

Title:

A narrative review of the naturally occurring inhibitory neurotransmitter gamma-aminobutyric acid (GABA) called phenibut in dietary supplements.

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Abstract

A derivative of the naturally occurring inhibitory neurotransmitter gamma-aminobutyric acid (GABA) called phenibut is increasingly detected in dietary supplements marketed online. It is marketed as mood enhancer, for relaxation and assisting sleep, as exercise recovery aid for bodybuilders, as cognitive enhancer or ‘smart drug’, and for boosting sexual performance. Phenibut is not licensed as a medicine in European Union, the United States (US) or Australia, and was first detected in a 2011 seizure in Sweden. In the past two years, public health concerns have been raised around its presence in potentially harmful dietary supplements in France, Sweden, the US and Australia. Search engines have also recorded an increased trend in online interest into the purchasing of and information seeking around products containing phenybut. This short communication provides a comprehensive narrative review of extant literature currently available on this GABA derivative in relation to its legitimate clinical use, availability and use by the public, its effects, and clinical care of toxicity and dependence. It concludes with key recommendations for surveillance and regulation, public health, harm reduction, clinical care and health professional training.

Novel Psychoactive Substances

Novel psychoactive substances (NPS) remain a global public health concern and law enforcement challenge (Van Hout, 2014; Owen et al., 2016; Dolengevich-Segal et al., 2017; Barnard et al., 2017). The concept NPS is broad, and includes emerging trends in available substances, new compounds, new contexts of use, new routes of consumption and diffusion (for example the Internet) (Dolengevich-Segal et al., 2017). The United Nations Office on Drugs and Crime (UNODC) defines NPS as “*substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat*” (UNODC, 2013). The number and range of NPS continue to rise worldwide. In 2016, the number of NPS monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was over 560, with 70% new NPS detected in the past five years.

Of interest for *Performance Enhancement and Health* readership, is that substances with legitimate use as human or veterinary medicines or active pharmaceutical ingredients in medicines are incorporated within the NPS concept and are included in surveillance (EU Council Decision 2005/387/JHA). Medicines authorised in the EU are increasingly important to monitor within this surveillance, as well as medicines and derivatives contained in ‘*legal highs*’ and ‘*food supplements*’. One concerning trend is the increased notified detection of a derivative of the naturally occurring inhibitory neurotransmitter gamma-aminobutyric acid (GABA) called phenibut in dietary supplements (EMCDDA-Europol, 2013; EMCDDA, 2014). Phenibut is not licensed as a medicine in EU, the United States (US) or Australia (Wong et al., 2015; Li & Sundararajan, 2015; Owen et al., 2016), and was first detected in a 2011 seizure in Sweden. It was subsequently notified to EMCDDA as an NPS in 2012 (EMCDDA-Europol, 2013). Search engines have recorded an increased trend in online

interest into the purchasing of and information seeking around phenybut (Li & Sundararajan, 2015). In the past two years, public health concerns have been raised around this potentially harmful dietary supplement in a number of EU Member States (France, Sweden), the US and Australia (Schifano, 2015; Wong et al., 2015; Li & Sundararajan, 2015; Owen et al., 2016; Merchan et al. 2016; Sutherland et al., 2017; Barnard et al., 2017). This *Short Communication* provides a comprehensive narrative review of extant literature currently available on this GABA derivative.

Pharmacology and Clinical use of Phenybut

Phenibut was first created by Perekalin and his associates at the Department of Organic Chemistry of the Herzen Pedagogic Institute in St. Petersburg, Russia (Lapin, 2001). It was originally known as '*phenigamma*' (Khaunma, 1964; 1968; 1971; Maslova & Khaunina, 1965; 1967). It was synthesised as an organic derivative of GABA, with an extra phenyl ring attached to its second carbon (Lapin, 2001; Li & Sundararajan, 2015). The addition of the phenyl group and its position to the attached carbon was reported to enhance its pharmacological action in the cerebral neurons, and increase permeability to the blood-brain barrier (Lapin, 2001; Maslova & Khaunina, 1965). Phenibut is structurally and psychopharmacological similar to baclofen. It acts as a GABA-mimetic, primarily at GABAB and to some extent at GABAA receptors, stimulates the dopamine receptors and antagonizes α -phenethylamine (PEA), a putative endogenous anxiogenic (Lapin, 2001). Lapin (2001) reported that acute toxicity is dose dependent, and that phenibut has a half-life of 5.3 hours. Route of administration does not appear to affect the drug (Lapin, 2001).

In terms of its use in clinical practice, phenibut (brand names Noofen and Citrocard) has been an authorised neuro-psychotropic drug in Russia since the 1960s (Samokhvalov, et al., 2013).

It is used for its anxiolytic and nootropic effects (cognitive enhancing) in the treatment of neurological and psychiatric disorders (Lapin & Khaunina, 1964; Khaunina & Lapin, 1989; Lapin, 2001). Clinical use of phenybut in Russia centres particularly in its ability to reduce tension, relieve symptoms of anxiety and fear, in potentiating anti-parkinsonian and neuroleptic drugs, and in the treatment of alcohol withdrawal, insomnia in psychosomatic and neurotic patients, post-traumatic stress, paediatric stammering, and obsessive compulsive disorder (Goldblat & Lapin, 1986; Khaunina & Lapin, 1989; Ban et al., 1998; Lapin, 2001; Samokhvalov et al., 2013). It was also used by soviet cosmonauts for its calming, yet cognitive enhancing abilities (Samokhvalov et al., 2013).

Availability and Use of Phenybut

Products containing phenibut are marketed online in mainstream health food and fitness equipment websites, both on the surface internet (Amazon, eBay) and the Darknet (Samokhvalov et al., 2013; Owen et al., 2016; Van Hout & Hearne, 2017). Owen et al., (2016) have reported on internet vendors selling phenibut in amounts ranging from 5g (US\$1.60, £1.01/g) to 1000kg (US\$0.23, £0.14/g), with capsules (200mg-500mg) of between 6 and 360 sold in blister packs. Powdered formulations are also sold online, for self-administration into capsules at home (Li & Sundararajan, 2015). These products are marketed for the general population for use as mood enhancer, for relaxation and assisting sleep, as exercise recovery aid, as cognitive enhancer, and for boosting sexual performance (Högberg et al., 2013; Samokhvalov et al., 2013; Wong et al., 2015; Henselmans, 2015; Owen et al., 2016). The labelling of products containing phenybut as '*natural*', coupled with some consumer tendencies to purchase phenibut for self-medication of opiate, benzodiazepine and alcohol withdrawals, and for anxiety and insomnia, contributes to its potential harmful consequences (Samokhvalov et al., 2013).

Phenybut Tolerance and Withdrawal

Oral administration appears most common, with nasal and rectal administration by a minority seeking greater levels of intoxication (Owen et al., 2016). Average oral dosage ranges from approximately 240mg (Owen et al., 2016) to 250mg (Li and Sundararajan, 2015). Online discussions advise women to take lower doses of between 100 and 120mg per day. Onset of effect occurs somewhere between two and four hours after oral administration and peaks within four and six hours. This delayed onset is speculated to encourage first time or less experienced users to re-dose in the belief that the initial dose are not effective (Owen et al., 2016). It also heightens the potential for development of tolerance, acute toxicity and overdose. Rapid tolerance is observed (in as little as five days) (ReDNet Research Group, 2012), with users describing unpleasant withdrawals and difficulties ceasing use online (Högberg et al., 2013). In order to circumvent withdrawals, online discussions advise users to employ interval dosing of 1-2 weeks, or administer continued higher doses (25-30%) to achieve and maintain the desired outcomes. Sporadic dosage is however reported to contribute to insomnia and irritability. As a consequence, some displacement has occurred in the online supplement market with Schifano et al., (2017) reporting on interest in magnolia bark extract as a safer alternative to phenibut.

Clinical Care of Phenybut Toxidrome

Consumption of large doses of phenibut is hazardous, with very little known around potential complications or fatal overdose (O'Connell et al., 2014; Downes et al., 2015; Högberg et al., 2013; Samokhvalov et al., 2013; Li and Sundararajan, 2015). Warnings are evident from the clinical care profession, with continued reports on the concerning upward trend of emergency admissions with acute phenibut toxidromes characterised by severe behavioural disturbances, seizures and dissociation. Acute intoxication is characterized by altered mental status, visual

hallucinations, tachycardia, nausea, vomiting and tremor, with the possible occurrence of the serotonin syndrome (Ronn, 2003; Schmitt et al., 2013; Downes et al., 2015). Clinicians observe its similarity to baclofen toxicity which is more common within the critical care setting, and underscore that less is known about phenibut toxidromes (Li & Sundararajan, 2015; Wong et al, 2015). Phenibut is not visible in urine screenings, which can complicate clinical treatment regimens when patients are sedated, and clinicians are thus unaware of what may have been ingested (Högberg et al., 2013).

Treatment of Phenybut Withdrawals and Dependence

Treatment of phenibut withdrawals and dependency is particularly challenging given the complexity of symptoms, and cross tolerance with other substances such as opiates and benzodiazepines. Patients have described administering phenybut up to 10 times per day at more than 10 times the recommended dose (Högberg et al., 2013). Some experience severe withdrawals and related psychosis and suicidal ideation after discontinuation of phenibut (Odujebi & Nelson, 2008; Magsalin & Khan, 2010; Högberg et al., 2013; Samokhvalov,et al., 2013; O’Connell et al., 2014; Downes et al., 2015; Wong et al., 2015; Merchan et al. 2016; Sankary, Canino & Jackson, 2017). Withdrawal symptomatology is characterised by psychomotor agitation, visual and auditory hallucinations, anxiety, anger and irritability, derealization, depersonalization, increased light and sound sensitivity, balance and coordination impairment, and insomnia, often necessitating prolonged treatment of up to 24 weeks (Samokhvalov,et al., 2013; Schifano, 2015; Downes et al 2015; Owen et al., 2016). Symptoms are generally managed where possible with baclofen, benzodiazepines, phenobarbital, or gabapentin/pregabalin with supportive care ((Samokhvalov et al., 2013; Högberg et al., 2013; Bruner and Levy, 2017).

Conclusion

The unregulated status of phenybut and its visibility in the online dietary supplement market is a concern. A broader approach to the regulation, surveillance and risk identification of potentially harmful unlicensed (and unregulated) medicines, dietary and lifestyle supplements which are available to the general public is warranted. Public health and harm reduction efforts are advised to target both the psychonaut drug user populations, and the mainstream general public seeking to self-medicate with phenybut. It is possible that without stricter monitoring and legislative controls, and country sharing of risk alerts, that the incidence of phenibut toxidromes may increase further (Owen et al., 2016; Merchan et al., 2016; Sankary, Canino & Jackson, 2017). Ill-informed self-medication, particularly when used in combination with prescribed medicines or other dietary supplements can place consumers at risk of associated psychiatric disturbances, potential dependence or overdose, and can result in unique toxidromes affecting the central nervous and cardio-vascular systems (Merchan et al., 2016). Very little is known about phenybut in terms of long-term neurological sequelae (Li & Sundararajan, 2015). Further clinical research is therefore warranted to inform and train health professionals around clinical care of phenibut toxicity, and detoxification protocols. Care pathways and supportive treatment for those with presence of co-occurring mental health disorders and poly substance dependence are also needed.

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