



## **An Uncommon Case of Phenibut Toxicity in an Intensive Care Unit**

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### **Authors' contributions**

*This work was carried out in collaboration with both the authors. Author CKL wrote the detailed patient clinical record and the manuscript, conducted the review of literature and obtained consent from the patient's relative. Author KS was involved with the provision of clinical material relevant to the case, critical appraisal and editing of the manuscript including submission, revision and intellectual input. Both authors read and approved the final manuscript.*

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### **ABSTRACT**

Gamma-aminobutyric acid (GABA) agonists are used as exogenous neuromodulators for patients with chronic pain and refractory mental illness. Phenibut is a controlled GABA-B agonist, with an extensive use in Russia for psychiatric and perioperative patients. In recent times, its anxiolytic and nootropic properties are commercially marketed with an increased risk for recreational abuse. We present a case of a complicated admission of phenibut overdose in a 44-year-old Caucasian man and subsequent management in an intensive care unit (ICU). The drug was accessed over the Internet. The patient previously had multiple ICU admissions due to overdosing on this particular substance, with a fluctuating conscious state and a threatened airway that required intubation, ventilation, haemodynamic monitoring and vasoactive supports. His ongoing agitation over a course of several days mandated sedatives and hypnotics, and his admission was complicated by hypertensive crises and aspiration pneumonia. The clinical dilemma is yet to be addressed

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including the implications of this toxidrome and multi-organ dysfunction. The laboratory diagnosis (i.e. plasma phenibut level) are still investigational and needs more research. This report highlights the role of phenibut as an emerging psychotropic substance with a significant disease burden on the public health system. There is neither a consensus-based approach nor an antidote for this toxidrome, and its diagnosis often relies on accurate history alone. Long-term neurological sequelae and outcomes remain uncertain and more clinical surveillance and governance is needed in this particular area of toxicology and the nexus between e-commerce and substance abuse.

*Keywords: Phenibut; GABA agonist; polypharmacy overdose; anxiolytic; nootropic; agitation.*

## 1. INTRODUCTION

Phenibut is a commercially available product named after its chemical structure  $\beta$ -phenyl- $\gamma$ -aminobutyric acid [1]. Its use originated from the former Soviet Union in the 1960's for its clinical benefits in psychiatric and perioperative patients. Its main effects are anxiolytic and nootropic, i.e. reducing anxiety symptoms and enhancing cognition. It is also known as the "smart drug" for its indication in children with particular speech or developmental disorders [1].

In Australia, it is not licensed in Therapeutic Goods Administration (TGA) [2,3]. However in the recent eras, its commercial products are promoted and sold as a nutritional supplement, gaining increasing popularity, especially in people with body-building focus [4]. While it is only legal under controlled circumstances in Russia, the drug is now sold worldwide through the Internet and no present custom regulations limit its transportation. Phenibut is problematic as cases have been reported on its abuse potential in North America, Australia and Europe, suggesting that it is detrimental in consumption of large quantities with unknown potential complications including fatality [5-8].

Once known as phenigamma and structurally similar to baclofen, phenibut is synthesised as an organic derivative of the naturally occurring gamma-aminobutyric acid (GABA), with an extra phenyl ring attached to its second carbon. In animal models, it was shown the addition of the phenyl group and its particular position to the attached carbon enhance its action in the cerebral neurons. It was also shown to increase its permeability to blood-brain-barrier compared to GABA [1,9]. Phenibut exerts its effects mainly on GABA-B receptors, negligibly with GABA-A and dopamine receptors; in mice this conveys a strong sedative and hypothermic effects [1]. In addition, its anxiolytic effect comes from its antagonistic action towards the endogenous anxiogenic neurotransmitter  $\beta$ -phenethylamine

(PEA) [1]. According to Laptin, regardless of how phenibut is taken, the route of administration does not appear to affect the drug [1].

Little information was known about phenibut's pharmacokinetics. However, the acute toxicity is said to be low and is dose dependent [1]. In a Russian study, phenibut was administered orally at 250 mg to a group of healthy participants. It was found that the half-life was 5.3 hours and was renally excreted in an unchanged form [1]. In psychiatric patients, short-term use (1-2 weeks) of phenibut 250-500 mg three times daily improves mental and physical performance [1]. In children, phenibut is indicated in epilepsy, speech disorders and hyperactivity; it has been shown that it was superior to benzodiazepines as it does not induce irritability and fatigue, and does not affect performance [1].

## 2. PRESENTATION OF THE CASE

A 44-year-old Caucasian man was brought in by ambulance, presented acutely agitated and confused. His family noticed he was behaving bizarrely, lying supine, asleep on the wet lawn at home early on a rainy morning. Glasgow Coma Score was 12, he woke to voice and then started pacing irritably on the grass. Family recognised this was similar to his previous presentation of phenibut overdose for which he was also brought to the hospital, so gave him two tablets of 30 mg oxazepam. Upon arrival to the Emergency Department (ED), he remained agitated with fluctuating conscious state. Otherwise an unremarkable examination of cardiorespiratory, abdominal and musculoskeletal systems. Specifically there were no abnormal pupillary changes or focal neurological findings. No trauma or recent illness noted. Background history of anxiety, depression, insomnia, hypertension, gastro-oesophageal reflux disease and restless leg syndrome. In the last years, he was admitted to ICU multiple times for phenibut overdose as well as a history of polypharmacy overdose.

While in the ED, his agitation worsened, and his behaviour became disruptive. He started pulling on electrocardiogram (ECG) leads and equipment around him semi-consciously. Respiratory rate was 18 breaths and heart rate 111 beats per minute (bpm), blood pressure escalated from 145/57 mmHg to 201/88 mmHg, temperature 36.8°C and oxygen saturation was 95% on room air. Arterial blood gas showed mild-moderate metabolic acidosis. The ECG showed ST elevation of 1mm in anterior precordial leads, complete blood picture and the rest of the biochemistry, as well as the chest X-ray and CT brain were normal. Despite de-escalation and repeated dose of oxazepam and midazolam, he became increasingly uncooperative. His cognitive state declined, and he was subsequently intubated and sedated with intravenous (IV) midazolam, propofol and rocuronium. An arterial line was also inserted to monitor his blood pressure. A later result of paracetamol level was not elevated, and other substances including opiates, ibuprofen, benzodiazepines and alcohol were negative.

He was admitted to ICU for monitoring. He was put in a designated area as he was methicillin-resistant *Staphylococcus aureus* (MRSA) positive. On day 2 in ICU, he had a trial of weaning from mechanical ventilation. However, he continued to be very agitated, with frequent attempts to rise, clenching his jaw and manifesting signs of tardive dyskinesia. Subsequently he had to be sedated with propofol and fentanyl, adding regular doses of quetiapine for antipsychotic effect. He also developed signs of early onset pneumonia with blood stained sputum visible through the endotracheal tube; the temperature was 39.1°C. Chest X-ray-confirmed aspiration pneumonia for that he was commenced on IV antibiotics. His blood pressure went up to 185/95 mmHg and HR 115 bpm, and subsequently he was given clonidine and prazosin. On day three he was gradually weaned off sedatives, had become more awake and cooperative, and was extubated. He was reviewed by the mental health team from psychiatry, and corroborative history was obtained. He stated that he bought phenibut over the Internet, for which he took it regularly three teaspoons (~500-1500 mg) of the phenibut powder. Precipitating this admission, he had developed tolerance prior and this time so he took one big tablespoon the night before. He denied suicidal ideation and any particular trigger to this overdose. He had no recollection of this episode of confusion. On day 4, his agitation was

mostly resolved, but complained of a headache and anxiety, likely as a result of withdrawing from this substance. He continued coughing up yellow sputum with auscultated respiratory crepitations. The IV antibiotics continued. On day five he was transferred to the care of general medicine; his sputum culture grew MRSA, and he continued to be anxious but was afebrile and had no more coughing. Two days after being treated for pneumonia, he remained cooperative despite with mild anxiety, was discharged home with family and was arranged follow-up with Drug and Alcohol Services and psychiatry. He voiced determination to seek clinical management for his anxiety and depression, and not to use phenibut again. He was stable at discharge. A couple of weeks later on follow up with the chest clinic, he remained abstinent of phenibut.

### 3. DISCUSSION

In the critical care setting, baclofen toxicity is commonly seen, whereas, phenibut toxidromes are less common, and this report highlights the importance of that clinical entity. It is gaining popularity on the Internet with the spreading usage; in particular overdose has become an increasing problem. The drug is sold most frequently in the powdery form in an uncontrolled manner, such as in online pharmacy shops, Walmart and EBay, etc. Some websites exclusively focus on the promotion of this substance, and the information can be misleading to the consumers. Although not approved by the TGA, since there are no current regulations on customs and its import into the country is not restricted [2].

#### 3.1 Marketing of Phenibut

There has been an increase in the demand for 'phenibut' and this has come to light based on the hits obtained from search engines like Google. From various websites, its benefits have been described as "reducing negativity", "supporting better memory and learning", "unlocking your social side" and the drug for "good looking losers". There are axillary instruction books and digital measuring scales specifically for phenibut, as well as advocacy personal accounts in supplier websites. The recommended dose is 250 mg daily; however tolerance can develop relatively early, and users are mandated to use higher doses of phenibut to achieve desired effects. Many suppliers sell phenibut powders, some in capsules, with prices

ranging from AUD\$33.10 for 22.5 grams to AUD\$51.89 for 100 grams. Its powder tastes sour, and many consumers capped their own tablets or dissolve it in liquids as it is soluble. To attract customers, there is no need for website registration, no limited access, and many advertise for free shipping. On the other hand, there were several personal accounts disapproving phenibut use from people's own negative experience.

### 3.2 A brief Analogy to Baclofen

Although similar to baclofen, phenibut, being a newer agent, its adverse effects are not entirely understood. Hence caution should be made for its potentially dangerous effects. [5] While baclofen is used clinically for disorders of muscle spasm and multiple sclerosis, it is well-known for its potential of overdose and toxicity. [1,5,10] In 23 cases collected by Leung et al., the spectrum of baclofen toxicity varies from delirium, decreased the level of consciousness, arrhythmias, seizures and coma [10]. There were documented cases of intoxicated patients in very prolonged and profound coma, mimicking brain death [11]. Therefore, theoretically speaking, phenibut can equally cause adverse effects similar to baclofen if not worse. The clinicians should not assume safety of phenibut as its profile remains doubtful at this stage.

### 3.3 Clinical Features and Management of Phenibut Misuse

There are five documented cases in English literature for the past 24 months regarding concerns of the prevalent use of phenibut. [5-8] This reflected on the number of patient cases seen as a result of phenibut misuse, overdosing and withdrawal. From the cases documented, the patients were young, in their 20-40's, had problems with anxiety, insomnia, drug and alcohol issues or other mental health comorbidities. All of these patients presented with the altered mental state, mostly were associated with an abrupt dose increase of phenibut. Presentations were acute or subacute, ranging from drowsiness, confusion, and decreased consciousness state to severe irritability, agitation; psychotic features were also present in some and led to much distress in these patients. Often their physical examination, haematology, biochemistry and imaging are unremarkable, with occasional deranged acid-base status. The recovery can be transient, i.e. in hours, more commonly seen within two to five

days. Nearly all were managed in ICU setting, carefully monitored and supportively managed. Most were free from complications at the time of discharge. Long-term neurological sequelae remained unknown. Additionally, tolerance and dependence can develop for chronic users, making this group of phenibut users at particular risk for withdrawal.

In cases with a definite history of phenibut use and no co-ingestants from the personal or collateral account, it is straightforward that the clinical picture is due to phenibut use. However in many of these, the diagnosis is often based on presumptions due to possible co-administration of polypharmacy and clouding of mental state in patients at the time of diagnosis. Therefore, in obtaining history from phenibut users, the duration of its recreational use, regular and breakthrough doses, previous use of higher doses, effects and adverse effects, concurrent use of alcohol and other substances, presence of any triggers and underlying physical or mental comorbidities should be assessed and documented appropriately. In the critical care setting, the role of medical management is primarily supportive. Particular attention should be paid to managing the acute behavioural disturbance, anticipating needs for sedation and intubation, as well as close monitoring and prevention of nosocomial complications in ICU. The usual short-acting midazolam, propofol and fentanyl boluses or infusion can be used; in most cases, additional use of benzodiazepines and/or potent sedative antipsychotics may add to the clinical management if agitation is not adequately controlled on the induction agents alone. Frequent monitoring of neurological and haemodynamic status is warranted, as in the patient we documented above, the fluctuating blood pressures may necessitate active measures. Furthermore, management of overdosing co-ingested substances and potential interaction with other medications cannot be overlooked.

### 3.4 Laboratory Measure of Phenibut

Unlike clinical presentations such as paracetamol, salicylate or alcohol overdose, laboratory tests of the blood levels of phenibut is not readily available and its significance is doubtful. It is not routinely tested, and there are no validated methods for its measurement. In the two overdose cases reported on Clinical Toxicology, plasma phenibut concentration was quantified by application of liquid

chromatography-tandem mass spectrometry; one patient was measured 29.7 µg/mL and the other was 36.5 µg/mL. [6] As pointed out by the authors, laboratory confirmation of phenibut is not sufficient to exclude the clinical effect from another agent/other agents [6]. In comparison to paracetamol overdose, it can be argued the level of phenibut would only be meaningful and interpretable provided the time of ingestion and clinical course of withdrawing from the substance are known. It would be ideal knowing absent ingestion of other psychotropic substances concurrently. Additionally, even this laboratory data becomes available, the ultimate severe adverse effects of phenibut are not known, e.g. its potential harm in leading to organ failures and permanent neurological sequelae. The toxidrome of phenibut is dissimilar to another toxidrome (e.g. paracetamol) which has been known to cause fulminant hepatic failure and death and prompt action such as transplantation is required. From a toxicological perspective, the use of activated charcoal, gastric lavage or use of GABA antagonists, such as bicuculline, securinine, have not been considered nor used in practice, hence their clinical benefit in the setting of phenibut overdose is uncertain. Therefore, the measurement of phenibut level remains academic and of no practical use in clinical situations.

#### 4. CONCLUSION

In conclusion, the GABA-B agonist phenibut is an emerging psychotropic agent with anxiolytic and nootropic properties. The access to its uncontrolled use is easy, and presentations to healthcare facilities are on the rise. While its clinical benefits are widely accepted in psychiatric and perioperative patients in Russia, its recreational use in inappropriate doses can lead to problems of tolerance, dependence and overdose with significant adverse effects. In the majority of the documented cases of phenibut overdose, the clinical effects are manifested predominantly through the central nervous system and to a lesser extent with profound haemodynamic instability. In these patients, their severe altered mental state, delirium and agitation were managed in the critical care setting, requiring substantial sedation, intubation and supportive treatment. Care must be taken in excluding co-ingestion of other substances. The diagnosis is often delayed because of the lack of laboratory confirmation and hence it is mainly based on clinical history from personal or collateral accounts, which may not become

apparent until late in the treatment. Laboratory investigations of phenibut or GABA-B agonist are not readily available. Even if measured it may add very limited value to the management due to its uncertain pharmacodynamic and unpredictable pharmacokinetic properties.

Clinical management in the critical care setting is, therefore, presumptive and focuses on supporting patient's physiological homeostasis and careful monitoring of a patient's neurological state. The toxicological use of activated charcoal, gastric lavage and GABA antagonists has not been documented, and benefit in the acute setting remains uncertain and more data may throw light on this important problem.

#### CONSENT

Written informed consent was obtained directly from the patient for publication of this case report.

#### ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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