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Phenibut: Review and Pharmacologic Approaches to Treating Withdrawal

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Abstract

β-Phenyl-γ-aminobutyric acid (phenibut) is an analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) that was first synthesized in Russia in the early 1960s. It is marketed as a nootropic (smart drug) to improve cognitive performance, and to treat generalized and social anxiety, insomnia, and alcohol withdrawal. The use of phenibut is legal in the USA and it is widely available online without a prescription. Increased public awareness of phenibut has led to a growing number of reports of acute intoxication and withdrawal. In this review, we describe the pharmacology of phenibut, the presentation and management of acute intoxication, and regulatory issues, placing particular emphasis on the treatment of acute withdrawal, for which there are no comparative studies. Among 29 cases of phenibut withdrawal, patients were successfully treated with baclofen, benzodiazepines, and phenobarbital, as individual agents or in various combinations. Ancillary medications included antipsychotics, dexmedetomidine, gabapentin, and pregabalin. After stabilization, a number of patients did well on baclofen tapers, whereas others were weaned off benzodiazepines or phenobarbital. Phenobarbital may be preferred over baclofen, or used as an added agent, in patients at risk for seizures. As long as phenibut remains legal, cases of phenibut intoxication and withdrawal are likely to increase. As urine or plasma drug screening for phenibut is not widely available, it is vital that clinicians obtain a detailed medication history in patients presenting to the emergency department with nonspecific symptoms that may represent phenibut intoxication or withdrawal. Further, clinicians may wish to consult an addiction specialist or toxicologist in these situations.

Keywords

addiction medicine, baclofen, benzodiazepines, clinical pharmacology (CPH), drug abuse, GABA, phenibut, phenobarbital, toxicology (TOX), withdrawal

β-Phenyl-γ-aminobutyric acid (phenibut) is a glutamic acid analog, first synthesized by Perekalin and colleagues at the Herzen Pedagogic Institute in St Petersburg, Russia, in 1963.[1] The brand names for phenibut include Anvifen, Citrocard, Fenibut, Noofen, and others.[2,3] For over 50 years, phenibut has been available in Eastern European countries, including Belarus, Estonia, Kazakhstan, Latvia, Russia, and Ukraine, as a prescription medication. It is used to treat a variety of central nervous system disorders, including generalized and social anxiety, post-traumatic stress disorder (PTSD), depression, insomnia, vestibular disorders, alcohol withdrawal, stuttering, attention deficit hyperactivity disorder, motor tics, and restless leg syndrome.[1,4,5] Phenibut is also marketed as a "synthetic amino acid derivative" and nootropic (ie, "smart drug"), used to improve cognitive performance, as a mood enhancer, as an aid to boost sexual performance, and as an exercise recovery aid for body builders.[3,6] Over the last decade, phenibut has gained popularity in the USA, where it is used to reduce social anxiety, enhance empathy, produce sexual arousal, reduce alcohol and/or benzodiazepine cravings, increase physical and mental stimulation (at low doses), and produce euphoria, when recommended doses are exceeded.[7,8] Although phenibut is no longer considered a dietary supplement in the USA, it can still be purchased easily from online vendors without a prescription.[2,9]

Increased public awareness of phenibut and the ease with which it can be purchased from online vendors has led to increased reports of its abuse in the USA.[5,10,11] There have been over 60 case reports of acute phenibut intoxication or withdrawal, and accounts from poison control centers show an increase in calls pertaining to phenibut since 2018.[5] A Minnesota Poison Control System reported 56 calls pertaining to phenibut exposure over the last 19 years, with 48 of these calls (85.7%) occurring within 5 years of publication.[11] Between 2009 and 2019, US poison control centers received 1320 calls reporting phenibut exposures from all 50 states and Washington, DC.[10] Of note, 12.6% of patient cases experienced major effects, including significant disability, disfigurement, or life-threatening events.[10] Among reports of phenibut exposure, where it was the only agent involved, 10.2% of reports were associated with major effects, including 1 fatality.[10] This same investigation reported that long-term disability or life-threatening reactions occurred in 1 of every 8 phenibut

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exposures reported to US poison control centers; this included 80 cases of coma and 3 fatalities.[10] Phenibut, along with other psychoactive substances, was identified in 2 postmortem cases from North Carolina and in an additional case from Texas.[12,13] To this end, there are an increasing number of reports of phenibut intoxication and withdrawal. Although the management of phenibut intoxication is largely supportive, phenibut withdrawal often requires pharmacologic intervention and is rife with clinical challenges.

Methods

A comprehensive search strategy was used to identify relevant articles regarding phenibut. The primary indexing term used to identify potentially applicable articles was "phenibut." Articles were then assessed and categorized based on their status as reviews, basic science articles describing phenibut pharmacology, law and regulatory articles, case reports describing acute toxicity, and case reports describing dependence and withdrawal. Additional references were identified via a manual search of cited references. Cases describing phenibut withdrawal or acute abstinence were identified, and pertinent data were extracted and tabulated to allow for the assessment of treatment approaches to phenibut withdrawal. Where applicable, descriptive statistics were used to report the means and ranges of extracted data. Only English language publications involving human subjects were considered for inclusion.

Results

A literature search of the term "phenibut" identified 270 records. Only English language publications (n = 108) were considered, and this resulted in the exclusion of 1 French case report, describing phenibut withdrawal in 2 patients, and 162 articles written in Russian.[14] The title and abstract of each publication was analyzed, and records were divided into categories based on whether they primarily addressed phenibut toxicity, withdrawal, or basic pharmacology. Review articles that focused on phenibut were assessed for scope and timeliness (ie, year of publication), and the bibliographies were manually reviewed to identify pertinent references. This allowed us to identify a number of meeting abstracts that described cases of phenibut withdrawal. In total, 29 cases of phenibut withdrawal were identified and included.

Pharmacology

Although phenibut has been available for several decades, there is uncertainty regarding its pharmaceutical properties. Much of the information about phenibut in the scientific literature comes from a 2001 review by Lapin.[1] Unfortunately, there are multiple flaws with this article, including missing and inaccurate references, substantial enough to warrant identification by an Expert Committee of Drug Dependence associated with the World Health Organization.[2] This is problematic because nearly all publications involving phenibut cite this article.[4,5,14] As a result, information that cannot be validated continues to be perpetuated over time. Throughout this review, we will clarify when information being discussed was not retrieved from a primary source. Another challenge lies in the fact that most preclinical and clinical studies describing the pharmacologic effects of phenibut are published in Russian.

Formulations and Dosing Recommendations

Phenibut is available in capsules, solution, powder, and large crystals in 200-500 mg doses from online retailers.[15,16] In a US Centers for Disease Control and Prevention (CDC) report, Graves et al reported that phenibut is mainly ingested via the oral route, with inhalation and dermal absorption accounting for 3% and 4% of administrative routes, respectively.[10] Among 105 reports from 6 internet forums, 101 phenibut users took the drug orally, whereas 3 reported rectal administration, and 1 reported nasal insufflation.[17]

The recommended therapeutic dose of phenibut varies among product labels but is typically between 250 and 750 mg per day.[18] Some manufacturers recommend avoiding doses greater than 500 mg per day, and others recommend that phenibut not be used more than 2-3 days per week.[2,16] This recommendation of drug-free periods by manufacturers would appear to be a de facto acknowledgement that tolerance to phenibut occurs rapidly. This is consistent with reports of phenibut abuse, where individuals using phenibut for recreational purposes often ingest daily doses that far exceed those suggested by manufacturers.[17] Indeed, reports from 6 internet forums showed that the mean ± standard deviation phenibut dose taken by respondents was 2.43 ± 1.62 g, which represents nearly 5 of the 500 mg capsules.[17] The 2 most common desired effects from taking phenibut at these doses are the disappearance of social anxiety and euphoria.[17]

Chemical Structure and Mechanism of Action (MOA)

The molecular structure of phenibut is characterized by the assimilation of a phenyl ring at the β-position into the γ-aminobutyric acid (GABA) molecule (Figure 1). The phenyl ring enhances the entry of the drug into the brain.[19,20] Phenibut is a racemic mixture of the R-phenibut and S-phenibut enantiomers, with the R-enantiomer being the most pharmacologically active of the 2.[21–23] The pharmacologic effects of phenibut largely center on its role as a $GABA_B$ receptor agonist, similar to the structurally related compound

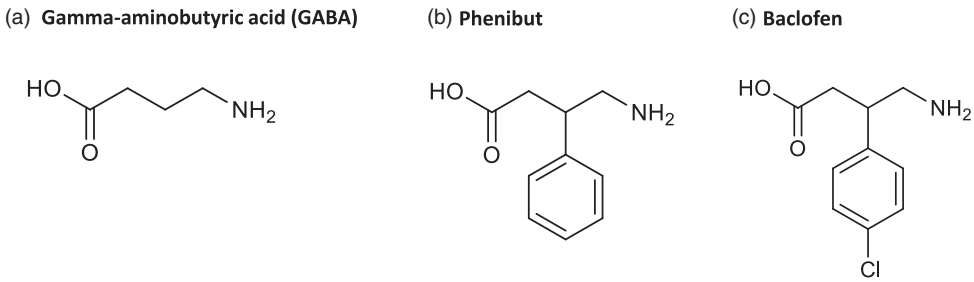

Figure 1. Chemical structures of (a) γ-aminobutyric acid (GABA); (b) phenibut; and (c) baclofen.

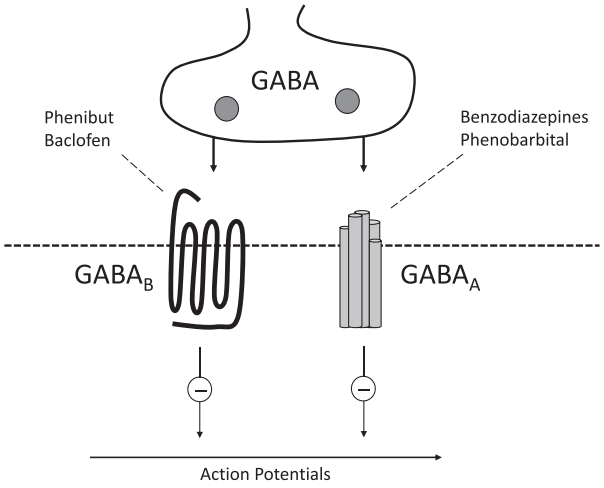

Figure 2. Mechanism of action of phenibut, baclofen, benzodiazepines, and phenobarbital at GABA receptors.

β-(4-chlorophenyl)-GABA (baclofen), which differs from phenibut by a p-choro group (Figure 1).[1,4] Although both phenibut and baclofen bind directly to the $GABA_B$ receptor, R-phenibut has an affinity for the $GABA_B$ receptor that is approximately 15 times weaker than that of baclofen.[21–23] The activation of the $GABA_B$ receptor by phenibut results in neurotransmitter inhibition, secondary to the triggering of voltage-gated calcium channels, which is analogous to the pharmacologic effects of gabapentin and pregabalin (Figure 2).[22–24] In addition to its $GABA_B$-mimetic activity, to a lesser extent phenibut also activates $GABA_A$ receptors, which are responsible for the pharmacologic activity of benzodizapines.[25] Phenibut has also been shown to increase dopamine and dopamine metabolite levels in rat striatum, and is suggested to produce sedative and tranquilizing effects via this mechanism.[26,27] Further, phenibut impacts voltage-dependent calcium channels (VDCCs), the same mechanism by which gabapentin produces its antinociceptive effects.[23] Finally, phenibut has been postulated to antagonize the effects of β-phenylethylamine (PEA), which is a presumed endogenous anxiogenic compound; this has been purported to explain the anxiolytic activity of phenibut.[1]

Pharmacokinetics

Information on phenibut pharmacokinetics is limited and is largely reported secondhand or as unreferenced data in the aforementioned review by Lapin.[1] Indeed, the following data presented by Lapin are not accompanied by original references. Following intravenous (IV) administration, phenibut does not undergo metabolism, but is instead excreted in the urine of rats, rabbits, cats, and dogs.[1] Phenibut was detected in the blood, kidneys, liver, and brain of these animals 15-90 minutes after IV administration, but by 180 minutes postdose only trace amounts remained (<4 mg%). In humans, 65% of an oral 250 mg dose of phenibut was excreted unchanged in the urine, and the renal clearance was roughly equivalent to the creatinine clearance.[1] Although phenibut is thought to forego clinically relevant hepatic metabolism, it is possible that the drug may be a substrate for uptake or efflux transporters; however, studies are needed to explore this possibility. The plasma half-life ($T_{\frac{1}{2}}$) of phenibut was reported as 5.3 hours.[1] Although there are no data describing the absorptive properties of phenibut powder or capsules in humans, recreational users routinely report a delay of 2-4 hours before experiencing the onset of effects.[2] These observations suggest that phenibut is slowly absorbed after oral administration.[2] This is consistent with a pharmacokinetic study in rats, which reported the time to maximum phenibut concentration (T_{max}) as 2 hours after oral administration of the phenibut brand Citrocard.[28] Although, to our knowledge, there are no human studies that characterize the impact of food on phenibut absorption and systemic availability, a popular Nootropics website recommends that users take phenibut on an empty stomach, stating that food delays the pharmacologic effects of the drug; they also infer that food reduces the bioavailability of phenibut.[29] However, it is not possible to confirm the accuracy of these statements.

Table 1. Signs and Symptoms Commonly Associated with Phenibut Toxicity and Withdrawal[2,5,6,11,30–35]

Toxicity	Withdrawal
Decreased muscle tone	Agitation and/or irritability
Insomnia	Increased sensitivity to stimuli ("primal fear")
Nausea ± vomiting ± diarrhea	Anxiety
Difficulty concentrating	Muscle tension
Palpitations	Restlessness
Tachycardia	Insomnia
Visual or auditory hallucinations	Reduced appetite
Paranoia	Nausea ± vomiting
Paradoxical presentation:	Palpitations
• Psychomotor agitation	Tachycardia
• Movement disorders	Visual or auditory hallucinations
• Delirium	Depersonalization
• Seizures	Cognitive deficits ("brain fog")
• Rhabdomyolysis	Fatigue
	Dizziness
	Depression

Intoxication

Phenibut has been reported to have a therapeutic index of 90, but the information used to calculate this number is not available.[2,4] Lapin identified the acute toxicity of phenibut as "low," with a median lethal dose (LD_{50}) of 700 mg/kg i.p. (intraperitoneal) in rats and of 900 mg/kg i.p. in mice.[1] In a recent study of the safety and tolerability of phenibut in humans, Kupats et al found that phenibut daily doses of >2 g were associated with a higher incidence of adverse reactions compared with daily doses of ≤2 g.[30] Specifically, cardiovascular symptoms defined as hypertension, tachycardia, and palpitations, hallucinations, and insomnia were more common in patients taking phenibut doses of >2 g/day compared with patients taking smaller doses.[30] Other adverse reactions associated with phenibut intoxication include a reduced level of consciousness, decreased respiratory rate, decreased muscle tone, stupor, and hypothermia.[5] In a recent investigation of online reports, phenibut users noted a wide range of effects, including euphoria, difficulty speaking, headache, difficulty concentrating, vision impairment, nausea, vomiting, and diarrhea.[6] Psychotic symptoms, including auditory or visual hallucinations, and paranoia may also be present (Table 1). Occasionally, patients experiencing acute phenibut toxicity will present paradoxically with psychomotor agitation, movement disorders, delirium, and seizures.[2] Elevations of creatine kinase (>800 U/L) and rhabdomyolysis have also been reported.[32–35] Occasionally, such behavioral agitation has required patients to undergo sedation and endotracheal intubation. Of the 56 cases reported to a Minnesota Poison Control System, 11 required intubation (19.6%).[11] Conversely, Weleff et al reported that 48.7% (19/39) of patients who presented with acute phenibut intoxication required intubation.[5] In this same study, 22 of these patients (56.4%) required admission to an intensive care unit (ICU).[5] Although this study reported a lone death, the prevalence of patients requiring intubation and ICU admission was notable.

Although phenibut dosages of >2 g/day have been associated with a higher incidence of adverse reactions, there is wide variability in the quantity of phenibut ingested by patients who present with acute toxicity.[7,13,30,36–62] One patient reported with symptoms of phenibut toxicity after taking 3 g daily for 4 days, which is only slightly higher than the daily dose recommended by some manufacturers.[63] This, however, would be considered atypical, as patients presenting with acute phenibut intoxication have been reported as taking a wide range of doses of up to 50 g daily.[9,11,17,33,47,52,62–65] In many of these cases, the exact dose taken by the patient is unknown and therefore not reported or is reported in a nonspecific manner (ie, "the patient took a tablespoon of phenibut powder").[34,35,66–74]

Few reports of acute phenibut toxicity have included data on plasma phenibut concentration.[17] A 20-year-old female was noted to have a phenibut plasma concentration of 29.7 μg/mL approximately 11 hours after taking 25 g of phenibut the previous day in 3 separate doses.[17] Analysis of the phenibut powder that the patient ingested was reported as containing 39.7% phenibut. A second patient from the same report, a 38-year-old male, was noted to have phenibut plasma concentrations of 36.5 μg/mL upon admission and 8.92 μg/mL 17 hours later. The phenibut dose in this patient was not reported. As there is no accepted therapeutic or toxic plasma concentration range, it is not possible to determine the clinical relevance of these numbers. Of note, the rate of decline between the 2 phenibut plasma concentrations, assuming first-order elimination, is consistent with a $T_{\frac{1}{2}}$ of 8.36 hours, which is close to the reported $T_{\frac{1}{2}}$ of 5.3 hours for phenibut.[1] However, this presupposes that phenibut is undergoing linear elimination during this 17-hour period, which may not be accurate. In a separate report, postmortem phenibut concentrations in 2 patients were 64.0 and <1.0 mg/L, respectively.[75] Lastly, Arndt et al described a deceased 26-year-old male who had a femoral blood concentration of phenibut of 2.5-5.0 mg/dL.[12] It should be noted that: (i) postmortem concentrations may not reflect premortem concentrations; (ii) phenibut products may not be accurately labeled, thus calling into question the actual quantity of phenibut consumed by a given patient; and (iii) data from these reports highlight the need to definitively characterize phenibut pharmacokinetics in humans. Without detailed pharmacokinetic

data, it is not possible to interpret phenibut plasma concentrations in any setting. Given the legality of phenibut in the USA (except for Alabama), such a study should not be impeded by federal laws and regulations.

The fact that there were 3 deaths reported among 1320 phenibut exposures between 2009 and 2019 suggests that fatalities associated with phenibut intoxication are relatively uncommon.[10] However, it must be noted that in many cases of phenibut intoxication, patients were taking concomitant medications; hence, it is challenging to assess the culpability of phenibut in multidrug overdose situations. Nonetheless, even though mortality associated with phenibut toxicity appears to be minimal, phenibut toxicity has been shown to result in significant morbidity.

A contributing factor to phenibut toxicity among recreational users is the aforementioned delayed onset of the drug.[2] Delayed onset has resulted in some users taking additional phenibut doses with the faulty assumption that the drug "isn't working." This has led to overdoses requiring medical intervention.[68] Another important aspect of phenibut toxicity is that signs and symptoms of intoxication are nonspecific and tend to mimic other conditions, such as serotonin syndrome or neuroleptic malignant syndrome (NMS).[2,32] In addition, patients presenting with phenibut toxicity frequently report taking other medications that may produce a similar clinical picture; these include alcohol, benzodiazepines, γ-hydroxybutyrate (GHB), kratom, and opioids.[5] Phenibut intoxication may also present similarly to phenibut withdrawal in some cases, as will be discussed below. Unfortunately, urine or plasma toxicology screening is not widely available to identify phenibut as a cause of intoxication. Phenibut may be detected by high-performance liquid chromatography (HPLC) mass spectrometry (MS); however, this methodology is not available in most clinical settings.[2] Hence, it is imperative that a thorough medication history, including online medication purchases, be obtained in overdose settings where symptoms are consistent with phenibut intoxication.

There is no antidote or specific pharmacologic treatment for the management of phenibut intoxication. Hence, treatment is largely supportive and primarily involves protecting the airway. Patients experiencing severe agitation or seizures should be sedated or treated with anticonvulsants, respectively, as appropriate. Most cases of phenibut intoxication resolve within 24 hours (approx. 4.5 phenibut half-lives), at which point phenibut is expected to be largely eliminated from the body.[7] Still, among 39 cases of acute phenibut toxicity, the average length of stay in the hospital was 5 days (with a range of 1-25 days).[5] Healthcare costs associated with phenibut intoxication have not been assessed, but given increased public awareness of phenibut as a recreational substance, this information is likely to become increasingly important.

Tolerance and Dependence

To our knowledge, there are no preclinical investigations that characterize the potential for physical dependence on phenibut.[2] Neither have such studies been conducted in humans, although there are a growing number of cases describing phenibut dependence.[3,7] These cases report the need for higher phenibut doses over time to achieve the same pharmacologic effect (ie, tolerance, resulting in dose escalation).[8,36] In some patients, tolerance can lead to massive phenibut ingestions. A case report of a 29-year-old male using phenibut for insomnia describes self-titration up to 50 g per day.[62] Notably, phenibut tolerance has been reported to occur within as little as 1-2 weeks of continuous use, and potentially as soon as 5 days. Unfortunately, the escalating dose requirement appears to potentiate a physical dependence on the drug, and withdrawal symptoms make it difficult to discontinue phenibut without medical support.[2,3,7,36]

Withdrawal

Phenibut withdrawal has been described as similar to the withdrawal from alcohol or benzodiazepines.[6] Abrupt cessation of phenibut is associated with an abstinence syndrome that can be severe, requiring hospitalization and, less frequently, admission to an intensive care unit (ICU).[2,5] Withdrawal symptoms associated with phenibut most commonly include insomnia, overwhelming anxiety, panic attacks, psychomotor agitation, irritability, depression, decreased appetite, nausea and vomiting, auditory and visual hallucinations, and disorganized thought patterns.[8,32,40,50] Palpitations, tachycardia, dizziness, muscle spasms, paranoia, inducible clonus, and seizures have also been observed.[2,6,37,42,43,49,51,54,55,62] As noted above, some of these symptoms may also occur during phenibut intoxication; they are also consistent with symptoms of intoxication or withdrawal from other medications. In some patients, the collection of symptoms may mimic serotonin syndrome.

Typically, phenibut withdrawal symptoms gradually become more severe within 24 hours of the patient's last dose. A wide variety of phenibut doses and durations have been associated with withdrawal when discontinued. Among published cases involving phenibut, the mean dose and duration were 12.4 g (0.875-50 g) and 7.1 months (0.25-36 months), respectively (Table 2). The quantity and duration of phenibut use that is associated with withdrawal symptoms upon abrupt discontinuation is unknown, although anecdotally higher phenibut doses (>5-10 g daily) over extended periods (>1-2 months) appear to be associated with more severe

Table 2. Cases of Phenibut Withdrawal and Pharmacologic Treatment

Ref.	Age (years)	Sex (M/F)	Phenibut daily dosage at time of cessation	Duration of use	Withdrawal symptoms	Pharmacologic treatment
[8]	35	M	8 g	10 months	Anxiety Anger Irritability	Baclofen started at 15 mg/day and titrated to a maximum of 60 mg/day over 9 weeks; phenibut was simultaneously tapered off during this time. Baclofen was then tapered off over the next 12 weeks (stopped when dose reached 20 mg/day)
[36]	26	M	1.0-1.5 g (frequency not reported)	"A few months" at 1.0-1.5 mg dose; >1 year at lower doses	Agitation Fidgeting anxiety Restlessness Burning under skin Irritability Poor sleep Pain Akathisia-like symptoms Suicidal ideation	Baclofen taper over 6 days: 5 mg TID for 2 days, then 5 mg BID for 1 day, then 5 mg Qam and 2.5 mg Qpm for 1 day, then 2.5 mg BID, then 2.5 mg once/day. The patient relapsed after 2 baclofen tapers and was treated with and maintained on clonazepam 1 mg TID
[37]	24	M	2-3 g	1 week	Palpitations Shortness of breath Anxiety Sweating	Initial 6 hours: lorazepam 2 mg + baclofen 130 mg + phenobarbital 780 mg. Then treated with baclofen 40 mg BID + phenobarbital 64.8 mg TID (duration unknown). Discharged on a "baclofen taper"
[38]	43	M	NR	"Chronic" (specific duration NR)	Psychomotor agitation	Initial 24 hours: lorazepam 16 mg + diazepam 50 mg + haloperidol 20 mg. After an unspecified time period (presumably 1 to 2 days) the patient received phenobarbital 20 mg/kg loading dose + baclofen 20 mg TID. Discharged on a "baclofen taper" on hospital day 6
[39]	34	M	34 g	NR	Auditory and visual hallucinations Tremor Agitation Altered mental status Sweating Respiratory distress Tonic-clonic activity	On admission: haloperidol + lorazepam + diphenhydramine (doses NR). Baclofen was recommended by psychiatry service; dose and duration NR
[40]	23	M	4-5 g	≤1 month	Anxiety Depressed mood Occasional auditory hallucinations Poor impulse control	"Benzodiazepines" (drug and dose NR) and gabapentin 100 mg TID for phenibut and alcohol withdrawal. Additional medications at hospital discharge included bupropion 150 mg QD + quetiapine 50 mg Qhs
[41]	34	M	28.5 g	3 years	Agitation Sweating Hallucinations Confusion Restlessness Impulsivity Encephalopathic Psychosis Twitching in all extremities	On admission: baclofen 10 mg once + lorazepam 1 mg twice. The patient was given olanzapine (dose and duration NR) + haloperidol (dose and duration NR) + lorazepam 17 mg. Diazepam 2.5 Q4h was added and haloperidol was discontinued. Baclofen 10 mg TID was started on hospital day 4 (HD4). Dexmedetomidine ("maximum dosage") + diazepam 10 mg (later decreased to 5 mg) Q2h + lorazepam 2 mg PRN, was given. Discharged home on HD11 on baclofen 20 mg TID + acamprosate 666 mg TID

(*Continued*)

Table 2. (Continued)

Ref.	Age (years)	Sex (M/F)	Phenibut daily dosage at time of cessation	Duration of use	Withdrawal symptoms	Pharmacologic treatment
[42]	Mid-twenties	M	12-20 g	2 months	Feelings of unreality Worthlessness Light and sound sensitivity Muscle pain and twitching Insomnia Anxiety and worries Palpitations Fatigue Visual/auditory hallucinations Intention tremor Disorientation Psychosis	On admission: gabapentin + promethazine + levomepromazine (doses and durations NR). Treated with haloperidol for hallucinations on HD4. On HD5 to HD6 patient was given olanzapine + promethazine (doses NR) for insomnia without success; ultimately, diazepam 30 mg + nitrazepam (dose and duration NR) produced sleep. Discharged on HD11 with "low-dose oxazepam" that was planned to be tapered off
[32]	23	M	16 g	Approx. 9-12 months	Progressive hallucinations Psychomotor agitation Increased muscular tone Inducible clonus Tremulousness Insomnia Nausea and vomiting Anxiety	On admission: lorazepam + haloperidol + diphenhydramine + melatonin + olanzapine (doses and durations NR). After ICU admission, baclofen + cyproheptadine + dexmedetomidine were administered (doses and durations NR). Dexmedetomidine was discontinued and gabapentin was "initiated and titrated" (dose NR). Baclofen and lorazepam were administered for SX control. DC medications NR
[43]	19	M	5 g	2 months	Anxiety Palpitations Insomnia	Baclofen 45 mg divided into 3 doses, tapered over 4 weeks by decreasing the dose 5 mg Q4 days. Hydroxyzine was prescribed PRN for insomnia (dose NR)
[44]	29	M	14-15 g	4 months	Anxiety Slight tremor Craving Muscle aches	Phenobarbital 64.8 mg QID for 1 day followed by a 25% to 50% dose reduction every 2 to 3 days over the next 8 days
[45]	50	F	Up to 5 g	"months"	Psychomotor agitation Confusion Abnormal motor behaviors Disorganized thinking Echolalia Visual hallucinations Insomnia	On admission, prior to information on phenibut use by the patient: delorazepam up to 6 mg + lorazepam, midazolam, diazepam haloperidol, and promazine (doses NR). After learning of phenibut use and abrupt cessation: diazepam IV up to 30 mg + haloperidol IM up to 5 mg. Patient was then treated with baclofen 20 mg/day. Patient was switched from diazepam to lorazepam 12 mg because of catatonia. Discharged after 25 days in hospital on risperidone 6 mg daily and lorazepam 10 mg daily
[46]	34	M	10 g	2 months	Agitation Visual hallucinations Tremulousness Sweating Disorientation	Upon admission: IV lorazepam (dose NR) then baclofen 5 mg TID for 72 hours + dexmedetomidine infusion (dose NR) for 24 hours + PRN benzodiazepines. Tapered off baclofen over 5 days

(*Continued*)

Table 2. (Continued)

Ref.	Age (years)	Sex (M/F)	Phenibut daily dosage at time of cessation	Duration of use	Withdrawal symptoms	Pharmacologic treatment
[47]	32	M	16 g	1 week at 16 g/day; unknown duration at lower dose of 8 to 10 g/day	Agitation with aggression Insomnia Disorientation Delusions Tremulousness Visual hallucinations Delirium	Presented with acute intoxication on HD1. SX of withdrawal appeared on HD2 for which he received "IM injections of antipsychotics." As SX worsened he was treated with scheduled olanzapine 5 mg BID, PO diazepam 10 mg Q4h PRN. On HD3, diazepam was DC'ed after paradoxical worsening in mental status after first diazepam dose, and baclofen 10 mg TID was initiated. Baclofen dose was titrated to 30 mg TID over 2 days. Ramelteon 8 mg was administered to treat sleep–wake cycle disruption. The patient was SX free on HD9 while taking baclofen 30 mg TID. The goal was to decrease baclofen dose by 10 mg per week
[48]	40	M	0.750-1.0 g	"Months"	Agitation Psychosis Hallucinations Insomnia	Benzodiazepines (drugs, doses, and durations NR) and "supportive care"
[49]	42	F	2.50-2.75 g	3 years	Hallucinations Tachycardia Tremors Insomnia Anxiety Weight loss	Loxapine 25 mg once followed by 50 mg once
[50]	21	M	1 g	10 days	Psychomotor agitation Irritation Nervousness Poor appetite Pounding/racing heart Nausea Insomnia	Patient reinitiated phenibut at one-half his typical dose (500 mg) and his SX abated. He decreased his phenibut dose by one-half every 4 days, completely weaning himself from the drug over 2 weeks
[51]	59	F	NR	"Recently added"	Agitation Hypertension Tachycardia	Benzodiazepines (drugs, doses, and durations NR)
[52]	27	M	5 g "multiple times per day"	NR	Hot and cold flashes Insomnia Restlessness Extreme irritability	Benzodiazepines taper (drug, dose, and duration NR)
[53]	30	M	18 g	1 year	Patient presented prior to onset of withdrawal SX During phenobarbital taper, the patient experienced: Headache Myalgia Paresthesia	HD1: baclofen 10 mg once. HD2: lorazepam 1 mg once, baclofen 10 mg 4 times, and clonazepam 0.5 mg twice. HD3: phenobarbital IV 218.4 mg twice and phenobarbital PO 64.8 mg twice. HD4: phenobarbital 32.4 mg twice. HD5: 32.4 mg once; patient requested discharge

(*Continued*)

Table 2. (Continued)

Ref.	Age (years)	Sex (M/F)	Phenibut daily dosage at time of cessation	Duration of use	Withdrawal symptoms	Pharmacologic treatment
[54]	Mid-thirties	M	25 -30 g	6 months	On first admission: Hypertension Tachycardia Tachypnea Lethargy At readmission after seizure at home: Tremors Hallucinations Nausea	Upon admission (HD1): lorazepam IV 1 mg; the patient was discharged on baclofen 10 mg TID on HD3. He returned 28 hours later after experiencing a brief generalized tonic-clonic seizure at home. Upon readmission he received baclofen 70 mg + lorazepam 6 mg with persisting SX. Patient was transferred to ICU and received phenobarbital 390 mg over 4 hours for agitation. He was much improved the next day and discharged on baclofen 40 mg TID + home doses of clonidine (0.1 mg BID) and gabapentin (600 mg TID). The baclofen dose was tapered by 5 mg daily each week
[55]	Newborn infant	M	Mother: 12 g at start of pregnancy, weaned to 5 g at delivery	≥9 months	Fever Tachycardia Continuous high-pitched cry Poor sleep Increased muscle tone Tremors	Initial TX: morphine PO with no response. TX switched to lorazepam PO 0.1 mg/kg Q6h; lorazepam was weaned (duration NR) and patient discharged
[56]	47	M	2 g	1 year	Anxiety Lower leg tremors Tachycardia Hypertension	Initial TX in ED: lorazepam IV (dose NR) and chlordiazepoxide (dose NR) were ineffective. The patient then received phenobarbital IV once (dose NR) in the ED and was subsequently managed successfully as an inpatient on phenobarbital PO + baclofen PO (doses and durations NR)
[57]	30	M	>4 g	NR	Hot flashes Restlessness Nausea Insomnia Cravings Tachycardia Sweating Hypertension Hallucinations Paranoid delusions	Lorazepam (route NR) up to 13 g Q24. Lorazepam was tapered, as was pregabalin (doses and durations NR)
[58]	68	M	7 g	Daily use (exact duration NR)	Anxiety Insomnia	Inpatient detoxification over 4 days: cumulative doses were baclofen 80 mg and phenobarbital 518.4 mg. Treated with diazepam 10 mg and lorazepam 3 mg for breakthrough withdrawal syndrome. Quetiapine, titrated to 100 mg was given to treat insomnia, and naltrexone 50 mg daily was administered to reduce cravings for alcohol and phenibut
[59]	21	M	"Much greater" than patient's usual 200 to 300 mg per day dose	Unclear	Visual hallucinations Overwhelming anxiety	Chlordiazepoxide 25 mg for 4 doses. Switched to baclofen taper: 5 mg TID for 2 days then tapered to 2.5 mg Q24h over the next approx. 7 days (then stopped)

(*Continued*)

Table 2. (Continued)

Ref.	Age (years)	Sex (M/F)	Phenibut daily dosage at time of cessation	Duration of use	Withdrawal symptoms	Pharmacologic treatment
[60]	25	M	33.0 to 34.5 g	2 years	SX arising from detoxification from phenibut and benzodiazepines: Changes in body temperature Depersonalization Locking of the jaw Paranoid delusions Insomnia Decreased appetite Cravings	Initiated on baclofen 25 mg QID with additional 5 mg doses for breakthrough withdrawal SX. Baclofen was tapered to 5 mg QID over approx. 7 weeks. After 6 to 12 months the baclofen dose was increased to 40 mg per day (from 20 mg per day) to reduce cravings. The patient was also treated with diazepam 9 to 10 mg per day, olanzapine 2.5 mg PRN, and pregabalin 125 mg TID
[61]	30	M	6 g	5 weeks	Insomnia Anxiety Palpitations	Upon presentation to ED, patient received baclofen 10 mg. Patient was instructed to continue phenibut 500 mg per day for 1 week and then stop; he was also instructed to take baclofen 10 mg Q8h PRN anxiety. Patient did not experience withdrawal SX and was able to DC baclofen after 8 days
[62]	29	M	50 g	"Years"	Insomnia Extreme agitation Altered mental status Sweating Unusual movements	At admission for phenibut use (3rd hospitalization), gabapentin 300 mg BID titrated up to 300 mg every morning and 600 mg at bedtime after 4th hospital presentation. The 5th hospital presentation was treated with gabapentin 300 mg BID, baclofen 30 mg BID, lorazepam 1 mg BID, and quetiapine 100 mg at bedtime. Medications continued on discharge and weaned over "months"

M, male; Qam, every morning; Qpm, every evening; Qhs, at bedtime; QD, every day; Q4h, every 4 hours; Q6h, every 6 hours; Q24h, every 24 hours; BID, twice daily; TID, 3 times daily; QID, 4 times daily; SX, symptoms; NR, not reported; DC, discontinued; ED, emergency department, PO, by mouth; IV, intravenous; TX, treatment; ICU, intensive care unit; HD, hospital day; PRN, as needed.

withdrawal symptoms and may require more intensive and longer pharmacologic treatment. Only 2 of the published cases of phenibut withdrawal involve doses at or below the manufacturers' recommended dose of 1 g.[48,50] Withdrawal symptoms in these cases were shorter in duration than those involving higher doses of phenibut for longer periods of time. One patient who took 1 g of phenibut powder daily for 10 days experienced nervousness, shakiness, psychomotor agitation, irritation, nausea, and insomnia, after abrupt cessation.[50] Although the daily phenibut dose in this patient was markedly lower than that seen in other published cases, and was consistent with the manufacturers' recommended daily dose of 1 g, they experienced withdrawal symptoms similar to those seen in patients taking higher doses. It is difficult to determine whether the withdrawal risk is related more to phenibut dose or duration, or whether they are contributing equally. In every published case of phenibut withdrawal the patient exceeded the common manufacturers' recommendation not to take phenibut for more than 5 consecutive days without a 2-day break.[2,16] It is unknown whether adhering to this recommended drug holiday would prevent or reduce phenibut tolerance, dependence, or withdrawal risk. Other patient-specific physiologic considerations may also contribute to phenibut withdrawal. The patient who took 1 g of phenibut powder for 10 days first began to experience withdrawal symptoms 2-4 hours after his final dose. This onset of withdrawal is inconsistent with the reported $T_{\frac{1}{2}}$ of 5.3 hours for the drug. It is possible that unknown factors such as unreported or unrecognized interactions or altered phenibut elimination contributed to this unexpected observation.[50]

The etiology of phenibut withdrawal is likely linked, at least in part, to the downregulation of $GABA_B$ receptors as a result of chronic use.[2] In an effort to self-treat their withdrawal symptoms, patients may ingest a variety of substances, including alcohol and benzodiazepines. At least 1 case of withdrawal in a newborn born to a mother who used phenibut throughout pregnancy has been reported. The infant's fever, tachycardia, insomnia, and muscle tone and tremors responded to lorazepam.[55]

Withdrawal Treatment

One of the main tenets of treating phenibut withdrawal is to substitute phenibut with a prescription drug that: (i) displays a similar mechanism of action (MOA) (ie, is a $GABA_B$ or $GABA_A$ agonist); (ii) has low(er) potential for abuse compared with phenibut; and (iii) has a well-described pharmacokinetic safety profile with which clinicians are familiar.[8] Medications commonly used to treat phenibut withdrawal are listed in Table 3, along with their respective MOAs and clinical considerations. Patients who present to the emergency department (ED) with nonspecific withdrawal symptoms can present a challenge to clinicians, many of whom may not be familiar with phenibut, and may assume that the patient is experiencing alcohol or benzodiazepine withdrawal. As it is not possible in most situations to screen plasma or urine for phenibut, clinicians must rely on the patient or their contacts to inform them of phenibut use. With the often severe nature of phenibut withdrawal symptoms, it is not surprising that patients are often treated initially with benzodiazepines and/or antipsychotics. However, it should be noted that if clinically appropriate and not contraindicated, benzodiazepines would be preferred over antipsychotics, based their mechanism of action.

As it acts as a $GABA_B$ agonist like phenibut, baclofen has been adopted by some clinicians as the cornerstone of treatment for phenibut withdrawal. Of the published cases, baclofen was included in 65% of treatment regimens (Table 2). However, this approach has been questioned, especially in patients who may be at risk of seizures.[54] Fortunately, there were no reported seizures in any of the published cases after baclofen initiation. However, given the known risk for seizures with of baclofen, caution should be taken when it is used. Unlike baclofen, benzodiazepines and phenobarbital are $GABA_A$ agonists with anticonvulsant activity. If baclofen treatment is chosen, it should be initiated as early as possible in the withdrawal process.[47] The mean (range) daily baclofen dose that was used when initiating a tapering regimen and tapering durations are presented in Table 3. Although there are no published data on the dose equivalency between phenibut and baclofen, Samokhvalov et al substituted 8-10 mg of baclofen per 1 g of phenibut to successfully treat a patient experiencing phenibut withdrawal.[8] If this suggested dose equivalency between phenibut and baclofen is accurate, it may explain why some patients experience breakthrough withdrawal symptoms while being tapered off of baclofen regimens that started with a baclofen dose below this ratio. For patients taking high doses of phenibut (ie, $\geq$8 g/day), this equates to a baclofen taper that begins at or above the manufacturers' maximum recommended dose of 80 mg per day, which clinicians may be hesitant to exceed.[93] However, when used to treat alcohol withdrawal, much higher daily doses of baclofen (ie, 310-630 mg) have been used for extended periods (1-22 months) with side effects being mostly minor and benign.[77]

In 10 of the 29 cases (34%) in Table 1, the patient was placed on a baclofen taper that ranged between 5 days and 24 weeks.[8,46] Given the risk of relapse in patients who are not adequately treated for phenibut withdrawal, longer tapers (ie, >90 days), higher doses (80-300 mg), and/or concurrent therapy with a benzodiazepine or phenobarbital may be necessary for patients

Table 3. Medications Used in the Treatment of Phenibut Withdrawal

Medication or class	Mechanism(s) of action	Doses/durations reported in Table 1 to treat phenibut withdrawal	Comments
Baclofen	Agonist for beta subunit of GABA[1]-B receptors on pre- and postsynaptic neurons in the central and peripheral nervous systems[76]	19/29 Patients (66%) in Table 1 received baclofen as part of their TX. The mean (range) daily baclofen dose that was used when initiating a tapering regimen was 46.5 mg (15 to 130 mg). Durations ranging from days to 6 months have been used[8,32,36–39,41,43,45–47,53,54,56,58–61]	A baclofen dose of 8-10 mg per gram of phenibut has been suggested for replacement therapy to treat phenibut withdrawal.[8] Other clinicians report having used lower baclofen doses with success, especially if other CNS depressants (ie, benzodiazepines or phenobarbital) are coadministered.[8] High baclofen doses ($\geq$300 mg) have been safely used to treat alcohol withdrawal[77]
Phenobarbital	Acts upon GABA-A receptor subunits. Phenobarbital also suppresses excitatory glutamate receptors[78–80]	7/29 Patients (24%) in Table 1 received phenobarbital. One patient received a single loading dose at 20 mg/kg (total dose NR), and another received a 518.4 mg dose. One patient received a cumulative dose of 780 mg within 6 hours of presentation. Others started phenobarbital tapers at 64.8 mg BID, TID, and QID, respectively. Phenobarbital was the lone/primary TX in 2 cases. One duration of TX was 8 days; others were not reported[37,38,44,53,54,56,58]	Phenobarbital has shown less agitation and delirium compared with benzodiazepines when used to treat alcohol withdrawal.[79,80] Phenobarbital has a longer half-life than lorazepam and diazepam, which may be advantageous when tapering therapy
Benzodiazepines	Activates the benzodiazepine receptor (BZ-R), which results in the entrance of chloride ions into the neuron, hyperpolarization, and CNS depression. Benzodiazepines increase the frequency in opening the GABA-A receptor chloride channel when GABA is present[81]	23/29 Patients (79%) in Table 1 received benzodiazepines (specific benzodiazepine NR in 4 cases). Benzodiazepines were used in combination with baclofen in 13 cases and with gabapentin in 4 cases. In 2 cases, benzodiazepines were switched to baclofen and phenobarbital, respectively. Lorazepam (n = 13), with repeated doses up to 16 mg/day acutely (1 patient was maintained on 10 mg/day) and diazepam (n = 7), with repeated doses up to 50 mg/day acutely, were the 2 most commonly administered benzodiazepines; others include chlordiazepoxide (n = 2), clonazepam (n = 2), oxazepam (n = 1), delorazepam (n = 1), midazolam (n = 1), and nitrazepam (n = 1).[32,36–42,45–48,51–60,62]	Benzodiazepines were typically used in the first 24 hours to treat symptoms of anxiety and insomnia. In 4 cases benzodiazepines were used as monotherapy. The potential for benzodiazepine misuse should be considered when treating individuals with a history of substance abuse
Gabapentin	Inhibits the alpha$_2$–delta (α_2–δ) subunit with an auxiliary subunit of voltage-sensitive calcium channels. This appears to inhibit the release of excitatory neurotransmitters[82,83]	5/29 Patients (17%) in Table 1 received gabapentin. Gabapentin 100 mg TID was used in combination with benzodiazepines (drug and dose NR) in 1 case of phenibut + alcohol withdrawal. Two other cases report gabapentin use (doses and duration NR); one of these cases used a gabapentin taper (doses and schedule NR). Two patients were prescribed gabapentin prior to admission and were discharged with this plus baclofen[32,40,42,54,62]	One patient escalated phenibut use despite being treated with gabapentin monotherapy.[62] Gabapentin monotherapy has shown mixed results when treating alcohol withdrawal. May be useful in maintaining abstinence from alcohol at higher doses (1800 mg per day).[82–84] It is unclear whether these data can be extrapolated to any degree to phenibut withdrawal
Pregabalin	Acts upon the α_2–δ protein, an auxiliary subunit of voltage-gated calcium channels, leading to a reduction in excitatory neurotransmitters[85,86]	2/28 Patients (7%) received pregabalin. Pregabalin dose and duration was NR in 1 case. In the other case pregabalin was administered 125 mg TID (duration NR)[57,60]	Sparse data suggest that pregabalin may be useful in treating alcohol withdrawal.[86,87] It is unclear whether pregabalin may have a role in treating phenibut withdrawal. The potential for pregabalin misuse should be considered when treating individuals with a history of substance abuse

(*Continued*)

Table 3. (Continued)

Medication or class	Mechanism(s) of action	Doses/durations reported in Table 1 to treat phenibut withdrawal	Comments
Haloperidol	Exerts its antipsychotic activity by blocking dopamine D2 receptors in the brain; also has noradrenergic, histaminergic, and cholinergic blocking properties[88]	6/28 Patients (21%) received haloperidol. Doses and durations were NR except for 1 patient who received IM doses "up to 5 mg" (number of doses NR) and another who received 20 mg in the first 24 hours[32,38,39,41,42,45]	May be useful as adjuvant TX during the first 24 hours of admission for phenibut withdrawal, especially for severe agitation, refractory insomnia, or psychotic manifestations, including auditory and visual hallucinations
Olanzapine	Exerts its action primarily on dopamine and serotonin receptors. Blocks dopamine D2 receptors in the mesolimbic pathway at the postsynaptic rceptor[89]	5/28 Patients (18%) received olanzapine. One patient received 5 mg BID, and another 2received 2.5 mg PRN. Doses and durations of olanzapine were not provided in the other 3 cases[32,41,42,47,60]	May be useful as adjuvant TX during the first 24 hours of admission for phenibut withdrawal, especially for severe agitation, refractory insomnia or psychotic manifestations, including auditory and visual hallucinations
Dexmedetomidine	Acts as a specific and selective α_2-adrenoceptor agonist. Activation of these receptors in the brain and spinal cord result in sedation, bradycardia, analgesia, and hypotension. Controls anxiety and autonomic hyperactivity associated with withdrawal syndromes[90]	3/28 Patients (11%) received dexmedetomidine, with doses and durations NR. Dexmedetomidine appears to have been used as adjunct therapy as single doses for the symptomatic control of phenibut withdrawal[32,41,46]	May be particularly useful for short-term symptomatic TX of severely agitated patients with concurrent hypertension
Naltrexone	Acts as a μ-opioid receptor antagonist, along with its active metabolite, 6-β-naltrexone. It is also a weaker antagonist of κ and δ receptors. Naltrexone also modifies the hypothalamic–pituitary-adrenal axis to suppress alcohol consumption[91]	1/28 Patients (3.6%) received concurrent naltrexone with baclofen, phenobarbital, and benzodiazepines. The patient was also being treated for alcohol withdrawal. Naltrexone was administered to reduce cravings for alcohol and phenibut[58]	May be useful in patients dependent on alcohol in addition to phenibut. There are no data on the impact of naltrexone on reducing phenibut cravings in individuals not also undergoing simultaneous alcohol withdrawal
Acamprosate	Modulates GABA-A transmission and NMDA receptor transmission to reduce glutamate in the setting of alcohol withdrawal, to elevate β-endorphin in patients with marked alcohol intake, and possibly to modulate the hypothalamo–pituitary-adrenal (HPA) axis[92]	1/28 Patients (3.6%) received concurrent acamprosate 666 mg TID with a baclofen taper (20 mg TID). The patient was also being treated for alcohol withdrawal. Naltrexone was administered to reduce cravings for alcohol and phenibut[41]	The patient did not have a history of alcohol dependence. Acamprosate was administered in the hope that its modulation of central glutamate would reduce symptoms of phenibut withdrawal and decrease cravings, similar to its use during alcohol withdrawal[41]

BID, twice daily; GABA, gamma aminobutyric acid; NR, not reported; PRN, as needed; QID, 4 times daily; TID, 3 times daily; TX, treatment.

who have taken high phenibut doses for extended periods. Coenen reported the detoxification of a patient taking phenibut (approximately 34 g/day for 2 years) and diazepam (20 mg QID for 1 year) using only approximately 3 mg of baclofen per gram of phenibut.[61] However, this patient was also receiving concurrent diazepam and pregabalin for diazepam detoxification, which likely reduced the need for a higher baclofen dose. Interestingly, the patient remained on baclofen 40 mg daily to prevent phenibut cravings, suggesting that baclofen might be useful for relapse prevention in cases of phenibut dependence.[60]

Of the 18 patients in Table 2 who received baclofen for phenibut withdrawal, 15 (83%) required at least 1 additional medication for management. Benzodiazepines were the most commonly used medications to treat acute phenibut withdrawal, appearing in the treatment regimens of 22 (76%) patients described in Table 2; benzodiazepines were coadministered with baclofen in 13 patients (72%). However, the frequency of benzodiazepine use may owe more to clinician familiarity with this class of drug in treating agitation, rather than a pharmaceutical advantage, and other medications may be more beneficial in some patients. Phenobarbital has been used successfully, either alone or with baclofen, for the treatment of phenibut withdrawal. Whereas benzodiazepines and phenobarbital both act as $GABA_A$ agonists, phenobarbital has the added advantage of suppressing excitatory glutamate receptors.[78] Phenobarbital has also been associated with less agitation and delirium compared with benzodiazepines when used to treat alcohol withdrawal; whether this is true when these drugs are used to treat phenibut withdrawal is unknown.[78–80] In addition, phenobarbital has a longer $T_{\frac{1}{2}}$ (80-120 hours) than most benzodiazepines (14-20 hours for lorazepam and

48 hours for diazepam), which may also be valuable in treating phenibut withdrawal, as phenobarbital has a tapering effect as the medication wears off.[80] Brunner et al used a phenobarbital taper, at a starting dose of 64.8 mg QID, over a 9-day period to treat phenibut withdrawal in a 29-year-old man.[44] The authors implied that they chose to treat their patient with phenobarbital instead of baclofen for the comparatively shorter duration of the therapy. This was based on a case report where baclofen was tapered over a 17-week period after the patient was weaned off phenibut, which they took concurrently with baclofen for 7 weeks.[8]

For patients at the greatest risk of developing seizures during phenibut withdrawal, phenobarbital, alone or with baclofen, is an attractive agent, given its role as an anticonvulsant.[54] This is of particular note considering that baclofen has been associated with a deterioration of seizure control in patients with epilepsy or a history of seizures.[93] Patients at risk for seizures include those taking medications that lower the seizure threshold or those taking excessive phenibut doses for lengthy durations. Patt et al described a patient who was treated for phenibut withdrawal with baclofen 10 mg TID after taking 25-30 mg of phenibut daily for 6 months.[54] The patient was readmitted 28 hours after discharge after experiencing a tonic-clonic seizure at home. The authors noted that their case highlights the risk of phenibut withdrawal symptoms worsening after initial presentation (ie, beyond 24 hours). Based on their observation, the authors questioned the use of baclofen monotherapy as the cornerstone of treating phenibut withdrawal. Indeed, baclofen monotherapy may be best reserved for patients at the lowest risk of experiencing seizures during phenibut withdrawal (ie, those taking lower phenibut doses for shorter periods of time without additional seizure risks). Concurrent therapy, or in some cases monotherapy, with phenobarbital or benzodiazepines may be a more appropriate choice for treating phenibut withdrawal than using baclofen alone. Clearly, comparative studies are needed to identify the most appropriate approach to treating phenibut withdrawal, taking patient-specific attributes into account, such as phenibut dose, duration of use, and secondary seizure risk.

A number of additional medications besides baclofen, benzodiazepines, and phenobarbital have been used to treat phenibut withdrawal (Table 3). In most cases, these agents have been used in a supplemental role for managing specific symptoms (ie, antipsychotics for delusions and hallucinations). Despite their similarity to phenibut in structure and MOA, gabapentin and pregabalin have been used infrequently to treat phenibut withdrawal. Only 5 patients in Table 2 were treated with gabapentin, and 2 were treated with pregabalin. In all cases, additional medications (ie, benzodiazepines) were used concurrently. One patient who was prescribed gabapentin for phenibut abuse and withdrawal was suspected to have actually increased their phenibut intake after starting gabapentin therapy.[62] Ultimately, the patient required multiple medications, including baclofen, to successfully stop taking phenibut.[62] At this time, it is unclear whether gabapentin and pregabalin have a role in treating phenibut withdrawal.

For many patients, even those who report taking a recommended daily dose of 1-1.5 g (keeping in mind that a patient's reported dose may not reflect their consumed dose, as the actual phenibut content may differ from that indicated on the product label), stopping phenibut abruptly (ie, going "cold turkey") may not be possible because of the intolerable withdrawal symptoms. In the study by Behmer Hansen et al, 23.3% of phenibut users reported having experienced withdrawal symptoms at some point.[6] As such, tapering phenibut may be necessary to effectively wean patients from the drug. One mental health website recommends decreasing the phenibut dose by 10% every 2-4 weeks, making adjustments (tapering faster or slower) based on the presence or absence of withdrawal symptoms.[94] Although this may be a reasonable approach, any attempt to taper off of phenibut must be done under medical supervision, as the addition of ancillary medications to treat breakthrough withdrawal symptoms may be warranted. This approach requires a strong therapeutic alliance between patient and prescriber, and might best be reserved for highly motivated patients. Another viewpoint is that phenibut should be stopped and substituted with baclofen or phenobarbital because it is not possible to accurately track a patient's phenibut input if they are undergoing a self-taper.[9]

Samokhvalov described an individual in an outpatient setting who tapered his phenibut dose from 8 g daily to 1 g daily over 7 weeks while simultaneously initiating a baclofen regimen that escalated from 15 mg daily to 60 mg daily.[8] From weeks 9 to 24, when the patient was off phenibut, he underwent a baclofen taper that started at 60 mg daily and ended at 20 mg daily before discontinuation. When the patient was discharged from the clinic after 24 weeks, he was not experiencing mood or anxiety symptoms and nor was he taking phenibut or other drugs of abuse.

Acamprosate and naltrexone were used as ancillary medications in 2 of the cases presented in Table 1.[41,58] Both of these agents have proven useful in treating alcohol dependence, which is why they were used in the setting of phenibut withdrawal.[41,91] It is unclear whether these medications offered any benefit in these 2 cases or whether acamprosate, naltrexone, or other agents used for alcohol or benzodiazepine dependence

have a role in treating phenibut withdrawal or preventing relapse.

Regulation and Availability

Outside of countries from the former Soviet Union, phenibut was largely unheard of until a shipment of the drug was seized in Sweden in 2011, which led to the notification of European authorities.[3] Following this seizure, concerns regarding phenibut misuse resulted in the drug being reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol. According to the EMCDDA–Europol 2012 Annual Report on the Implementation of Council Decision, phenibut was being marketed as a "dietary supplement" and a "research chemical" in several member states of the European Union.[95] Also in 2012, phenibut was classified as a new psychoactive substance (NPS) by the United Nations Office of Drug and Crime (UNODC).[3] An NPS is loosely defined as a substance of abuse that is not controlled according to the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but may pose a threat to public health.[3,7] Of note, the UNODC clarifies that the "new" in NPS does not necessarily refer to a new compound, but may describe a previously recognized substance that has only recently being recognized for its abuse potential, as is the case with phenibut.[96]

Few countries list phenibut as a controlled substance. Those that do include France, Hungary, Italy, and Lithuania.[2] In 2018, Australia designated phenibut as a Schedule 9 (prohibited) substance because of: (i) substantial risks associated with phenibut use that appear to outweigh benefits; (ii) increased phenibut use associated with widespread online availability; (iii) the growing number of published cases of overdose and withdrawal; and (iv) the rapid progression to tolerance and dependence observed with phenibut use.[97] In the UK, phenibut is unscheduled and may be legally possessed for personal use; however, it is unlawful to sell or supply it.[2]

Phenibut is not approved by the United States Food and Drug Administration (FDA) as a prescription medication.[2] However, it is legal to buy, sell, and possess phenibut in the USA except for Alabama, where phenibut was recently designated as a Schedule I substance by the Alabama Department of Public Health.[98,99] However, the FDA has prohibited the marketing of phenibut as a dietary supplement, and has mandated that all dietary supplement products listing phenibut as an ingredient be removed from retail shelves.[98] The FDA issued 3 warning letters in April 2019 to US companies who were manufacturing and selling products containing phenibut. These letters stated that "Because phenibut does not fit in any of the dietary ingredient categories under Section 201(ff)(1) of the (Federal Food, Drug, and Cosmetic) Act, it is not a dietary ingredient as defined in the Act. Declaring phenibut in your product (and) labeling (it) as a dietary ingredient causes your product to be misbranded … in that the labeling is false or misleading."[100] Cohen et al analyzed 4 brands of dietary supplements labeled as containing phenibut before and after the issuance of these warning letters. Prior to the FDA warnings, 2 of the 4 products contained phenibut (484 and 487 mg, respectively).[101] Ironically, after the FDA warning was issued, all 4 products still contained phenibut, ranging between 21 and 1164 mg per product. Of note, none of the products analyzed in this investigation were manufactured by companies who received an FDA warning letter.[101] Although limited in scope, this study suggests that the FDA warning letters regarding phenibut may not be serving as a deterrent to manufacturers who continue to include this prohibited compound in their products, which they label as dietary supplements.

Conclusions

An increase in public awareness and ease of internet availability have led to an increasing number of cases of phenibut intoxication and dependence. Evaluating a patient who may be suffering from phenibut intoxication or withdrawal is challenging. This is because many symptoms of phenibut intoxication and withdrawal are nonspecific and may mimic alcohol or benzodiazepine intoxication or withdrawal. Further, patients who present with phenibut intoxication may express some of the same symptoms as those presenting with acute withdrawal (Table 1). As urine or plasma drug screening for phenibut is not widely accessible, it is imperative that clinicians obtain a detailed medication history, including medications purchased over the internet, in patients presenting to the ED with nonspecific symptoms of intoxication or withdrawal.

As there is no antidote or specific pharmacologic intervention for phenibut intoxication, treatment is largely supportive and involves protecting the airway. With its relatively short $T_{\frac{1}{2}}$, most cases of phenibut intoxication resolve within 24 hours. At that point, depending upon a patient's dose and duration of phenibut use, they are likely to experience withdrawal symptoms in the absence of continued pharmacologic intervention.

Numerous pharmacologic approaches have been described to treat withdrawal in individuals undergoing phenibut detoxification (Box 1). Currently, there are no controlled studies comparing treatment modalities for phenibut withdrawal. Anecdotal case reports suggest that baclofen, phenobarbital, and benzodiazepines appear to be useful as individual agents or in various

Table 1. Questions to Consider when Treating Phenibut Withdrawal[a]

What are the most common medications used for the treatment of phenibut withdrawal?
- Baclofen, benzodiazepines (ie, diazepam or lorazepam), and phenobarbital

Why are these medications frequently chosen for this purpose?
- Baclofen
  - Is a $GABA_B$ agonist that is mechanistically and structurally similar to phenibut
  - Has been used successfully alone and in combination (usually with a benzodiazepine) for the treatment of phenibut withdrawal
- Benzodiazepines
  - Act as $GABA_A$ agonists
  - Have been used alone or in combination with baclofen in the majority of published phenibut withdrawal cases
  - Are effective in treating common symptoms of phenibut withdrawal, including severe anxiety, insomnia, psychomotor agitation, and irritability
  - May prevent seizures in predisposed individuals
- Phenobarbital
  - Acts as a $GABA_A$ agonist and also suppresses excitatory glutamate receptors
  - Has been used alone and in combination with baclofen in patients experiencing phenibut withdrawal
  - May also prevent seizures in predisposed individuals

Why are these medications often used in combination?
- Benzodiazepines or phenobarbital may be added to baclofen for additional control of withdrawal symptoms, especially in patients taking high doses of phenibut for extended periods of time; they may also be added to prevent seizures in predisposed individuals

What are the potential advantages and disadvantages of these medications?
- Baclofen
  - Same mechanism of action (MOA) as phenibut
  - Less abuse potential compared with benzodiazepines and perhaps phenobarbital
  - May be better suited for prolonged outpatient treatment if clinically indicated
  - Possible increase in seizure risk may be a disadvantage in some individuals
- Benzodiazepines
  - Have been used more frequently (alone or in combination) compared with baclofen or phenobarbital to treat phenibut withdrawal
  - May be most useful during the first 24 hours of phenibut withdrawal to treat anxiety and insomnia
  - Potential for misuse may be a disadvantage when used in the outpatient setting
- Phenobarbital
  - Has a longer half-life than lorazepam or diazepam, which may be helpful during tapering therapy
  - May be associated with less agitation and delirium compared with benzodiazepines

How long should a person be treated for phenibut withdrawal?
- Optimal treatment duration is unknown and varies based on the individual patient situation
- Patients taking higher doses of phenibut for longer periods may require longer tapering regimens (a regimen of 6 months has been reported)

What other medications have been used to treat phenibut withdrawal?
- Acamprosate, antipsychotics, dexmedetomidine, gabapentin, naltrexone, and pregabalin have been used as adjunctive therapy; the role of these agents, if any, in the treatment of phenibut withdrawal is currently undefined

[a] There are no clinical trials comparing different pharmacologic agents or combinations of agents for the treatment for phenibut withdrawal. The treatment options discussed here are based on anecdotal case reports, comparative mechanisms of action, and patient-specific factors, such as polysubstance abuse, seizure history, and dose and duration of phenibut use.

combinations for treating phenibut withdrawal. Based on currently available data, the combination of baclofen and a benzodiazepine such as diazepam or lorazepam represents a logical therapeutic approach for treating patients experiencing acute phenibut withdrawal. Once severe symptoms are under control, it may be possible to taper off the benzodiazepine and treat the patient with baclofen monotherapy, using a prolonged taper (ie, over a period of months). For patients with a seizure history, it may not be prudent to discontinue benzodiazepine therapy; in fact, benzodiazepine monotherapy may be indicated to treat protracted withdrawal. Phenobarbital is also a reasonable choice for patients who may be at risk of seizures; however, potential drug interactions with phenobarbital should be considered, as it is a potent inducer of several cytochrome P450 (CYP) enzymes.[102]

Besides baclofen, benzodiazepines, and phenobarbital, other medications used to treat phenibut withdrawal have included antipsychotics, dexmedetomidine, gabapentin, and pregabalin. Although the role of these agents (if any) remains to be defined, short-term antipsychotic therapy may be useful in patients experiencing hallucinations or other symptoms of psychosis. As gabapentin and pregabalin inhibit the release of excitatory neurotransmitters, they may also have a role in treating phenibut withdrawal; however, to date, this role has not been defined. Gabapentin and pregabalin may be considered as ancillary therapy in patients whose symptoms are not well controlled on baclofen, benzodiazepines, or phenobarbital. Any role for dexmedetomidine also remains to be defined; it is likely best suited as an additional agent for patients not responding to the medications discussed above.

As long as phenibut remains legal in nearly the entire USA, cases of phenibut intoxication and withdrawal are likely to continue to be reported. Although the management of acute phenibut intoxication is largely straightforward, studies are needed to determine the most appropriate treatment for patients experiencing phenibut withdrawal. Studies are also needed to confirm phenibut absorption and disposition in humans, as the studies describing phenibut pharmacokinetics were published over 50 years ago and are in Russian. Hence, much of the information on phenibut pharmacokinetics and pharmacodynamics has been repeated from a 2001 review article. To this end, clinicians should be aware of phenibut as a drug of abuse and become familiar with common treatment approaches to phenibut withdrawal. Owing to the clinical complexities of treating phenibut withdrawal, clinicians may wish to consult with specialists (ie, addiction specialists or toxicologists) who have expertise in this area.[54]

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Conflicts of Interest

Both authors declare that they have no conflicts of interest associated with this work.

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