'. For example tryptophan, which is a precursor for serotonin (5-HT) and tyrosine, a precursor for dopamine. Acute 5-HT and dopamine depletion are recognised effects of amphetamine misuse. Additional electrolytes, amino acids and herbal extracts such as Black Pepper or Ginseng extract are also added, presumably to promote the image of being natural, healthy and therefore safe. For example 'Frenzy' contains:[1]

Benzylpiperazine: 50mg
Amino Acids: 410mg

(Glutamine, Phenylalanine, Taurine, Tyrosine, Glycine, Alanine, Tryptophan, Aspartic Acid)
Piper Nigrum Extract: 40mg
Capsicum Annum Extract: 32mg
Paullinia Cupana Extract: 40mg

The recommended dose is to take two capsules and wait an hour then take two more if necessary, potentially 600mg of benzylpiperazine.

Paullinia cupana sp. also known as Guarana, contains guaranine, more commonly known as caffeine and extracted from the coffee bean or tea leaf.

Other examples include 'Altitude' which comes as a pack of six tablets along with a 'recovery pack'. Each tablet is said to contain:

Piperazine blend: 60mg
Amino Acid Blend: 100mg
B vitamins: 34 mg
Vitamin C, Minerals, Citrus biflavonoid, Ginseng extract

The recommended dose is one or two tablets, wait for two hours and take another two tablets if necessary. Piperazine blend is often a combination of BZP/TFMPP in a 3:1 ratio.

The 'recovery pack' of tablets each contain:

5-HTP, minerals, amino acid blend, vitamin B, C and E.

Acute effects

In a literature search using the PubMed search engine (1/10/2005) and the keywords benzylpiperazine and brain, only 11 publications were available from 1950 to the present day, a significant proportion of these relate to the synthesis of analogues, animal and in vitro studies. After further searching, only two peer reviewed studies investigating the effects of BZP on humans are available. Both suggest that BZP causes the same subjective and physiological effects as dexamphetamine.[6,8] In fact, in former dexamphetamine 'addicts' BZP rated higher in subjective 'liking' than dexamphetamine, as determined by the use of a simple questionnaire.[8] Rodent research further supports the proposal that BZP is an amphetamine-like stimulant by suggesting that BZP, amphetamine and methamphetamine release dopamine from non-vesicular pools.[9] In addition, in rats trained to recognise a bupropion (Zyban) cue, BZP will substitute in a dose-dependent manner as does amphetamine and methylphenidate.[10]

The effects of TFMPP on humans have never been scientifically investigated although in rodents it has been shown that the main effects of TFMPP are serotonergic in nature and that it will substitute for MDMA in drug-discrimination studies.[11,12] Shulgin suggested in 1991 that the HBr salt (50mg) is an active hallucinogen and further anecdotal reports suggest that TFMPP is MDMA-like.[13–15]

In New Zealand there have been both anecdotal and newspaper reports of Party Pill or BZP induced-seizures[16] in addition to a case report of BZP-induced psychosis.[17]

Recently a prospective study was carried out over a five month period in the Emergency Department of Christchurch Hospital, New Zealand. This study reports the presentation of 61 patients on 80 occasions with suspected BZP toxicity who exhibited a range of symptoms varying from mild to severe; symptoms reported include insomnia, anxiety, confusion, nausea, vomiting, dystonia, urinary retention and sinus tachycardia, with some showing QTc prolongation. In this study, drug consumption was self reported and the presence of BZP or other illicit substances was confirmed in urine or blood analysis only in those exhibiting severe toxicity. Fifteen patients displayed toxic seizures and two suffered from status epilepticus. However, most resolved spontaneously and did not require benzodiazepines.[18] The details of two specific case studies were reported in which seizures occurred and urinalysis was carried out to confirm that only BZP or its metabolites were present. A number of patients also reported taking other substances such as marijuana (12/80), nitrous oxide (10/80) and alcohol (39/80). Four patients also used other drugs such as MDMA, LSD and methylphenidate.

Summary

Within the scientific literature it is clear that there is very little evidence to support the safety of either acute or long-term use of products containing BZP and/or TMFPP. There has been no comprehensive assessment of the basic pharmacokinetic parameters or the metabolism of either BZP or TFMPP, their cognitive-perceptual effects on, for example, eye-hand coordination or reaction time, their ability to induce dependence or mood disorders or finally, their ability to cause memory or cognitive deficits.

Due to the lack of information surrounding the pharmacological effects of BZP and/or TFMPP, medical treatment of any undesirable effects must remain symptomatic. The study by Gee et al.[18] recommended that if acute toxicity occurs, patients should receive an electrocardiogram and have their plasma sodium measured. Moderate to severe toxicity might also require benzodiazepines, intravenous fluids and antiemetics with observation for as long as six to eight hours to detect delayed seizures.

The use of illegal stimulants such as MDMA and methamphetamine has undergone a dramatic increase in recent years.[27] Preliminary evidence suggests that BZP/TFMPP are also amphetamine-like stimulants undergoing a dramatic increase in use. An awareness of their possible effects and urgent investigation into their pharmacokinetic parameters and neurological effects is vitally important for the safety of public health.

Interestingly TFMPP can increase the frequency of cocaine-induced seizures in rodents, although paradoxically TFMPP alone appears to protect against seizures.[19,20]

The measurable effects of BZP in the study by Bye and colleagues[6] reportedly took as long as two hours or more to occur following oral ingestion which could explain why many people exceed the recommended dose. In the study by Paul Gee et al.[18] patients had taken on average 4.5 tablets with some taking

as many as 25 because the first or even the second failed to produce the desired effect.

Metabolism

In addition to a lack of general clinical information about the subjective effects of BZP/TFMPP, there is scant information available regarding their pharmacokinetics in humans. The metabolism of BZP and TFMPP has been studied in rodents and the urinary metabolites identified in humans. Additional work has also assessed the metabolic pathway responsible for the metabolism of BZP in the rat and TFMPP in insect cell microsomes containing human cDNA-expressed CYPs.[21-23] Involvement of these pathways in human tissue has yet to be confirmed, therefore the ability to reliably predict significant drug interactions remains uncertain. The half-life and excretion rate of both parent compounds and their metabolites remain unknown.

The paucity of pharmacokinetic data leads to further concerns relating to the potential impact that BZP/TFMPP might have on a user's ability to drive or function normally within the workplace within a defined time period following drug ingestion.

Long-term effects

The ability of BZP and/or TFMPP to cause mood disorders, dependence or promote other neurological sequelae has never been investigated. A significant body of literature exists demonstrating that misuse of other amphetamines, specifically MDMA or methamphetamine, can cause long-term deficits in mood, memory and cognitive function in humans. Both methamphetamine and MDMA to a lesser extent are also known to induce dependence.[24,25] The observation that BZP alone is an amphetamine-type stimulant and that when given in combination with TFMPP, mimics the neurochemical response produced by MDMA and other amphetamines in rodents[26] raises significant concerns regarding the frequent use and long-term safety of BZP/TFMPP containing products.

Competing interests

None declared.

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