Unedited - Advance copy

Pre-Review Report:

PHENIBUT

Expert Committee on Drug Dependence

Forty-fourth Meeting

Geneva, 11-15 October 2021

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

Executive Summary

Phenibut is a psychotropic drug that was developed in Russia where it is purportedly clinically used to treat a multitude of health issues, such as tension, anxiety, depression, stuttering, migraine headaches, tension headaches, alcohol withdrawal, restless leg syndrome, post-traumatic stress syndrome, insomnia, and fear, however limited information in this regard is available. Its specific indications and its off-label use are unknown. It is also purportedly used clinically in a few other Eastern European countries, including Latvia, Estonia, Belarus, Kazakhstan and Ukraine, but its medicinal use throughout other parts of the globe is minimal. While phenibut is not approved as a medication in Western countries it is easily obtained through the internet. Countries where phenibut is not a controlled substance and is purchased online as a dietary supplement include the United Kingdom, the United States of America (U.S.), Canada, and China.

Phenibut's ease of accessibility and its reputation as a 'natural high', nootropic, anxiolytic, mood enhancer and sleep aid have promoted its status in the internet world of self-medication and recreational use. Published reports, conference proceedings and online drug user sites on its misuse, overuse, toxicity, tolerance and withdrawal (physical dependence) are numerous.

Phenibut purportedly has anxiolytic, antinociceptive and cognitive enhancing properties, although much of the scientific data on these properties is unavailable.

Phenibut is similar in chemical structure and function to baclofen and gabapentin, acting primarily as an agonist at the GABA B receptor, similarly to its analog, baclofen; and at the α2–δ subunit of voltage dependent calcium channels, like its analog, gabapentin.

Randomized controlled trials of phenibut for any of its purported indications are not available. According to the limited literature, use of phenibut was not well documented outside of Russia and a few other Eastern countries until 2011. At that time, a drug seizure in Sweden raised concerns and led to its eventual classification as a new psychoactive substance (NPS) in 2012. There are a multitude of case studies describing emergency care situations involving phenibut, with the earliest documentation in the literature reported in 2010. In these cases, medically unsupervised use of phenibut obtained via the internet at doses much higher than those used clinically is leading to claims of its dependence potential and adverse effect profile. These cases provide evidence that the recreational use of phenibut can lead to escalated dosing (tolerance), overdose with significant adverse effects, and a withdrawal syndrome upon abstinence. Phenibut-containing products are labelled as 'natural' with consumers purchasing phenibut to self-treat various ailments (i.e., insomnia, anxiety). Consumers report beliefs that phenibut is safer to take and easier to obtain than registered pharmacological treatments prescribed by doctors. Consumers are also purchasing phenibut to self-medicate withdrawal symptoms stemming from other psychotropic drugs including opiates, benzodiazepines and alcohol.

Multiple cases of emergency hospital admissions involving phenibut are published in the literature, that are associated with nonmedical use of phenibut that was purchased online. Because there is no readily available urine toxicology screen for phenibut, it is difficult to identify its use in patients that present to the emergency room. Generally, information on phenibut use is gleaned from family/friends. Once it is determined that phenibut overdose or withdrawal might underlie the presenting symptoms, symptoms are generally managed with benzodiazepines, phenobarbital, baclofen or gabapentin along with supportive care. Symptoms generally remit in 24 hours.

Acute phenibut intoxication has presented with depressive symptoms (i.e., decreased level of consciousness, muscle tone, stupor, depressed respiration), temperature dysregulation, hyper- or hypotension and tachycardia. However, in other cases individuals have presented with psychomotor agitation, hallucinations, seizures, and delirium. In some cases, severe behavioral agitation has necessitated sedation and airway protection with endotracheal intubation.

Symptoms of phenibut withdrawal include insomnia, psychomotor agitation, delusions, psychosis, disorganized thought patterns, auditory/visual hallucinations, overwhelming anxiety, depression, fatigue, dizziness, seizures, decreased appetite, nausea and vomiting, palpitations, and tachycardia.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

1078-21-3 (racemate)
35568-36-6 (βR)-β-(Aminomethyl)benzenepropanoic acid
62596-63-8 (βS)-β-(Aminomethyl)benzenepropanoic acid
1256483-50-7 Benzenepropanoic acid, β-(aminomethyl)-, hydrate (1:1) (ACI)
3060-41-1 Benzenepropanoic acid, β-(aminomethyl)-, hydrochloride (1:1)
52992-48-0 Benzenepropanoic acid, β-(aminomethyl)-, hydrochloride (1:1), (βR)-
52950-37-5 Benzenepropanoic acid, β-(aminomethyl)-, hydrochloride (1:1), (βS)-
103095-38-1 Benzenepropanoic acid, β-(aminomethyl)-, hydrobromide (1:1)
2265218-18-4 Benzenepropanoic acid, β-(aminomethyl)-, lithium salt (1:1)
1201689-48-6 Benzenepropanoic acid, β-(aminomethyl)-, potassium salt (1:1)
697285-57-7 Benzenepropanoic acid, β-(aminomethyl)-, ethanedioate (2:1)
1379536-43-2 Benzenepropanoic acid, β-(aminomethyl)-, (2Z)-2-butenedioate (2:1)
1379536-45-4 L-Glutamic acid, β-(aminomethyl)benzenepropanoate (1:2)
697285-58-8 Butanedioic acid, 2-hydroxy-, compd. with β-(aminomethyl)benzenepropanoate (1:2)
1379536-44-3 3-Pyridinecarboxylic acid, compd. with β-(aminomethyl)benzenepropanoate (1:1)
1393708-43-4 Benzoic acid, 2-hydroxy-, compd. with β-(aminomethyl)benzenepropanoate (1:1)
697285-55-5 Benzenepropanoic acid, β-(aminomethyl)-, 2-hydroxy-1,2,3-propanetricarboxylate (3:1)
131420-80-9 4-Pyrimidinecarboxylic acid, 1,2,3,6-tetrahydro-2,6-dioxo-, mono[β-(aminomethyl)benzenepropanoate]

C. Other Chemical Names

Hydrocinnamic acid, β-(aminomethyl)- (6CI, 7CI, 8CI)
β-(Aminomethyl)benzenepropanoic acid (ACI)
(±)-Fenibut
(±)-β-Phenyl-GABA
3-Phenyl-4-aminobutanoic acid
4-Amino-3-phenylbutanoic acid
4-Amino-3-phenylbutyric acid
DL-4-Amino-3-phenylbutanoic acid
DL-β-Phenyl-γ-aminobutyric acid
Anvifen
Fenibut
Fenigam
Fenigama

P-GABA
Phenibut
Phenigam
Phenybut
Phenygam
PhGABA
β-Phenyl-GABA
β-Phenyl-γ-aminobutyric acid
γ-Amino-β-phenylbutyric acid

D. Trade Names

Anvifen
Fenibut
Bifren
Noofen
Phenyl-GABA
From the REGISTER OF MEDICINES OF RUSSIA® RLS® (RLS®, 2017):
Phenibut-Akrikhin
Phenibut-VERTEX
Phenibut-LekT
Phenibuta tablets
PHENORABIN®

Phenibut is marketed (brand names as the racemic HCl salt Anvifen, Fenibut, Bifren, and Noofen and as citrate Citrocard) in Russia and several other eastern European countries (Kent et al., 2020).

Phenibut is available as a medication in the form of tablets, capsules or powder for oral administration ["Фенибут (Phenybutum)" Fenibut (Phenybutum)]; it has also been reported as a solution at a concentration of 10 mg/mL for infusion (Kent et al., 2020).

Phenibut is available as a supplement from many online stores and e-commerce sites.

E. Street Names

Fenibut
Pbut
Noofen
Phenigam
PhGABA
Pgaba
Phenigamma
Phenygam
Party Powder
Smart Pill

Brain Booster
Russian Wonder Drug
Soviet Smart Drug

F. Physical Appearance

Phenibut formulations include tablets, powder and fine crystals (phenibut HCL) (white).

Free base: white solid (Ghislieri et al., 2015); orange solid, m.p. 188-190 °C (C. R. M. D'Oca, 2017).

Phenibut HCl: crystalline solid (Cayman, 2016).

G. WHO Review History

Phenibut has not been formally reviewed by WHO and is not currently under international control. Phenibut has been under ECDD surveillance due to reports from Member States of its abuse potential and dependence potential. A pre-review was initiated following a proposal with supporting information from members of the Expert Committee regarding published reports on dependence, abuse, and toxicity.

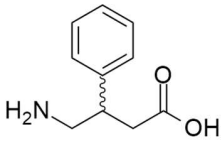
2. Chemistry

A. Chemical Name

IUPAC Name: 4-Amino-3-phenylbutanoic acid
CA Index Name: Benzenepropanoic acid, β-(aminomethyl)- (9CI, ACI)

B. Chemical Structure

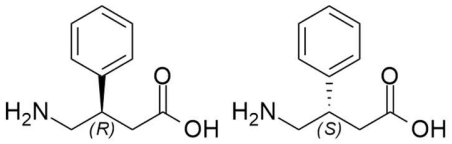
Free base:



Molecular Formula: $C_{10}H_{13}NO_2$
Molecular Weight: 179.22 g/mol

C. Stereoisomers

The presence of a chiral center at the β-carbon gives rise to the enantiomeric pair of (3*S*)- 4-Amino-3-phenylbutanoic acid ((*S*)-phenibut) and (3*R*)- 4-Amino-3-phenylbutanoic acid ((*R*)-phenibut), respectively. However, phenibut are used clinically as racemate.



D. *Methods and Ease of Illicit Manufacturing*

Phenibut was synthesized by Perekalin and his associates at the Department of Organic Chemistry of the Herzen Pedagogic Institute in St. Petersburg, the Russian Federation. In initial publications phenibut was known as phenigamma (Lapin, 2001, V. V. Perekalin, 1954).

All reported synthetic procedures require the use of chemical reagents, which are easy to be purchased, but they have to be carried out in a well-equipped chemical laboratory and by specialized personnel.

In particular, the synthetic process employed by Perekalin et al. involved a condensation of (2-nitrovinyl)benzene with diethyl 2-(2-nitro-1-phenylethyl)malonate to give diethyl 2-(2-nitro-1-phenylethyl)malonate, that is subjected to hydrogenation in the presence of Raney nickel giving ethyl 2-oxo-4-phenylpyrrolidine-3-carboxylate. This refluxed with HCl give phenibut.

Since the first patent by Perekalin et al., numerous synthetic pathways of phenibut have been the subject of scientific publications and patents (J. Cologne, 1962, Cignarella et al., 1968, G. A. Gareev, 2002, Y. Su, 2011, V. Liepins, 2015) (M. P. Zelenov, 2001).

Recently a flow-reaction method of phenibut was published with a yield of 65% which includes 5 steps (Ghislieri et al., 2015). This type of synthesis requires a particular instrumental equipment and allows to obtain phenibut not in a single batch, but in a continuous flow. Such instrumentation is not easy to be acquired and the procedure cannot be performed by non-specialized users.

Although phenibut is utilized clinically as a racemic compound, (*R*)-phenibut has been shown to be the biologically active isomer from pharmacological studies (Allan et al., 1990, Zvejniece et al., 2015).

Two methods have been reported before 1990 where phenibut has been resolved by fractional crystallization of the cinchonidine salts and α-methylbenzylamine salts of the N-carbobenzyloxy protected racemate (SobocjDska et al., 1974). This is a simple method to obtain the single enantiomers of phenibut as it does not require specialized equipment or personnel.

Another synthetic strategy proposed the use of an enzyme (α-chymotrypsin) in a buffered solution at pH 7.4 to eventually obtain the pure enantiomer (*R*)-phenibut. (Felluga et al., 2005).

Other synthetic strategies tried to simplify the procedure reducing the number of steps, but they all required a well-equipped synthetic chemistry laboratory (Biewenga et al., 2019, C. R. M. D'Oca, 2017) (Biswas et al., 2014) (Liu et al., 2017) (V.V. Sivchik, 2012). .

Also, several methods for the resolution of racemic 3-aryl-4-aminobutyric acids into *R*- and *S*-enantiomers are documented in literature. These are mainly chromatographic separations with or without preventive protection (Allan et al., 1990, Langlois et al., 1996, Zelle, 1991, Vaccher et al., 1991) (G. Veinberg, 2007). Some methods reported a separation

by preferential crystallization of diastereoisomeric salts using optically active bases cinchonidine or L-(-)-α-methylbenzylamine as the resolution agent (M. Sobocinska, 1979, A. F. Wildervanck, 2000). Such methods involve the use of specific and specialized equipment of a preparative chiral chromatography laboratory.

E. Chemical Properties

Melting point

Racemate: 209 °C (V. V. Perekalin, 1954); 206 °C (Sattur, 1956).

(*S*)-phenibut: 194-196 °C (Allan et al., 1990); 190-191 °C (Felluga et al., 2005); 193 °C (Langlois et al., 1996).

(*R*)-phenibut: 190-191 °C (Felluga et al., 2005); 193-194 °C (Allan et al., 1990); 193 °C (Langlois et al., 1996).

Boiling point

No information could be identified.

Solubility

Free base: 35 mg/mL in DMSO (195.29 mM) at 25 °C (SellekChem, 2019).

Hydrochloride salt (Cayman, 2016): 25 mg/ml in DMF; 20 mg/ml in DMSO; 14 mg/ml in ethanol; 10 mg/mL in PBS (pH 7.2).

F. Identification and Analysis

The analysis of phenibut can be pursued by several methods. Some authors described the measurement of phenibut concentrations in solution by means of an ion-selective membrane containing poly(vinyl chloride) (PVC), plasticizer (dioctyl phthalate (60.0-75.0)), and an electrode-active substance (trioctoxybenzolsulfonate γ-amino acid β-phenylbutyric acid (0.05-5.00)) (G. L. Starobinets, 1985).

On the same line, Veveris and Luse determined phenibut concentration in alkaline DMSO solution by differential potentiometric titration; the method was based on Pt or glassy-calomel electrode (A. Veveris, 1990).

Phenibut was also analyzed in its mixture with orotic acid with a spectrophotometric method by combining UV-spectrophotometry and color reaction of the amino group with 2,4,6-trinitrobenzenesulfonic acid (A. Veveris, 1991).

Other methods reported in the literature are based on chromatographic techniques and are herein reported.

Grinberga et al. developed a high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method for the quantification of phenibut in biological matrices (Grinberga et al., 2008).

HPLC-MS/MS was also used to determine phenibut in urine after either acidic hydrolysis or dilution of the sample (Azaryan et al., 2016). The LOQ was set at 0.2 ng/mL and the linear range was 0.5-50 ng/mL. The highly sensitive analytical system ensures its use for the determination of narcotic preparations within a certain time after their intake, which may be of particular importance for forensic examinations.

HPLC coupled to high-resolution mass spectrometry (HPLC-HRMS) was used to analyze phenibut in urine samples from portable stand-alone urinals in a city center on a monthly basis over 5.5 years (Archer et al., 2020). The study was aimed to determine long-term trends in the use of new psychoactive substances.

Another HPLC method, but coupled to a UV detector (205 nm) was developed by Smirnova et al. in 2020 (Smirnova et al., 2020).

Gas chromatography coupled to mass spectrometry (GC-MS) fails in providing correct identification and quantification of the drug of interest because of unwanted phenomena of thermal degradation, cyclisation and/or side reactions. Lee et al. overcame these issues either after derivatization of phenibut or by decreasing the temperature in the injector port to 200 °C and maintaining the GC oven temperature below 190 °C (Lee et al., 2017).

Tyurenkov et al. used an ion-pair chromatography method with a RP-C18 column and UV detection (210 nm) for the quantitative analysis of phenibut in rat plasma (Tyurenkov et al., 2011). The linear range was 1-200 µg/mL.

Synthetic phenibut and its enantiomers were also characterized by ^{1}H NMR, ^{13}C NMR, IR, UV, optical rotatory power and circular dichroism (Ghislieri et al., 2015, C. R. M. D'Oca, 2017, Allan et al., 1990, Felluga et al., 2005, Biewenga et al., 2019).

Chromatographic methods were also employed for chiral resolution of the (*R*)- and (*S*)- enantiomers of phenibut. In particular, Vaccher et al. presented a cyclodextrin capillary electrokinetic chromatography achieving complete resolution with 25 mM phosphate buffer at pH 2.5 containing 3 (w/v) of highly sulfated cyclodextrins at 25° with an applied field of 0.30 kV/cm and capillaries dynamically coated with polyethylene oxide (Vaccher et al., 2006).

Sobocinska et al. developed a fractional crystallization of the cinchonidine salt of the N-carbobenzyloxy derivative of phenibut followed by removal of the protecting group by hydrogenolysis on a Pd catalyst (M. Sobocinska, 1979).

Highly stable Zr-based metal-organic frameworks (MOFs) proved to be efficient chiral stationary phases for RP-HPLC (Jiang et al., 2021).

3. Ease of Convertibility Into Controlled Substances

It is not known from the literature that phenibut can be converted into a controlled substance.

4. General Pharmacology

A. Routes of administration and dosage

Phenibut (40-98% purity) (Downes *et al.*, 2015; Wong *et al.*, 2015) is available as a powder, crystals or capsules in 200-500 mg doses via online websites (Liftmode, 2021). According to a U.S. CDC report (described later), phenibut is predominantly orally ingested (93.2%) but is sometimes inhaled (2.8%) and other routes of administration have also been

documented (i.e., dermal (4%))(Graves and CDC, 2020). The recommended therapeutic dose is between 250-750 mg per day (pipelinepharma, 2021). Consumption for recreational use ranges from 1000-2000 mg per day, but it is sometimes recommended that it is used only 2-3 days a week (interspersed with drug-free days) as tolerance to the drug occurs rapidly, and that no more than 1000 g is consumed over a 24-hour period (pipelinepharma, 2021). It is also sometimes recommended that women take smaller doses. Nonetheless, reports show that much higher amounts are consumed such as up to 8, and even as high as 16 grams daily (Samokhvalov *et al.*, 2013; Joshi *et al.*, 2017).

In 40.2% of the cases of adult exposure reported to the American Association of Poison Control Centers phenibut was ingested with one or more additional substances (Graves and CDC, 2020).

B. Pharmacokinetics

Information on the pharmacokinetics of phenibut is limited. Lapin 2001 (Review) states that phenibut is not metabolized following intravenous administration to either rabbits or rats and that it is largely excreted unmetabolized in the urine by glomerular filtration in rats, rabbits, cats and dogs (Lapin, 2001). Further, it is stated that phenibut was found in the liver, kidneys, brain, blood and urine following intravenous administration that dissipated to trace levels by 3 hours post-injection. In humans, 65% of a 250 mg oral dose was unmetabolized and excreted in urine and its clearance mimicked creatinine clearance. The plasma half-life was found to be 5.3 hours. In the published review by Lapin et al 2001 none of these statements include references, preventing examination of the primary studies (Lapin, 2001). All other literature discussing any of these effects cites Lapin 2001. Grinberga et al have reported that phenibut is found in rat brain tissue 1 hour following intraperitoneal administration of 100 mg/kg daily for 3 days (Grinberga et al., 2008).

Recreational users report the onset of effects within 2 to 4 hours following oral administration, with peak 'high' effects occurring approximately 6 hours after ingestion. The duration of effects lasts anywhere from 15 to 24 hours (Owen et al., 2016).

C. Pharmacodynamics

Phenibut is structurally and functionally similar to the GABA derivatives, gabapentin and baclofen. Phenibut is a GABA agonist that crosses the brain blood barrier more readily than GABA itself. This is due to the presence of a phenyl group on the beta carbon (Maslova and Khaunina RA, 1967). The affinity of phenibut for the GABA B receptor is approximately 15 times lower than the GABA B agonist, baclofen (Dambrova et al., 2008).

Baclofen is used to treat anxiety, alcohol dependence and muscle spasticity (Morley et al., 2014), while gabapentin is used as an anti-epileptic and also to treat neuropathic pain (Kukkar et al., 2013). Like its structural analog baclofen, evidence shows that phenibut acts as a GABA B receptor agonist (Buu and Van Gelder, 1974), and thus some of its actions are thought to reflect its interactions at the GABA B metabotropic G protein–coupled receptor, the primary means of inhibitory neurotransmission within the brain. Similarly to GABA and its

analogs, phenibut was shown to reversibly reduce the firing rate of isolated cat neurons (Davies and Watkins, 1974).

In a comprehensive set of experiments conducted in rodents Dambrova et al. examined the comparative pharmacological activity of optical isomers of phenibut (Dambrova et al., 2008). Administration of racemic phenibut and its R-enantiomer showed dose-dependent decreases in open field activity, increased analgesia in the antinociception test and decreased immobility during the forced swim test. Pretreatment with a GABA B antagonist blocked these effects. The S-enantiomer showed low to no effects. Results are congruent with the antidepressant and anxiolytic properties of phenibut. GABA B agonists such as baclofen are used to treat spasticity however, much higher doses (30- fold higher) of phenibut were needed to impact muscle function than were needed to affect open field behavior. Given its minimal effect on muscle function, the authors hypothesize that an unexplored potential clinical avenue for phenibut may be in treating disorders wherein muscle relaxation is not required

Radioligand binding studies conducted within the same set of experiments as above showed that baclofen, racemic phenibut and R-phenibut demonstrated an affinity for GABA B receptors, with Ki constants of 6 ±1, 177±2 and 92±3 μM, respectively, while the S-enantiomer did not bind to GABA B receptors (Dambrova et al., 2008). Phenibut's actions on GABA B receptors have been shown to activate an outward-rectifying potassium current, suppressing the generation of action potentials (Irie, Yamazaki and Kikura-Hanajiri, 2020), highlighting its depressant properties.

Importantly however, although phenibut binds directly to the GABA B receptor (Dambrova et al., 2008), phenibut also has high affinity for the α2–δ subunit of voltage dependent calcium channels (VDCCs) (Zvejniece et al., 2015), which is the same mechanism associated with the anti-nociceptive properties of gabapentin. Data show that the binding affinity of R-phenibut for the α2–δ subunit of the VDCC is 4 times higher than its affinity for the GABA B receptor. Calculated Ki values of 23±6 μM, 39±5 μM and 156±40 μM were observed for R and S-phenibut and baclofen, respectively. Further, in rodent models testing the anti-nociceptive effects of R-phenibut, it was shown that antagonism of the α2–δ subunit of the VDCC blocked the anti-nociceptive effects of phenibut while GABA B antagonism did not (Zvejniece et al., 2015). In other words the anti-nociceptive effects were not mediated by phenibut's activity at the GABA B receptor, rather its effects at the α2–δ subunit of the VDCC. Thus, in line with its structural similarity to gabapentin, phenibut also behaves in a functionally similar manner and may be a suitable candidate to treat neuropathic pain.

Lapin 2001 discusses actions of phenibut at the GABA A receptor, which is a major mechanism of action of benzodiazepines (Lapin, 2001). However, there is no available literature showing that phenibut has actions at the GABA A receptor. In other literature discussing phenibut's actions at the GABA A receptor Lapin 2001 is cited, however, the primary study cited by Lapin was not accessible.

5. Toxicology

Although it is noted by Kupats 2020 et al, and others, that phenibut has a therapeutic index of 90 (Kupats et al., 2020), the information used to calculate the index is not available. Kupats et al 2020 cites the Lapin 2001 review. Lapin 2001 states that the acute median lethal dose (LD50) is 900 mg/kg following intraperitoneal administration in mice but the original study is not cited. The median effective dose (ED50) is 10 mg/kg (Dambrova et al., 2008).

Phenibut is not detected in routine urine toxicology screens (Joshi et al., 2017; Li and Madhira, 2017; Sankary, Canino and Jackson, 2017). Its concentration can be detected using liquid chromatography mass spectrometry (Downes et al., 2015), however this technique is not readily available in emergency room situations. Thus, medical personnel have typically relied upon any available history and/or reports provided at the time of emergency room (ER) admittance to gather information on quantity of phenibut consumed and when last consumed (O'Connell et al., 2014; Sankary, Canino and Jackson, 2017; Ahuja et al., 2018; Hardman, Sprung and Weingarten, 2019). Further, little is widely known to medical personnel about the withdrawal syndrome associated with abstinence or the symptoms of overdose. This makes it difficult to determine whether an individual presenting at the ER needs treatment for withdrawal or overdose (Hardman, Sprung and Weingarten, 2019) (Review).

Phenibut intoxication has presented with depressive symptoms (i.e., decreased level of consciousness, muscle tone, stupor, depressed respiration, temperature dysregulation, hyper- or hypotension and tachycardia. However, in other cases individuals have presented with psychomotor agitation, hallucinations, seizures, and delirium (Hardman, Sprung and Weingarten, 2019; McCabe et al., 2019) (Review). In some cases severe behavioral agitation has necessitated heavy sedation requiring airway protection with endotracheal intubation (Downes et al., 2015; Wong et al., 2015; Joshi et al., 2017; Li and Madhira, 2017). In a study reporting on the clinical effects of phenibut exposures at a poison control center, a 19.6% intubation rate was observed in a total of 56 calls (McCabe et al., 2019). There is a large variability in doses leading to toxicity, with doses of 3 grams daily for 4 days, and an acute 30 gram dose both implicated in phenibut intoxication (O'Connell et al., 2014; Wong et al., 2015). Generally, phenibut intoxication is resolved within 24 hours (Owen et al., 2016).

Two cases of analytically-confirmed phenibut toxicity are described by Downes et al (Downes et al., 2015). In case 1, a 20-year old female presented to the ER exhibiting decreased consciousness, with delirium when roused. Evidence was provided upon admittance of phenibut use. Supportive care was provided without intervention. The patient recovered within 24 hours and reported online purchase and use of 25 g of phenibut in 3 doses the day prior to ER admittance. Plasma phenibut concentration was 29.7 mg/ml.

In case 2, a 38-year-old male presented to ER exhibiting agitated delirium. Information provided upon admittance was that the patient had co-ingested phenibut,

alcohol and tetrahydrocannabinol. To reduce his extreme behavioral agitation he was heavily sedated with multiple medications over the next 24 hours and thus required intubation. The next day he confirmed recreational use of phenibut while consuming alcohol. Plasma phenibut concentration was 36.5 mg/ml on admission and 8.92 mg/ml 17 hours afterwards. In neither case was other toxicological testing performed.

A case of presumed toxicity is described in a young adult alcohol-dependent male with depression (O'Connell et al., 2014). The patient was found unconscious and taken to the ER. Examination revealed a depressed level of consciousness while vital signs and routine laboratory testing were within normal limits and EKG, computerized tomography scan, and chest radiographs were unremarkable. The patient reported consuming 3 grams of phenibut per day for 4 days. In this case phenibut was purchased from the internet (unknown purity), and use was not biologically confirmed. The patient denied other drug use, and was negative for alcohol. The patient was taking therapeutic doses of venlafaxine and mirtazapine, with the authors suggesting a possible interaction or potentiation between phenibut and the neuroleptics.

In an abstract presented at the Annual Meeting of the North American Congress of Clinical Toxicology (NACCT), 4 cases of presumed phenibut toxicity reported to a poison center were presented with little available details (Marraffa et al., 2014). One of the cases was complicated by withdrawal. All patients recovered within 24 hours (Marraffa et al., 2014).

Sankary et al 2017 describe a case of a 25-year old male presenting to the ER with a decreased level of consciousness (Sankary, Canino and Jackson, 2017). A friend of the patient indicated that the patient had used phenibut pills recreationally that were purchased from the internet. The patient was treated with intravenous fluids to enhance excretion and left the hospital against medical advice (Sankary, Canino and Jackson, 2017).

Li and Madhira describe a case wherein phenibut's toxic effects and abstinence effects were difficult to differentiate (Li and Madhira, 2017). A 24-year old male with a history of anxiety and attention deficit hyperactivity disorder (ADHD) presented to the ER with severe agitation and psychosis. The patient routinely consumed multiple supplements and anabolic steroids and was taking dextroamphetamine to treat his ADHD. The patient was consuming up to twenty 250 mg tablets of phenibut daily for the prior 2 months. Urine toxicology was negative except for amphetamine. Due to the extreme agitation the authors speculate that the patient was suffering from withdrawal, despite not having reduced intake of phenibut, rather than toxicity, which generally manifests in respiratory depression and lethargy (O'Connell et al., 2014; Sankary, Canino and Jackson, 2017).

Li and Sundararajan 2015 describe a case of a 44-year old man who regularly took 500-1500 mg of phenibut per day but increased his dose due to tolerance (Li and Sundararajan, 2015). Phenibut was accessed from the internet. The patient had a significant history of hospital visits related to overdosing phenibut. He presented to the ER in an agitated state with a fluctuating level of consciousness. Despite pharmacotherapy with

benzodiazepines, he became increasingly agitated and was intubated and sedated. He experienced a hypertensive crisis and developed pneumonia. By day 3 he was able to be weaned off of sedatives but still had some anxiety and headaches.

Isoardi et al 2020 describe a case cluster of phenibut poisoning among five teenage boys (Isoardi, Kulawickrama and Isbister, 2020). While attending school the boys ingested multiple capfuls of phenibut powder, accessed through the internet. All of the boys showed severe symptoms of agitation. Four of the boys showed fluctuating episodes of sedation with 3 progressing to coma. All patients had to be intubated to protect the airway and manage agitated behavior. Four patients were extubated uneventfully within 24 hours while one patient continued to have symptoms and was finally extubated after 4 days. Phenibut use was confirmed by liquid chromatography/quadrupole time-of-flight mass spectrometry.

6. Adverse Reactions in Humans

The WHO's VigiAccess has been monitoring phenibut use since 2012. Twenty one adverse drug reactions (ADRs) were reported in 2019 and 14 ADRs were reported in 2020. Three have been reported in 2021 as of July 26, 2021. Since its listing in VigiAccess (2012), the majority of phenibut ADRs have occurred in males (83%) between the ages of 18-44 years (also 83%) within the Americas (55%) and Europe (28%), in countries wherein phenibut is not approved for clinical use. Reported ADRs in the order of highest to lowest were: nervous system disorders (17); psychiatric disorders (13); general disorders and administration site conditions (13); injury, poisoning and procedural complications (9); cardiac disorders (5); investigations (5); vascular disorders (5); musculoskeletal and connective tissue disorders (4); respiratory, thoracic and mediastinal disorders (3); skin and subcutaneous tissue disorders (3); eye disorders (2); gastrointestinal disorders (2); infections and infestations (2); metabolism and nutrition disorders (2); renal and urinary disorders (2); and social circumstances (1) (World Health Organization, 2021).

In the U.S. where phenibut is not FDA-approved as a pharmaceutical drug, but legal to possess, the Center for Disease Control (CDC) conducted an analysis of phenibut exposures reported to poison centers from 2009 to 2019. Exposures were extracted from the national database maintained by the American Association of Poison Control Centers (Graves and CDC, 2020). Exposures were captured from calls made to poison centers using the search terms 'phenigam' (from 2009-19); then in 2012 '4-Amino-3-phenylbutyric acid' was added as a search term; and in 2015 'phenibut' was added. Over the 10-year period 1320 phenibut exposures were reported, with numbers increasing over the years as search terms were added. Exposures were not biochemically confirmed. The majority of exposures occurred in young adult males. According to the report, adverse effects include drowsiness or lethargy (29.0%), agitation (30.4%), tachycardia (21.9%), and confusion (21.3%). Coma was reported in 6.2% cases, including one involving an adolescent. In 49.6% of cases, exposure resulted in moderate effects (i.e., no long-term impairment). In 12.6% of cases, exposure resulted in major effects (i.e., life-threatening or resulting in significant disability). Three deaths were reported. In 29.6% of cases co-exposure to other drugs or agents occurred in individuals less than 18 years of age and in 40.2% of all adult cases. In exposures

wherein phenibut was used in isolation, 10.2% were associated with major effects, including one death.

One death that occurred in Russia in a male child (age 2-14) is reported in UNODcP (UNODC, 2021). The child orally ingested a combination of phenibut, the cannabinoid agonist, JWH-081 and potentially other substances.

There are no randomized controlled trials of phenibut for any indication. In a review, that reported on open-label trials, adverse events were reported to be low. Kupats et al, 2020 summarizes the results of 11 phenibut clinical trials (583 patients) and reports that 5.66% of patients reported adverse events with the most commonly reported event being somnolence (1.89 %). None of the clinical trial reports discussed in the review are available in English and none of the abstracts contain statistical analyses, preventing further analysis of these studies (Kupats et al., 2020). Fourteen case reports wherein phenibut was purchased on the internet and used without medical supervision and at higher doses than medically indicated were also reviewed by Kupats et al 2020. Adverse effects in these case studies included cardiovascular effects, insomnia, severe anxiety and agitation, hallucinations, depressed level of consciousness, decreased muscle tone, respiratory effects, temperature dysregulation, seizures, and delirium. The published and available case studies summarized in Kupats et al 2020 are described in this report.

7. Dependence Potential

A. Animal Studies

There are no studies conducted in animals examining phenibut's dependence potential.

B. Human Studies

The available literature suggests that phenibut use can lead to escalating dosage (tolerance), taking more drug than intended, and not being able to stop using, all of which are signs of dependence. Many of the internet sites that promote and/or sell phenibut are warning their clientele of these possibilities (Hennselmans, 2014; Liftmode, 2021). Tolerance to the drug has been reported in as short as one to two weeks contributing to its potential addiction liability (Owen et al., 2016). Others report that tolerance can be observed in as little as five days (unknown original source; (Van Hout, 2018)).

A cardinal feature of dependence is the presence of an abstinence syndrome with abrupt cessation. Abrupt discontinuation of phenibut induces a withdrawal syndrome which can be severe and require hospitalization. This is likely due at least partially to downregulation of GABA B receptors during chronic use. Phenibut withdrawal symptoms include insomnia, psychomotor agitation, delusions, psychosis, disorganized thought patterns, auditory/visual hallucinations, overwhelming anxiety, depression, fatigue, dizziness, seizures, decreased appetite, nausea and vomiting, palpitations, tachycardia (Hardman, Sprung and Weingarten, 2019; Zheng, Khan and Espiridion, 2019).

Hardman et al 2019 conducted a literature search to identify the presence and severity of a phenibut abstinence syndrome. Ten cases of phenibut withdrawal, plus a new case study presented by the authors, were described. In 7 of the 11 cases co-ingestion of other substances occurred. Several of the cases described by Hardman et al 2019 are conference proceedings/abstracts containing limited information (Goertemoeller et al., 2015; Huntington et al., 2015; Elamin et al., 2016; Deyo et al., Unkown; Teter, Varne and Kruse, Unknown). The published case studies are described briefly below.

Magsalin and Khan, 2010 describe a case report of a healthy male who experienced withdrawal from phenibut that was similar to benzodiazepine withdrawal (Magsalin and Khan, 2010). The patient took 1 g of powdered phenibut in a glass of water for 10 days to self-treat Restless Legs Syndrome. Phenibut was accessed from the internet and purity was unknown. The patient experienced relief of symptoms. The patient abruptly stopped taking phenibut and within hours experienced nervousness, psychomotor agitation, irritability, tension, fatigue, loss of appetite, heart palpitations, nausea, and insomnia. The patient tested whether his symptoms were withdrawal-related by taking ½ gram of phenibut. The patient experienced relief from symptoms and therefore continued to wean himself off of phenibut over the course of 4 days. Use of phenibut was not biochemically verified.

Samokhvalov et al 2013 describe a case of phenibut WD wherein the patient used 8 grams daily to self-medicate anxiety, dysphoria, insomnia and alcohol craving (Samokhvalov et al., 2013). Concomitant medications included 18 grams of daily kratom. The report states that use of both substances was biochemically verified in the laboratory but the methodology was not described. The patient was unable to quit taking phenibut on his own because he experienced severe anxiety, anger and irritability. Thus, he sought medical assistance. Kratom use was discontinued without intervention with the patient experiencing only mild WD symptoms. Over the course of 9 weeks, baclofen was titrated upwards while tapering down phenibut dose to manage alcohol craving, anxiety and irritability. Over the next 15 weeks, baclofen dose was reduced while citalopram was added to mitigate symptoms.

Joshi et al 2017 describe a case of phenibut intoxication and prolonged withdrawal presenting with agitated delirium (Joshi et al., 2017). A 32-year old male in a dissociative state was brought to the ER following a suicide attempt. The patient reported not having slept for 4 nights. The patient reported 8-10 g/day of phenibut use escalating to approximately 16 g/day in the week prior to hospitalization. The patient was co-using self-injected anabolic steroids. Blood alcohol and urine toxicology reports were negative. The patient was treated with a series of benzodiazepines and intravenous fluids and symptoms remitted. On the second day the patient required intramuscular antipsychotics to treat a growing agitation, insomnia, and disorganized thought patterns. Additional benzodiazepines were administered but symptoms worsened. The patient was then taken off of benzodiazepines and baclofen was administered on the third day. To improve sleep, 8 mg ramelteon was also administered. By day 9 the patient was in complete remission.

Ahuja et al 2018 describe a case study wherein baclofen was used successfully to treat phenibut withdrawal (Ahuja et al., 2018). A 21-year old male with a history of alcohol binging behavior and anxiety presented to the ER following 3 days of increasing anxiety, insomnia and a one-week binge drinking episode. The patient had a significant history of alcohol binging and abstaining, though he denied ever having experienced alcohol withdrawal. The patient had been taking phenibut purchased from the internet for several months at the recommended dose (1 scoop, equating to 100-300 mg). During the alcohol binge the patient added phenibut to his alcoholic drinks in escalating but unknown doses. Upon admission he was treated for alcohol withdrawal but continued to report visual hallucinations and overwhelming anxiety. Phenibut withdrawal was suspected, the patient was treated with baclofen and symptoms remitted.

Hardman et al 2019 describe the case of a 23-year-old male with an extensive polysubstance abuse history and anxiety/depression managed with the selective serotonin reuptake inhibitor, sertraline (Hardman, Sprung and Weingarten, 2019). The patient presented to the ER with hallucinations and psychomotor agitation. He reported that he had been using 4 grams of phenibut every six hours and had stopped using it 2 days prior. Phenibut use was not biochemically verified. The patient denied other current drug use, which was verified by urine toxicology. Multiple pharmacological treatments were unsuccessful in reducing worsening symptoms (i.e., lorazepam, haloperidol, diphenhydramine, melatonin, and olanzapine). He developed tachycardia, increased muscular tone, and inducible clonus. The patient became severely agitated and was physically restrained. Additional pharmacotherapies were administered (i.e., dexmedetomidine infusion, lorazepam, baclofen, and gabapentin) and over the course of the next 3 days symptoms finally abated.

8. Abuse Potential

A. Animal Studies

There are no animal studies examining the abuse potential of phenibut.

B. Human Studies

There are no human studies examining the abuse potential of phenibut.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

In the Russian Federation, where phenibut has been approved as a medicine since the 1960s, it is purportedly widely used to treat a multitude of neuropsychiatric disorders including insomnia, anxiety, depression, stress and post-traumatic stress disorder. It has also been used to treat general weakness, stuttering and vestibular disorders. It is also reported, but unsubstantiated, to be used similarly in Latvia, Estonia, Belarus, Kazakhstan and Ukraine (Kupats et al., 2020; pipelinepharma, 2021). Latvia is mentioned in New Zealand's Medical Device Safety report (New Zealand Medicines and Medical Devices Safety Authority, 2018).

Lapin 2001 reports on a placebo-controlled double-blind study conducted in psychotic patients versus healthy controls. Phenibut was administered orally at 250 to 500 mgs, three times a day over 1 to 2 weeks. Lapin states that phenibut improved intellectual function, enhanced physical strength, exhibited behavioral motivating properties and reduced weakness and tiredness. The reference provided for these statements is a study that is described earlier in the review as a preclinical study and is in Russian and unavailable (Mehilane, Rago and Allikmets, 1990).

A table of clinical indications of phenibut is provided in Lapin 2001. The table lists positive effects of phenibut on conflict, seizures, cognitive and emotional processes, learning, nystagmus, withdrawal (e.g., alcohol and morphine), neuroprotection (e.g., in trauma, edema, stress), and hypoxia. Slight or inconsistent effects were found for its effects on central muscle relaxation and memory improvement. There are only 3 references for the listed indications. The papers cited are in Russian and unavailable. All other articles refer to the Lapin 2001 review and the Kupats 2020 review when providing background information on phenibut. Neither of these reviews provides available and verifiable information on clinical indications.

Although most studies mention phenibut's nootropic properties, and it is described on the internet as a nootropic agent, only one published study examined its nootropic effects through a series of experiments conducted in mice in 1990. The article, purportedly in Russian, is inaccessible (Mehilane, Rago and Allikmets, 1990), but the results are described by Lapin 2001. The passive avoidance task was used in this study, which is used to evaluate learning and memory. The authors report that mice treated with phenibut spent less time in the environment paired with an aversive stimulus compared to untreated mice. In addition, phenibut reversed chloramphenicol-induced amnesia and enhanced performance in the swimming and rotating rod tests. Purportedly, mice became tolerant to phenibut's sedative properties while its nootropic effects were enhanced.

10. Listing on the WHO Model List of Essential Medicines

Phenibut is not listed on the 20th WHO Essential Medicines List (EML) or on the 6th WHO Essential Medicines List for Children (EMLc).

11. Marketing Authorizations (as a Medicinal Product)

A website selling phenibut states that phenibut is authorized as a medicinal product in Russia Ukraine, Belarus, and Latvia (pipelinepharma, 2021). Kupats et al 2020 also states that phenibut is authorized in these countries as well as in Estonia and Kazakhstan (Kupats et al., 2020). Information on whether other Eastern countries have authorized the use of phenibut and for what indications was not retrieved.

Phenibut is manufactured by a number of companies. In China alone there are 129 phenibut manufacturers and suppliers (Made-in-China, 2021).

12. Industrial Use

No known industrial use.

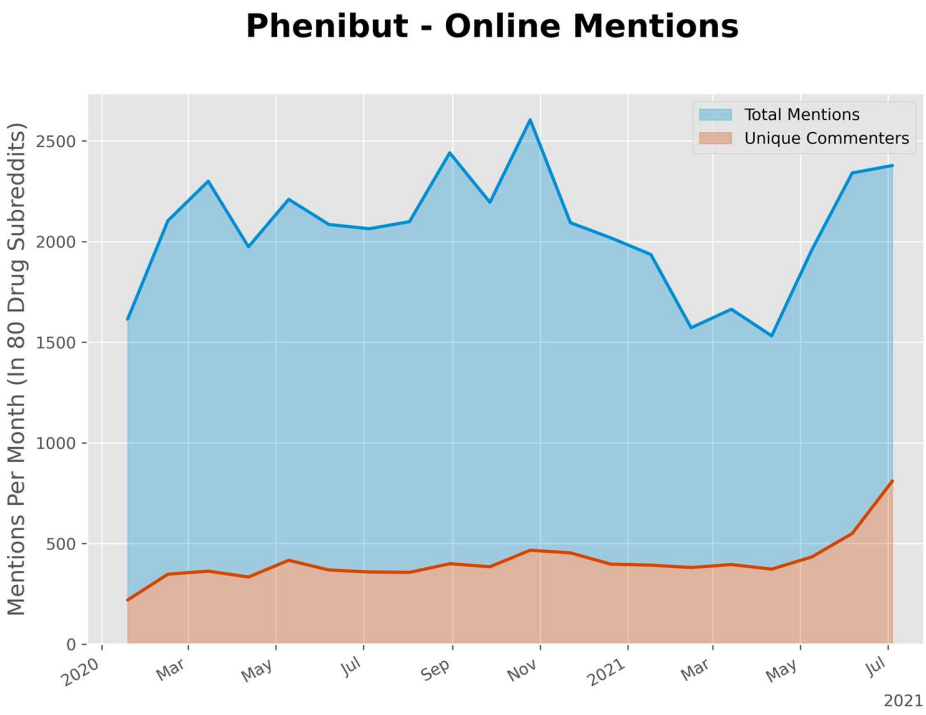
13. Non-Medical Use, Abuse and Dependence

When purchased from the internet, phenibut has a wide range of purity. Using liquid chromatography mass spectroscopy Downes et al, 2015 report ~40% purity and Wong et al., 2015 report 98% (Downes et al., 2015; Wong et al., 2015). The price varies depending on the vendor, the formulation and the quantity purchased. It generally costs between $0.30 to $2.00 per gram of powder and $0.19 to $0.34 a pill per 250 mg pill (pipelinepharma, 2021). People have reported administering up to 16 grams per day of phenibut (Joshi et al., 2017) , which is at least 16 times the recommended dose even when considering the highest doses recommended (Hennselmans, 2014; Liftmode, 2021; pipelinepharma, 2021).

Commercially available phenibut is used widely as an anti-anxiety supplement. Advertisements include phrases such as “unlock your social side” and “it is calming, mood lifting, eases stress and supports a positive, social mood.” It is also used recreationally to get high. In 56 exposure calls from 2000-2009, to a Poison Control Center in Minnesota, U.S., 48% cited ‘to abuse’ as the reason for use while 23% cited ‘to treat anxiety’ (McCabe et al., 2019). Some internet sites describe its potential to increase growth hormone citing literature from the 1980s on the potential of GABA-ergics to stimulate growth hormone production (Cavagnini et al., 1980; Hennselmans, 2014; Psychonaut, 2021).

The use of phenibut has increased rapidly in recent years. It is easily available and is described as being a ‘safe and natural’ alternative to psychiatric medication. For example, phenibut is one of the more widely discussed drugs on Reddit, the largest internet forum in existence where people discuss and comment on news, information, etc. Phenibut has its

own online forum (i.e., subreddit) (Redditt, 2021). It is mentioned ~10 times less than the most frequent terms (e.g. fentanyl), but ~10 - 100 times more than most other substances in drug subreddits (Personal communication: Paul Morris, Co-lead, U.S. National Drug Early Warning System (NDEWS). The graph (see figure below) is a compilation of Redditt comments beginning in January 2020 until present. As shown, phenibut is mentioned consistently, although the recent rise in mentions by unique commenters is outpacing the growth of Reddit in general. The "Unique Commenters" metric counts how many mentions of phenibut in a 4-week period were first mentions of the drug by commenters who had never mentioned it previously on Reddit (Personal Communication, Paul Morris). Discussion revolves around how much to take and when, how to mitigate bad effects that occur on off days, when to stop using it altogether and withdrawal effects (Redditt, 2021). Currently, much of the discussion relates to concerns that phenibut will be banned based on the WHO's placing it on the list of substances to be pre-reviewed to determine whether it should be investigated further. Many individuals describe 'stocking up' in the event that it is banned.



Many of the discussions on drug user sights such as Bluelight and Erowid describe the use of phenibut to minimize withdrawal from benzodiazepines, opiates, alcohol, etc (Bluelight.org, 2021; Erowid, 2021). There are many discussions on how it is relatively easy to become dependent on phenibut, that tolerance builds rapidly and people on these forums sometimes warn others not to try it (Bluelight.org, 2021; Erowid, 2021; Redditt, 2021). There are also discussions of its use as a sexual enhancer (in males),(Hennselmans, 2014; Liftmode, 2017), which are not clearly supported by the literature.

In a review conducted in 2015, 48 unrelated internet suppliers selling phenibut in the U.K. alone were discovered (Owen et al., 2016). A recent (July 2021) google chrome internet search using search terms 'phenibut' and 'buy' revealed 21 suppliers: Nootropics Depot; Zack attack; Liftmode; HR (Hard Rhino) Supplements; SportPoeders; Primaforce; Raw Powders; Nootropic Source; MOSPharma; Grabr; SG Asesores Industriales; Cosmicnootropic; Absorb Health; Newmind; ELV Bioscience; Intellimeds; SuperSmart; RUPharma'Science.bio; TheSmartShopOnline; Cosmic Nootropic; NutriVitaShop; [Phenibut is no longer available on Amazon or Walmart](Daniel, 2020; Morris, 2020).

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

News articles have been written, sparked by incidents such as the case of 5 adolescent boys in Australia (Isoardi, Kulawickrama and Isbister, 2020), about the nonmedical use of phenibut but the scope of the problem is not discussed (McNeilage, 2018; Mellor, 2018).

Several addiction treatment centers provide information on phenibut and offer treatment but again, the scope of the problem is not discussed (Recovery, 2019; American Addiction Centers and 2021, 2021; Nova Recovery Center, 2021).

The RADARS system does not currently acquire data on phenibut (Personal Communication, Elise
Bailey, MSPH, Client Operations Manager; RADARS® System.

15. Licit Production, Consumption and International Trade

No information on the licit production or consumption of phenibut was found, although it is a registered product in Russia.

16. Illicit Manufacture and Traffic and Related Information

No incidents involving phenibut have been communicated through IONICS to date (International Narcotics Control Board, 2021).

17. Current International Controls and Their Impact

Phenibut is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

Phenibut was relatively unknown outside of Russia until 2011 when a drug seizure in Sweden prompted an alert to the European authorities (unknown original source, reported in (Van Hout, 2018)). Due to concerns of abuse/misuse, following the seizure, the European Monitoring Centre for Drugs and Addiction noted that it is consumed as a dietary supplement and sold illegally (The European Monitoring Centre for Drugs and Drug Addiction, 2013). Following the notification to EMCDDA, phenibut was classified as a new

psychoactive substance (NPS) in 2012 by the United Nations Office of Drug and Crime (UNODC)(Van Hout, 2018).

Phenibut is approved for medical use with a prescription in Russia. It may also be approved in

Belarus, Latvia, Kazakhstan, Estonia and Ukraine (Kupats et al., 2020; pipelinepharma, 2021).

Phenibut is not controlled in the U.S. but it is unlawful for any product sold in the U.S. to contain it because it does not meet the definition of a dietary ingredient under the Federal Food, Drug, and Cosmetic Act (FD&C Act). The FDA is currently requesting public comment which will be used to prepare an evaluation of phenibut to provide to the World Health Organization (Regulations.gov, 2021). In the United Kingdom is it legal for personal use but it is illegal to supply it or sell it (unscheduled). Phenibut remains unscheduled in Canada and most of Europe. New Zealand put a request into their Medications Classification Committee but thus far it remains uncontrolled (New Zealand Medicines and Medical Devices Safety Authority, 2018).

Phenibut is listed as a controlled psychoactive substance in only a few countries. These include Hungary (Walters-Kluwer, 2021), Italy (Ministry of Health, 2020), Lithuania (MINISTER OF HEALTH OF THE REPUBLIC OF LITHUANIA, 2019) and France (Official Journal of the French Republic, 2021). In 2018, Australia declared phenibut a schedule 9 substance (prohibited substance) because 1) the perceived benefits outweigh the substantial risks; 2) its use, although prohibited in Australia is becoming increasingly prevalent as consumers access it through the internet; 3) published reports of its toxicity are showing significant risks associated with overdose and withdrawal; and 4) rapid development of tolerance and dependence (Australian Government, Office of Health, Therapeutic Drugs Administration, 2017).

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

Much of the information in the literature on phenibut has been retrieved from a review article by Lapin, 2001. Unfortunately, the article is flawed. In many places the references are not provided and in other places, they are inaccurate. For example, within Lapin 2001, there are only 3 references listed that could potentially be considered clinical trials. One is cited within the paper but not discussed. The abstract was retrievable and describes an open-label small trial (Gol'dblat and Lapin, 1986). One is listed as being published in an English indexed journal but it does not come up in a search. Further, although it is listed in the reference section of the article, it is not mentioned in the body. The reference provided only lists 1 page so it may be an abstract (Lapin, Krupitsky and Melnik, 1995). The last is cited within the body of the manuscript when discussing results of preclinical studies (Orlikov, 1994). Because other articles, including reviews, such as Kupats et al 2020 and Hardman et al 2019, cite Lapin, 2001, information that cannot be verified is

being perpetuated in the literature. Where information was not retrieved from primary studies this has been noted in this pre-review.

References

A. F. Wildervanck, M. R. C., J. L. Scott, L. R. Nassimbeni, R. Clauss, B. R. D. Easter. 2000. Process for the optical resolution of 3-(p-chlorophenyl)-glutaramide.

A. G. Chigarev, D. V. I. 1967. β-Phenyl-γ-aminobutyric acid. USSR patent application.

A. Veveris, I. L. 1990. Potentiometric differential titration of β-phenyl-γ-aminobutyric acid hydrochloride and its synthetic intermediates. Khimiko-Farmatsevticheskii Zhurnal, 24, 77-80.

A. Veveris, V. K., I. A. Birska, M. Markuns 1991. Spectrophotometric determination of orotic and γ-amino-β-phenylbutyric acids in their mixtures. Khimiko-Farmatsevticheskii Zhurnal, 25, 72-75.

Ahuja, T. et al. (2018) 'Phenibut (β-Phenyl-γ-aminobutyric Acid) Dependence and Management of Withdrawal: Emerging Nootropics of Abuse', Case Reports in Psychiatry, 2018, p. 9864285. doi: 10.1155/2018/9864285.

Allan, R., Bates, M., Drew, C., Duke, R., Hambley, T., Johnston, G., Mewett, K. N. & Spence, I. 1990. A New Synthesis, Resolution and in vitro Activities of (R)- and (S)-²-Phenyl-GABA. ChemInform, 21.

American Addiction Centers and 2021 (2021) Phenibut: A Guide to History, Side Effects & Risk of Addiction, American Addiction Centers. Available at: https://americanaddictioncenters.org/phenibut (Accessed: 23 August 2021).

Archer, J. R. H., Mendes, F., Hudson, S., Layne, K., Dargan, P. I. & Wood, D. M. 2020. Evaluation of long-term detection trends of new psychoactive substances in pooled urine from city street portable urinals (London, UK). Br J Clin Pharmacol, 86, 517-527.

Australian Government, Office of Health, Therapeutic Drugs Administration (2017) 3.3 Phenibut, Therapeutic Goods Administration (TGA). Australian Government Department of Health. Available at: https://www.tga.gov.au/book-page/33-phenibut (Accessed: 26 July 2021).

Azaryan, A., Temerdashev, A., Svetlichnaya, E., C, A. & Balabaev, I. 2016. Determination of Some Cathinones, Tropane Alkaloids, and " Pharmaceutical Narcotics " in Urine. Journal of Analytical Chemistry, 71, 955-964.

Biewenga, L., Saravanan, T., Kunzendorf, A., Van Der Meer, J.-Y., Pijning, T., Tepper, P. G., Van Merkerk, R., Charnock, S. J., Thunnissen, A.-M. W. H. & Poelarends, G. J. 2019. Enantioselective Synthesis of Pharmaceutically Active γ-Aminobutyric Acids Using a Tailor-Made Artificial Michaelase in One-Pot Cascade Reactions. ACS Catalysis, 9, 1503-1513.

Biswas, K., Gholap, R., Srinivas, P., Kanyal, S. & Sarma, K. D. 2014. β-Substituted γ-butyrolactams from mucochloric acid: synthesis of (±)-baclofen and other γ-aminobutyric acids and useful building blocks. RSC Advances, 4, 2538-2545.

Bluelight.org (2021) Search results for query: phenibut, Bluelight.org. Available at: https://www.bluelight.org/xf/search/1265872/?q=phenibut&o=date (Accessed: 23 August 2021).

Buu, N. T. and Van Gelder, N. M. (1974) 'Biological actions in vivo and in vitro of two gamma-aminobutyric acid (GABA) analogues: beta-chloro GABA and beta-phenyl GABA', British Journal of Pharmacology, 52(3), pp. 401–406. doi: 10.1111/j.1476-5381.1974.tb08609.x.

C. R. M. D'oca, F. F. N., J. C. Silva, E. P. Guedes, C. C. Moro, M. G. M. D'oca, L. S. Santos, F. M. Natchigall, D. Russowsky 2017. New multicomponent reaction for the direct synthesis of β-aryl-γ-nitroesters promoted by hydrotalcite-derived mixed oxides as heterogeneous catalyst. J. Braz. Chem. Soc., 28, 285-298.

Cavagnini, F. et al. (1980) 'Effect of gamma-aminobutyric acid on growth hormone and prolactin secretion in man: influence of pimozide and domperidone', The Journal of Clinical Endocrinology and Metabolism, 51(4), pp. 789–792. doi: 10.1210/jcem-51-4-789.

Cayman. 2016. Phenibut hydrochloride. Product information [Online]. Cayman Chemical Company. Ann Arbor, MI, USA. Available: https://www.caymanchem.com/product/9002652/phenibut-(hydrochloride [Accessed 19/07/2021].

Center, A. R. 2020. The small pill (Phenibut) [Online]. Asheville Recovery Center. Available: https://www.ashevillerecoverycenter.com/party-smart-pill-phenibut/ [Accessed 19/07/2021].

Cignarella, G., Fontanella, L., Aresi, V. & Testa, E. 1968. [Derivatives of phenylbutyrates. 3. Synthesis of compounds with potential anti-inflammatory activity correlated to 3,3'-diphenyl-N,N'-dipyrrolidine-2,2'-dione]. Farmaco Sci, 23, 321-43.

Dambrova, M. et al. (2008) 'Comparative pharmacological activity of optical isomers of phenibut', European Journal of Pharmacology, 583(1), pp. 128–134. doi: 10.1016/j.ejphar.2008.01.015.

Daniel (2020) 'Wondering Where to Buy Phenibut? A Summary of 13 Vendors That Carry The Powder and Capsules – Orgonlight Health'. Available at: https://www.orgonlighthealth.com/phenibut-powder-capsules-vendors/ (Accessed: 27 July 2021).

Davies, J. and Watkins, J. C. (1974) 'The action of beta-phenyl-GABA derivatives on neurones of the cat cerebral cortex', Brain Research, 70(3), pp. 501–505. doi: 10.1016/0006-8993(74)90258-3.

Deyo, Z. et al. (Unkown) 'Nootropic-lnduced Psychosis: A Case Report', in College of Psychiatric and Neurologic Pharmacists.

Downes, M. A. et al. (2015) 'Acute behavioural disturbance associated with phenibut purchased via an internet supplier', Clinical Toxicology (Philadelphia, Pa.), 53(7), pp. 636–638. doi: 10.3109/15563650.2015.1059945.

Elamin, M. et al. (2016) '36th International Congress of the European Association of Poisons Centres and Clinical Toxicologists, Madrid, Spain', Clinical Toxicology, 54(4), pp. 344–519. doi: 10.3109/15563650.2016.1165952.

Erowid (2021) Erowid Search Results for phenibut. Available at: https://erowid.org/search.php?exclude=&q=phenibut&x=11&y=3 (Accessed: 23 August 2021).

Felluga, F., Gombac, V., Pitacco, G. & Valentin, E. 2005. A short and convenient chemoenzymatic synthesis of both enantiomers of 3-phenylGABA and 3-(4-chlorophenyl)GABA (Baclofen). Tetrahedron: Asymmetry, 16, 1341-1345.

G. A. Gareev, V. V. B., V. A. Kovalev, V. V. Kovalev. 2002. Synthesis of 3-phenyl-4-aminobutanoic acid derivatives.

G. L. Starobinets, E. M. R. K., Yu. M. Sednev, T. I. Borshchenskaya, A. L. Pertsovskii, A. V. Bazilevich, J. Laurs, V. G. Gredin. 1986. Determination of phenybut and the composition of a membrane of the ion-selective electrode for this determination. USSR patent application.

G. L. Starobinets, E. M. R. K., Yu. M. Sednev, Ya. F. Lushchik. 1985. Composition of ion-selective electrode membrane for determining concentration of phenibut in solutions. USSR patent application.

G. Veinberg, M. V., A. Lebedevs, A. Chernobrovijs, I. Kalvinsh. 2007. Enzymatic resolution of racemic 3-aryl-4-aminobutyric acids. P-06-28 (2006) PCT/EP2007/051538.

Ghislieri, D., Gilmore, K. & Seeberger, P. H. 2015. Chemical Assembly Systems: Layered Control for Divergent, Continuous, Multistep Syntheses of Active Pharmaceutical Ingredients. Angewandte Chemie International Edition, 54, 678-682.

Goertemoeller, S. et al. (2015) 'Retrospective review of Phenibut exposures reported to Ohio poison control centers Sheila Goertemoeller, Alysha Behrman, Robert Goetz, HA Spiller', in. Annual Meeting of the North American Congress of Clinical Toxicology, p. 2.

Gol'dblat, I. V. and Lapin, I. P. (1986) '[Phenibut potentiation of the therapeutic action of antiparkinson agents]', Zhurnal Nevropatologii I Psikhiatrii Imeni S.S. Korsakova (Moscow, Russia: 1952), 86(8), pp. 1146–1148.

Graves, J. M. and CDC (2020) 'Notes from the Field: Phenibut Exposures Reported to Poison Centers — United States, 2009–2019', MMWR. Morbidity and Mortality Weekly Report, 69. doi: 10.15585/mmwr.mm6935a5.

Grinberga, S. et al. (2008) 'Quantitative analysis of phenibut in rat brain tissue extracts by liquid chromatography-tandem mass spectrometry', Biomedical chromatography: BMC, 22(12), pp. 1321–1324. doi: 10.1002/bmc.1059.

Hardman, M. I., Sprung, J. and Weingarten, T. N. (2019) 'Acute phenibut withdrawal: A comprehensive literature review and illustrative case report', Bosnian Journal of Basic Medical Sciences, 19(2), pp. 125–129. doi: 10.17305/bjbms.2018.4008.

Hennselmans, M. (2014) 'Phenibut: The Soviet smart drug', MennoHenselmans.com, 31 October. Available at: https://mennohenselmans.com/phenibut-dosage-effects/ (Accessed: 24 August 2021).

Högberg, L., Szabó, I. and Ruusa, J. (2013) '[Phenibut yielded withdrawal symptoms and psychosis. Drugs for cosmonauts--now marketed as dietary supplements online]', Lakartidningen, 110(16), pp. 825–827.

Huntington, S. et al. (2015) 'GABA GABA Hey (I wanna be sedated): Phenybut Exposures Reported', in. North American College of Clinical Toxicology.

International Narcotics Control Board (2021) IONICS. Available at: https://www.incb.org/incb/en/project_ion/ionics.html (Accessed: 29 July 2021).

Irie, T., Yamazaki, D. and Kikura-Hanajiri, R. (2020) 'F-phenibut (β-(4-Fluorophenyl)-GABA), a potent GABAB receptor agonist, activates an outward-rectifying K+ current and suppresses the generation of action potentials in mouse cerebellar Purkinje cells', European Journal of Pharmacology, 884, p. 173437. doi: 10.1016/j.ejphar.2020.173437.

Isoardi, K. Z., Kulawickrama, S. and Isbister, G. K. (2020) 'Severe phenibut poisoning: An adolescent case cluster', Journal of Paediatrics and Child Health, 56(2), pp. 330–331. doi: 10.1111/jpc.14605.

J. Cologne, J. M. P. 1962. Preparation of 2-pyrrolidones and γ-amino acids. Bull. Soc. Chim. Fr., 598-603.

Jiang, H., Yang, K., Zhao, X., Zhang, W., Liu, Y., Jiang, J. & Cui, Y. 2021. Highly Stable Zr(IV)-Based Metal–Organic Frameworks for Chiral Separation in Reversed-Phase Liquid Chromatography. Journal of the American Chemical Society, 143, 390-398.

Joshi, Y. B. et al. (2017) 'Dissociative intoxication and prolonged withdrawal associated with phenibut: a case report', Journal of clinical psychopharmacology, 37(4), pp. 478–480. doi: 10.1097/JCP.0000000000000731.

Kent, C. N., Park, C. & Lindsley, C. W. 2020. Classics in Chemical Neuroscience: Baclofen. ACS Chemical Neuroscience, 11, 1740-1755.

Kukkar, A. et al. (2013) 'Implications and mechanism of action of gabapentin in neuropathic pain', Archives of Pharmacal Research, 36(3), pp. 237–251. doi: 10.1007/s12272-013-0057-y.

Kupats, E. et al. (2020) 'Safety and Tolerability of the Anxiolytic and Nootropic Drug Phenibut: A Systematic Review of Clinical Trials and Case Reports', Pharmacopsychiatry, 53(5), pp. 201–208. doi: 10.1055/a-1151-5017.

Langlois, N., Dahuron, N. & Wang, H.-S. 1996. Enantioselective syntheses of (R)-3-phenyl GABA, (R)-baclofen and 4-arylpyrrolidin-2-ones. Tetrahedron, 52, 15117-15126.

Lapin, I. (2001) 'Phenibut (β-Phenyl-GABA): A Tranquilizer and Nootropic Drug', CNS Drug Reviews, 7(4), pp. 471–481. doi: 10.1111/j.1527-3458.2001.tb00211.x.

Lapin, I., Krupitsky, E. and Melnik, V. (1995) 'Phenibut (â-phenyl-GABA) and baclofen (chlor-Phenibut) in treatment of affective disorders in alcoholic patients.', Alcohol and Alcoholism, 30, p. 549.

Lee, H. Z. S., Ong, M. C., Lim, J. L. W. & Yap, T. W. A. (2017). Challenges in GC-MS analysis: Case studies on phenibut and ethylphenidate. Forensic Sci Int, 277, 166-178.

Li, C. and Sundararajan, K. (2015) 'An Uncommon Case of Phenibut Toxicity in an Intensive Care Unit', International Journal of Medical and Pharmaceutical Case Reports, 5, pp. 1–621689. doi: 10.9734/IJMPCR/2015/21689.

Li, W. and Madhira, B. (2017) 'Phenibut (β-Phenyl-γ-Aminobutyric Acid) Psychosis', American Journal of Therapeutics, 24(5), pp. e639–e640. doi: 10.1097/MJT.0000000000000618.

Liftmode (2017) Does Phenibut Support a Healthy Libido? Top 3 Facts Explored, LiftMode Blog. Available at: https://liftmode.com/blog/phenibut-libido-connection/ (Accessed: 23 August 2021).

Liftmode (2021) Buy The Best Brain Boosters & Dietary Supplements. Available at: https://liftmode.com/ (Accessed: 23 August 2021).

Liu, H., Yuan, J., Tian, Q., Ji, N. & He, W. (2017). An Efficient Synthesis of Enantiomerically Pure γ-Aminobutyric Acid (GABA) Derivatives. Journal of Materials Science and Chemical Engineering, 05, 25-32.

M. P. Zelenov, P. S. Z., S. I. Smirnov, N. Ya. Koryakov, Yu. A. Arevkov, V. N. Andreev, V. V. Aniskevich, A. Ya. Chukurov, M. M. Aleksandrov, V. S. Sikora, I. V. Krauklish, T. N. Grigorov. 2001. Method of preparation 3-phenyl-4-aminobutyric acid or 3-phenyl-4-aminobutyric acid chlorohydrate. Russian Federation patent application.

M. Sobocinska, M. M. Z., V. V. Perekalin, G. Kupryszewski 1979. Configuration of 4-aryl-2-pyrrolidinones and their 3-carboxy derivatives. Pol. J. Chem., 53, 435-446.

Made-in-China (2021) Phenibut Manufacturers & Suppliers, China phenibut Manufacturers & Factories. Available at: https://www.made-in-china.com/manufacturers/phenibut.html (Accessed: 27 July 2021).

Magsalin, R. M. M. and Khan, A. Y. (2010) 'Withdrawal symptoms after Internet purchase of phenibut (β-phenyl-γ-aminobutyric acid HCl)', Journal of Clinical Psychopharmacology, 30(5), pp. 648–649. doi: 10.1097/JCP.0b013e3181f057c8.

Marraffa, J. et al. (2014) 'Phenibut: One poison center's experience', Clinical Toxicology, 52, pp. 736–737.

Maslova, M. and Khaunina RA (1967) 'Penetration of gamma-aminobutyric acid and its phenyl derivative into the brain and their pharmacological effects in mice and rats during ontogenesis.', Evol Neirofiziol Neirokhim, 5, pp. 186–191.

McCabe, D. J. et al. (2019) 'Phenibut exposures and clinical effects reported to a regional poison center', The American Journal of Emergency Medicine, 37(11), pp. 2066–2071. doi: 10.1016/j.ajem.2019.02.044.

McNeilage, A. (2018) 'Drug used by cosmonauts may have caused Queensland students' overdose', the Guardian, 23 February. Available at: http://www.theguardian.com/australia-news/2018/feb/23/banned-anti-anxiety-drug-phenibut-may-have-caused-gold-coast-students-overdose (Accessed: 24 August 2021).

Mehilane, L., Rago, L. and Allikmets, L. (1990) 'Pharmacology and clinic of phenibut. Tartu: Izd. TGU, 1990 (in Russian with English summary).', Tartu: Izd. TGU, Article not available.

Mellor, L. (2018) 'The cosmonaut drug that may have caused a school overdose', ABC News, 22 February. Available at: https://www.abc.net.au/news/2018-02-23/what-is-phenibut-the-drug-suspected-in-school-overdose/9475814 (Accessed: 24 August 2021).

MINISTER OF HEALTH OF THE REPUBLIC OF LITHUANIA (2019) V-1431 Regarding the Minister of Health of the Republic of Lithuania in 2000 January 6 order no. 5 "On Narcotics ... Available at: https://e-seimas.lrs.lt/portal/legalAct/lt/TAD/9aff1ef11ce911eaadfcfdb735b57421?jfwid=-bgd9aafbv (Accessed: 26 July 2021).

Ministry of Health (2020) Official Gazette. Available at: https://www.gazzettaufficiale.it/eli/id/2020/08/21/20A04540/SG?fbclid=IwAR2NYeYWpr9u2AwfyTESbUZxtsKg7ZxLQ05X3GB7VSwH2AE4sh9AcIPKBns (Accessed: 26 July 2021).

Morley, K. C. et al. (2014) 'Baclofen for the Treatment of Alcohol Dependence and Possible Role of Comorbid Anxiety', Alcohol and Alcoholism (Oxford, Oxfordshire), 49(6), pp. 654–660. doi: 10.1093/alcalc/agu062.

Morris, W. (2020) '5 Legit Places You Can Safely Buy Phenibut From', Morris Health. Available at: https://medium.com/morris-health/places-you-can-safely-buy-phenibut-from-71d30af15cff (Accessed: 27 July 2021).

New Zealand Medicines and Medical Devices Safety Authority (2018) 5.5.1-Phenibut-submission.pdf. Available at: https://www.medsafe.govt.nz/profs/class/Agendas/Agen60/5.5.1-Phenibut-submission.pdf (Accessed: 26 July 2021).

Nova Recovery Center (2021) Phenibut Addiction: Side Effects, Detox, Withdrawal, and Treatment, Nova Recovery Center Near Austin Texas. Available at: https://novarecoverycenter.com/drugs/phenibut/ (Accessed: 23 August 2021).

O'Connell, C. W. et al. (2014) 'Phenibut, the appearance of another potentially dangerous product in the United States', The American Journal of Medicine, 127(8), pp. e3-4. doi: 10.1016/j.amjmed.2014.03.029.

Official Journal of the French Republic (2021) Search results, page 1 - Légifrance. Available at: https://www.legifrance.gouv.fr/search/all?tab_selection=all&searchField=ALL&query=phenibut&page=1&init=true (Accessed: 26 July 2021).

Orlikov, A. (1994) 'Comparison of efficacy of imipramine, diazepam, baclofen, propranolol and placebo in patients with panic disorders', Obozr Psikh Med Psikhol Bekhtereva, 4, pp. 43–48.

Owen, D. R. et al. (2016) 'Phenibut (4-amino-3-phenyl-butyric acid): Availability, prevalence of use, desired effects and acute toxicity: Phenibut and acute toxicity', Drug and Alcohol Review, 35(5), pp. 591–596. doi: 10.1111/dar.12356.

pipelinepharma (2021) Phenibut manufacturers, suppliers, distributors, Pipelinepharma. Available at: https://www.pipelinepharma.com (Accessed: 27 July 2021).

Psychonaut (2021). Available at: https://www.psychonaut.fr/portal.php (Accessed: 27 July 2021).

Recovery, L. (2019) What Is Phenibut?, Landmark Recovery. Available at: https://landmarkrecovery.com/what-is-phenibut/ (Accessed: 14 July 2021).

Redditt, P. (2021). Available at: https://www.reddit.com/r/phenibut/ (Accessed: 16 July 2021).

Regulations.gov (2021) International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; 4F-MDMB-BICA (4F MDMB-BUTICA); Brorphine; Metonitazene; Eutylone (bk-EBDB); BMDP (3,4-Methylenedioxy-N benzylcathinone); Kratom (mitragynine, 7-hydroxymitragynine); Phenibut; Request for Comments. Available at: https://www.regulations.gov/document/FDA-2021-N-0739-0001 (Accessed: 26 July 2021).

Rls® 2017. Аминофенилмасляная кислота (Acidum aminophenylbutyricum). REGISTER OF MEDICINES OF RUSSIA®.

Samokhvalov, A. V. et al. (2013) 'Phenibut dependence', BMJ Case Reports, 2013, p. bcr2012008381. doi: 10.1136/bcr-2012-008381.

Sankary, S., Canino, P. and Jackson, J. (2017) 'Phenibut overdose', The American Journal of Emergency Medicine, 35(3), p. 516.e1-516.e2. doi: 10.1016/j.ajem.2016.08.067.

Sattur, N. B. K., S. N.; Nargund, K. S. 1956. Possible plant hormones. II. Journal of the Karnatak University, 1, 56-60.

Sellekchem. 2019. Phenibut [Online]. UK. Available: https://www.selleckchem.com/datasheet/phenibut-S489200-DataSheet.html [Accessed 25/07/2021].

Smirnova, L. A., Ryabukha, A. F., Kuznetsov, K. A., Velikopol'skaya, M. V., Perfilova, V. N., Vasil'eva, O. S., Tyurenkov, I. N. & Ganicheva, L. M. 2020. Method Development for Quantitative Determination of the Gaba Derivative Solifen. Pharmaceutical Chemistry Journal, 53, 1090-1092.

Sobocjdska, M., Kupryszewski, G. & Zobaczewa, M. M. 1974. RESOLUTION OF RACEMIC BETA-PHENYL-GAMMA-AMINOBUTYRIC ACID INTO ITS ENANTIOMERS AND DETERMINATION OF THEIR ABSOLUTE CONFIGURATION. ChemInform, 5.

Teter, C., Varne, S. and Kruse, C. (Unknown) 'Phenibut: High school vital sign lows, patient woes, and poison center kudos', in Clinical Toxicology.

The European Monitoring Centre for Drugs and Drug Addiction (2013) The EU Early Warning System on new psychoactive substances (NPS) | www.emcdda.europa.eu, 2012 Annual Report on the implementation of Council Decision 2005/387/JHA. Luxembourg: Publications Office of the European Union; 2013. Available at: https://www.emcdda.europa.eu/publications/topic-overviews/eu-early-warning-system_en (Accessed: 29 July 2021).

Tyurenkov, I., Perfilova, V., Smirnova, L., Ryabukha, A., Suchkov, E. & Lebedeva, S. 2011. Development of a chromatographic method for quantitative analysis of phenibut in biological samples. Pharmaceutical Chemistry Journal, 44.

UNODC (2021) UNODC Early Warning Advisory (EWA) on New Psychoactive Substances (NPS). Available at: https://www.unodc.org/LSS/Home/NPS (Accessed: 29 July 2021).

V. Liepins, A. L., J. Revjuka. 2015. Method for producing intermediates of phenibut. Latvia patent application.

V. V. Perekalin, A. S. S. 1954. Synthesis of derivatives of γ-amino acids. Doklady Akademii Nauk SSSR, 95, 993-995.

V.V. Sivchik, H. O. G., V.L. Survilo, T.V. Trukhachova 2012. Synthesis of β-phenyl-γ-aminobutyric acid (phenibut). Фармакологический фундамент современной медицины, проблемы и пути их решения (Pharmacological foundation of modern medicine, problems and solutions).

Vaccher, C., Berthelot, P., Flouquet, N. & Debaert, M. (1991). Preparative liquid chromatographic separation of isomers of 4-amino-3-(4-chlorophenyl)butyric acid. Journal of Chromatography A, 542, 502-507.

Vaccher, M. P., Bonte, J. P. & Vaccher, C. (2006). Capillary Electrophoretic Resolution of Enantiomers of Aromatic Amino-Acids with Highly Sulfated α-, β- and γ-Cyclodextrins. Chromatographia, 64, 51-55.

Van Hout, M. C. (2018) 'A narrative review of the naturally occurring inhibitory neurotransmitter gamma-aminobutyric acid (GABA) called phenibut in dietary supplements', Performance Enhancement & Health, 6(1), pp. 33–35. doi: 10.1016/j.peh.2018.02.001.

Walters-Kluwer, H. (2021) 55/2014. (XII. 30.) EMMI Decree substances or groups of compounds classified as new psychoactive substances55/2014. (XII. 30.) EMMI rendelet az új pszichoaktív anyaggá minősített anyagokról vagy vegyületcsoportokról - Hatályos Jogszabályok Gyűjteménye. Available at: https://net.jogtar.hu/jogszabaly?docid=A1400055.EMM&searchUrl=%2Fgyorskereso%3Fkeyword%3Dphenibut (Accessed: 26 July 2021).

Wong, A. et al. (2015) 'Analytically confirmed recreational use of Phenibut (β-phenyl-γ-aminobutyric acid) bought over the internet', Clinical Toxicology (Philadelphia, Pa.), 53(7), pp. 783–784. doi: 10.3109/15563650.2015.1059944.

World Health Organization (2021) VigiAccess. Available at: http://www.vigiaccess.org/ (Accessed: 26 July 2021).

Y. Su, L. Z., Q. Zhang. 2011. Method for preparing 4-amino-3-phenylbutyric acid. China patent application.

Yu. A. Polkovnikova, A. I. S. 2018. Method for quantitative determination of phenibut in microcapsules by capillary electrophoresis. Russian Federation patent application.

Zelle, R. E. 1991. Resolution of 4-Phenyl-2-pyrrolidinone: A Versatile Synthetic Intermediate. Synthesis, 1991, 1023-1026.

Zheng, K. H., Khan, A. and Espiridion, E. D. (2019) 'Phenibut Addiction in a Patient with Substance Use Disorder', Cureus, 11(7), p. e5230. doi: 10.7759/cureus.5230.

Zvejniece, L. et al. (2015) 'R-phenibut binds to the α2–δ subunit of voltage-dependent calcium channels and exerts gabapentin-like anti-nociceptive effects', Pharmacology Biochemistry and Behavior, 137, pp. 23–29. doi: 10.1016/j.pbb.2015.07.014.

Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Data were obtained from 98 Member States (12 African Region, 12 Eastern Mediterranean Region, 37 European Region, 14 Region of the Americas, 7 South-East Asia Region and 16 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire was 9 (1 African Region, 2 Eastern Mediterranean Region, 2 European Region, 2 Region of the Americas, 1 South-East Asia Region and 1 Western Pacific Region), leaving 89 countries that agreed to provide data.

Of the 89 countries who agreed to provide data, 22 countries had information on phenibut (Table 1).

Table 1. Numbers of countries providing information on phenibut

Region	Number of countries without information	Number of countries with information on substance
African	5	0
Eastern Mediterranean	6	0
European	14	16
Region of the Americas	8	4
South-East Asia	5	0
Western Pacific	7	2
Total (67)	45	22

APPROVED MEDICAL, SCIENTIFIC OR INDUSTRIAL USE

Medical use

One country (European) reported approved human medical products containing phenibut - “Phenibut is used for anxiety, asthenia, trouble sleeping (insomnia), speech disorder and tics in children, Meniere's disease, dizziness and etc.”

Scientific use

No countries reported phenibut was being currently used in medical or scientific research (excluding use as an analytical standard) in their country (such as in clinical trials for any human or veterinary indication).

Industrial or other non-medical/non-scientific use

One country (European) reported phenibut was used for industrial or other non-medical/non-scientific purposes in their country – that phenibut was sold on the internet as a food supplement.

EPIDEMIOLOGY OF NON-MEDICAL USE

Twelve countries (9 European, 3 Region of the Americas) reported evidence of the use of phenibut for non-medical use in their country (use outside of the medical, industrial or scientific context). Six countries cited evidence from seizure data, and four countries described that phenibut was sold on the internet, sometimes as a dietary supplement.

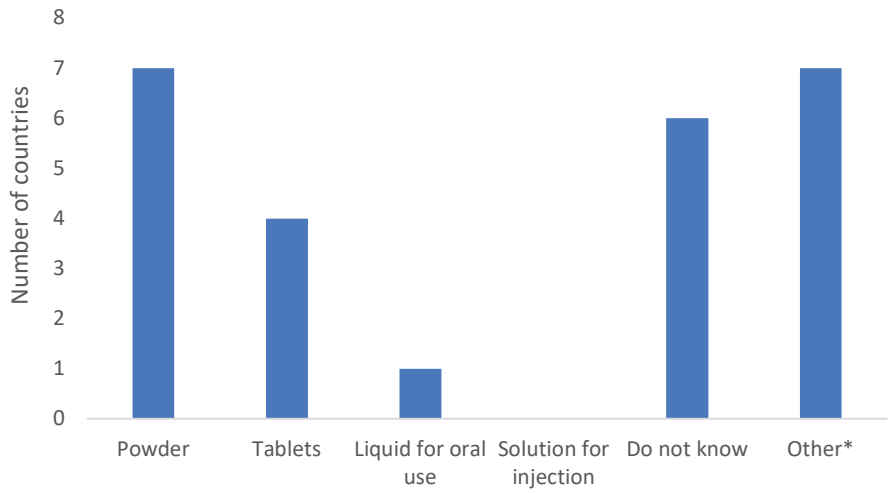
Routes of administration and formulations

The only reported route of phenibut administration was oral (Table 2), and the most commonly reported formulations of phenibut were powder, tablets and capsules (Figure 1).

Table 2. Reported routes of phenibut administration

Route of administration	Number of countries
Oral	10
Smoking	0
Inhalation	0
Sniffing	0
Injection	0
Other	0
Do not know	7

Figure 1. Formulations of phenibut

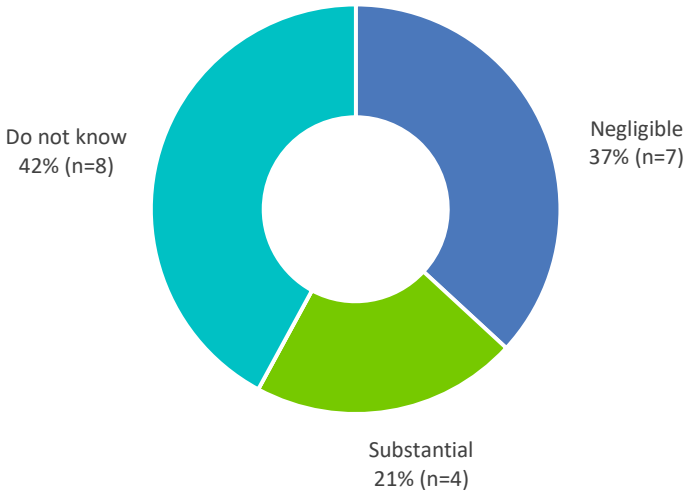


* Other formulations all described capsules (n=7).

Perceived negative health impact

Four countries (3 Region of the Americas, 1 European) reported the level of negative health impact due to phenibut's non-medical consumption was "substantial" (Figure 2).

Figure 2. Countries reporting negative health impact of the non-medical consumption of phenibut



Three countries (1 European, 2 Region of the Americas) reported further information on the extent and magnitude of public health problems or social harm caused by the use of phenibut. One country (European) noted phenibut-related seizures and poisoning centre calls.

One country (Region of the Americas) described "Phenibut use and misuse can result in sedation, respiratory depression, and reduced levels of consciousness, as well as withdrawal symptoms including anxiety, agitation, and acute psychosis", and that "Phenibut has also been encountered on the illicit drug market".

A second country in the Region of the Americas reported from their adverse reaction database a report from a hospital of one patient who "consumed oral phenibut which is the suspected cause of the below adverse effects. The patient had also consumed a Red Bull energy drink, l-arginine, and omega-3". The adverse effects were: agitation, decorticate posture, drug withdrawal syndrome, hypertension, hypothermia, overdose, restlessness, tachycardia, and urinary incontinence.

Emergency Department visits

Three countries (2 European, 1 Region of Americas) were aware of emergency room/department (ED) visits related to phenibut. One country (European) further described clinical symptoms from when phenibut was used in combination with other drugs: a Glasgow coma scale score of three, bradycardia, slight prolongation of QT, hypertonia, agitation, stereotyped movements, intubation with sedation, fluctuating hyperthermia, encephalopathy, rhabdomyolysis, persistent vomiting, drowsiness then transition into a state of euphoria, excitement and aggression, tremors, chills, tachycardia, hallucinations, mydriasis, insomnia, obnubilation, and extrasystole.

Deaths

No countries reported deaths where phenibut was involved.

Drug Dependence

Three countries (2 European, 1 Region of the Americas) reported they were aware of people presenting for drug dependence treatment in their country due to use of phenibut.

CURRENT DRUG CONTROL

Eight countries (6 European, 1 Western Pacific, 1 Region of the Americas) responded phenibut is currently controlled under national legislation to regulate its availability. Table 3 shows reported activities involving phenibut.

Table 3. Reported activities involving phenibut for purposes other than medical, scientific or industrial use.

Activity	Number of countries
Internet sales (other or location of sellers and website unknown)	6
Internet sales (from abroad to buyers in respondent's country)	3
Internet sales (seller or website located in respondent's country)	2
Smuggling (from other countries)	2
Trafficking	2
Direct sales	1
Do not know	7
Other*	2

*Other – two other countries described seizures, but with an unknown or unspecified source

Seizures

Four countries (2 European, 2 Region of Americas) reported seizures of phenibut in 2021. Seizure numbers ranged from 3 to 16, and seizure quantities ranged from 19 to 911 grams (Table 4).

Eight countries (5 European, 1 Region of Americas, 1 Western Pacific) reported seizures of phenibut in 2020. Seizure numbers ranged from 1 to 19, and seizure quantities ranged from 50 grams to 126 kg.

Seven countries (5 European, 2 Region of the Americas) reported seizures of phenibut in 2019. Seizure numbers ranged from 1 to 26, and seizure quantities ranged from 49 grams to 40 kg.

Table 4. Reported seizures of phenibut

Year	Number of countries reporting seizures	Number of seizures
2021	4	26
2020	7	55
2019	7	51

Nineteen countries (14 European, 2 Western Pacific, 3 Region of the Americas) reported having the forensic laboratory capacity to analyse phenibut.