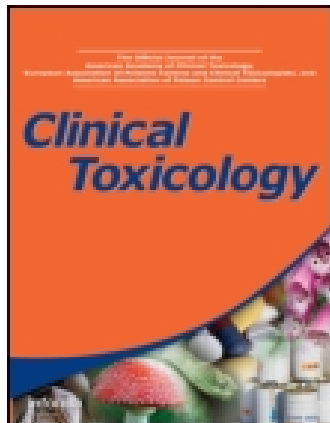


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BRIEF COMMUNICATION

# Acute behavioural disturbance associated with phenibut purchased via an internet supplier

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**Context.** Toxicity from recreational substances marketed for other purposes is a well-documented clinical entity. We present two cases of phenibut toxicity procured via the internet. **Case Details.** A 20-year-old female presented to the emergency department (ED) having used phenibut the prior day. The main finding was a decreased level of consciousness, however when roused she became delirious. Supportive care only was required with no specific intervention. The patient made a full recovery over a 24-hour period and admitted to use of phenibut purchased online. Plasma phenibut concentration was 29.7 µg/ml. A 38-year-old male presented to ED with an agitated delirium. The prior evening he had used tetrahydrocannabinol or THC, alcohol and phenibut, the latter purchased via the internet. His behavioural state had a suboptimal response to parenteral sedation. He was subsequently intubated for airway protection in the context of ongoing sedation to optimally manage his behavioural state. Post extubation the next morning he admitted using phenibut. Plasma phenibut concentration was 36.5 µg/ml. **Discussion.** Altered mental status was the predominant manifestation of phenibut toxicity in these cases. Clinicians to be aware of how phenibut toxicity may present as the internet has widened access to such substances.

**Keywords** Phenibut; Toxicity; Poisoning; Internet

## Introduction

The use of novel psychoactive substances is testament to internet influence in opening access to a wide range of recreational agents of abuse.<sup>1</sup> Phenibut ( $\beta$ -phenyl- $\gamma$ -butyric acid), a  $\gamma$ -aminobutyric acid (GABA) receptor agonist structurally similar to baclofen,<sup>2</sup> is an agent marketed on internet sites as a nutritional supplement but in practice used for psychotropic effects. Since it is used therapeutically in Russia for anxiolytic and drug withdrawal states for many years, most of the literature has been published in Russian. Reports available in English focus more on phenibut-related withdrawal symptoms and dependence states as opposed to acute overdose. We report manifestations of 2, analytically confirmed, cases of acute phenibut toxicity.

## Case Details

A 20-year-old female was brought to the emergency department (ED) with a decreased level of consciousness.

Pre-hospital information communicated by her friends suggested she ingested Phenibut purchased on the internet the prior evening and empty packets were transferred along with the patient. On arrival her Glasgow Coma Score (GCS) was 9 – eye opening, verbalising sounds to painful stimuli and localising pain. She was protecting her airway and asleep but when stimulated awoke briefly and appeared confused. She was afebrile, oxygen saturation was 97% without supplemental oxygen, blood pressure was 120/80 mmHg and pulse rate was 73 bpm. A 12-lead ECG showed normal sinus rhythm, paracetamol was undetectable in serum and electrolytes were within normal limits apart from a serum bicarbonate level of 21 mmol/L (reference range: 23–28). Blood glucose level was 6 mmol/L. She was prescribed venlafaxine 150 mg per day for a mild depressive illness.

After 3 h observation in ED she was transferred to the ED observation unit, under the care of the toxicology service. She remained confused with GCS 11. This increased to 15 over the next 12 h.

The following day she confirmed ingestion of 25 g of phenibut in 3 separate doses the day before she presented to the ED for recreational purposes. She had misinterpreted the supplier's (WILD DISTRIBUTIONS <http://stores.ebay.com.au/wilddistributions>) dosing recommendations.

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Plasma phenibut concentration, quantified using liquid chromatography–tandem mass spectrometry or LC–MS/MS (see appendix for details, to be found online at <http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1059945>), was 29.7 µg/ml approximately 11 h post the last ingestion. Analysis of the powder revealed 39.7% phenibut. No other toxicological testing was performed.

Several days after the above presentation, a 38-year-old male was brought to a neighbouring ED by police and ambulance services having awoken from sleep that morning with an agitated delirium. A friend reported him consuming alcohol, tetrahydrocannabinols or THCs and phenibut the prior evening. Sedation was attempted with droperidol 10 mg intramuscularly on two occasions and subsequently 4-mg/kg intramuscular ketamine. This settled the patient initially and allowed vital signs to be recorded. Blood pressure was 150/96 mmHg, pulse rate was 110 bpm and oxygen saturation was 100% on supplemental oxygen. Approximately 2.5 h after ketamine the patient awoke in an agitated state. It was decided that in order to sedate him effectively endotracheal intubation was required for airway protection.

Intubation was uncomplicated using thiopentone (100 mg) and suxamethonium (200 mg). After a normal head CT the patient was transferred to another metropolitan hospital ICU, the same facility that had looked after the previous case, under the care of the toxicology service. He was extubated approximately 15 h post intubation. He required sedation with 47-mg morphine and 62-mg midazolam post intubation until 6 h prior to extubation. Propofol was used in the 6 h prior to extubation requiring a total dose of 270 mg. He admitted to using phenibut for recreational purposes along with alcohol the evening prior to hospital presentation. He denied any significant medical problems and current use of prescription drugs.

Plasma phenibut concentration was 36.5 µg/ml on admission and 8.92 µg/ml 17 h after admission. No other toxicological testing was performed.

## Discussion

Phenibut is a GABA receptor agonist with greater activity at GABA<sub>B</sub> receptors compared with GABA<sub>A</sub>.<sup>3</sup> It is structurally similar to baclofen which likewise has GABA<sub>B</sub> agonistic properties. This GABA mimetic action may explain its use in substance withdrawal states.<sup>3</sup> Animal models report phenibut producing an anxiolytic effect dependent on the emotional reactivity of the animals such that it could suppress fear in anxious and passive animals but produce an aggressive reaction when provoked.<sup>3</sup> This has some similarities to the behavioural pattern of our first case.

The agitated delirium that occurred in the second case required significant sedation and ultimately intubation. The mechanism of this delirium has not been elucidated but it is not dissimilar to the delirium reported with large baclofen overdoses.<sup>4</sup>

O'Connell et al described presumed phenibut toxicity in a 25-year-old, alcohol-dependent male taking 1.5 g per day

for four days.<sup>5</sup> The minimally responsive patient was transferred to hospital and he regained consciousness over 7 h. Further assessment following resolution of altered mental status suggested that there was no acute, large ingestion of phenibut or any other agent. However, the daily dose of phenibut did exceed that recommended by 1000 mg.

Maraffa et al describe four cases of presumed phenibut toxicity reported to a poison centre with<sup>6</sup> all four cases recovering within 24 h. One case required benzodiazepines to manage agitation whilst another had two tonic-clonic seizures, also a known complication of baclofen toxicity.<sup>6</sup>

The authors report withdrawal complicating at least one of these cases<sup>6</sup> a problem described elsewhere in the medical literature, in some cases mandating prolonged treatment from several days to a number of weeks.<sup>7,8</sup>

## Limitations

One should bear in mind when interpreting these case findings that we did not undertake routine testing for other toxins but were guided by the clinical information presented. Thus it is theoretically possible that another, unmentioned toxin could have contributed to the clinical picture. Likewise phenibut confirmation in plasma does not necessarily exclude a clinical effect by another agent.

## Conclusion

Based on the case details presented, and limitations thereof, phenibut toxicity appears to manifest as an alteration in mental status as the predominant finding, particularly agitated delirium. The growing popularity of phenibut and likely increasing cases of toxicity encountered should contribute to our knowledge of this compound.

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## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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## Appendix

### Drug Analysis Method for quantification of Phenibut

#### Methods

A liquid chromatography-mass spectrometry (LCMS/MS) method was developed for the quantification of phenibut in plasma. Plasma (50  $\mu$ L) was spiked with metformin as internal standard and the plasma proteins were precipitated with 100  $\mu$ L of acetonitrile. The supernatant (5  $\mu$ L) was injected onto a Kinetex 2.6  $\mu$ m HILIC (Phenomenex) 50  $\times$  2.1 mm column using isocratic flow with 15% solvent A (20 mM ammonium acetate) and 85% solvent B (20 mM ammonium acetate in 95:5 acetonitrile: water). The positive-ion mass spectrometric

detection method used electrospray ionization and the multiple reaction monitoring (MRM) mode. The MRM ion transitions were 180.00  $\rightarrow$  117 and 130  $\rightarrow$  71 for phenibut and metformin respectively. The retention times of phenibut and metformin were 2.53 min and 2.85 min respectively.

The analysis was performed using an API 2000 (Applied Biosystems/MDS Analytical Technologies Inc., Foster City, CA, USA) triple quadrupole mass spectrometer equipped with atmospheric-pressure chemical ionization (APCI). The HPLC system consisted of a Shimadzu SLC-10A VP system controller with three LC-10AD pumps and a SIL-20AC-HT autosampler operated at 15°C.

Linearity was achieved from 0.78 to 800  $\mu$ g/ml of phenibut. The precision and accuracy for both intra- and inter-day determination of all analytes were acceptable (< 15%). The lower limit of detection was 0.4  $\mu$ g/ml and lower limit of quantification was 1.3  $\mu$ g/ml.