Review Article

# Therapeutic benefits of phenibut – A review

**Nathasha A. P. Sivakumar[1], Anitha Roy[2], Dhanraj Ganapathy[1]***

**ABSTRACT**

Phenibut is a neuropsychotropic drug that was discovered in Russia. Chemically, it is known as β-phenyl-γ-aminobutyric acid (GABA). It is available in powdered and capsule form. It has anxiolytic and nootropic effects. It acts as a GABA-mimetic, primarily at GABA G and, to some extent, at GABAA receptors. It also stimulates dopamine and antagonizes β-phenylethylamine, a putative endogenous anxiogenic. Phenibut is widely used in Russia to relieve tension, anxiety, and fear, to improve sleep in psychosomatic or neurotic patients or regular individuals with insomnia, as well as a pre- or post-operative medication. It is also used in therapy of disorders characterized by asthenia and in cases of insomnia and anxiety.

**KEY WORDS:** Neurotransmitter, Phenibut, Psychoactive drugs, γ-aminobutyric acid

## INTRODUCTION

Phenibut has been sold under the brand names of Anvifen, Fenibut, and Noofen among others. It is a central nervous system depressant with anxiolytic and sedative effects which is used in Russia, Ukraine, and Latvia for the treatment of anxiety, insomnia, and a variety of other causes. It is not approved for the clinical use in the United States and most of Europe, but it has been sold over the internet as a supplement and purported nootropic.[1]

Phenibut is structurally related to the neurotransmitter γ-aminobutyric acid (GABA) and hence is a GABA analog. It is thought to be as a $GABA_B$ receptor agonist, as same as baclofen and γ-hydroxybutyrate (GHB). Following many researches have found that it is also a blocker of subunit-containing voltage-dependent calcium channels (VDCCs) and has a similar action to gabapentinoids such as gabapentin and pregabalin.[2]

Phenibut, which is β-phenyl-GABA or phenyl-GABA, is a GABA-B agonist that was developed in the Soviet Union in the 1960s and it is used in treating an array of conditions that include insomnia, anxiety, depression, asthenia, post-traumatic stress disorder, stuttering, and vestibular disorders. It is not an approved medication in Western countries, but it can be purchased online as a supplement. The extent of its use, safety profile, and societal and medical burden associated with such supplements is not known. There is one documented report of phenibut withdrawal.[3]

There has been a global increase in the handiness and use of novel psychoactive substances (NPS) over the past decade. A psychoactive drug, psychopharmaceutical, or psychotropic are a chemical substance that changes the brain function and that results in changes in perception, mood, or consciousness. There are few main functions of the psychoactive substances. It can act as the anesthetic agent. It may also help in pain management. It is advised in the management of mental disorders. It also used in recreation.[4]

Phenibut is the commercial name of beta-phenyl-GABA HCl is a neuropsychotropic drug that was discovered in the Soviet Union. It is introduced into the clinical practice in Russia in the 1960s. It has the anxiolytic and nootropic which has cognition-enhancing effects. It acts as a GABA-mimetic, primarily at GABA (B) and, to some extent, at GABA (A) receptors. It initiates the stimulation of dopamine receptors as it antagonizes beta-phenethylamine (PEA), a putative endogenous anxiogenic.[5] The psychopharmacological activity

| Access this article online | |
|---|---|
| Website: jprsolutions.info | ISSN: 0975-7619 |

[1]Department of Prosthodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [2]Department of Pharmacology, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

***Corresponding author:** Dr. Dhanraj Ganapathy, Department of Prosthodontics Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, 162, Poonamallee High Road, Chennai - 600 077, Tamil Nadu, India. Mobile: +91-9841504523. E-mail: dhanrajmganapathy@yahoo.co.in

Received on: 21-03-2019; Revised on: 24-04-2019; Accepted on: 28-05-2019

of phenibut as similar to that of the baclofen, a p-Cl-derivative of phenibut. This article reviews the structure–activity relationship of phenibut and its derivatives. Emphasis is placed on the importance of the position of the phenyl ring, the role of the carboxyl group, and the activity of optical isomers.

The comparison between phenibut with piracetam and diazepam reveals few features which are similar to one another and differences in their pharmacological and clinical effects. Phenibut is widely used in Russia to relieve tension, anxiety, and fear, to improve sleep in psychosomatic or neurotic patients, as well as a pre-or post-operative medication. It is also used in the therapy of disorders characterized by asthenia and depression, as well as in post-traumatic stress, stuttering, and vestibular disorders.[6]

Phenibut (β-phenyl-GABA) is a GABA B agonist that is used as an NPS. Phenibut is a GABA agonist designed and has been used as an anxiolytic in Russia, but in Western countries, phenibut is not a registered medication, but it is available through online stores as a supplement.[7] Phenibut is a neuropsychotropic drug that was discovered and introduced into the clinical practice in Russia in the 1960s. It has anxiolytic and nootropic which has cognition-enhancing effects. The psychopharmacological activity of phenibut is similar to that of baclofen, a p-Cl-derivative of phenibut. Phenibut is definitely psychoactive, so in a sense, patients could experience a high from it. The phenibut high is somewhere in the neighborhood of benzodiazepines and alcohol, but not as powerful. It can give the patients the effect of lower inhibition, not caring about stuffs, and sedative-like effects. Phenibut users can become somewhat dependent on phenibut. It is known to cause withdrawal symptoms in those who use it regularly and then suddenly stop.[8]

Withdrawal symptoms are typically similar to those of benzodiazepines, but less severe. It may cause some troubles in sleeping, restlessness. It can create anxiety to the patients and also cause loss of appetite other than causing inability to concentrate on daily life basis.[9]

These are all things that can happen if the patient takes too much of phenibut and then suddenly stop taking it. There is no evidence that phenibut withdrawal can kill as is the case with benzodiazepine withdrawal, but it is definitely unpleasant.[10]

Phenibut is used in Russia, as a pharmaceutical drug to treat anxiety and to improve sleep. It is mainly used in treated patients with insomnia. It is also used for various other uses including the treatment of asthenia, depression, alcoholism, alcohol withdrawal syndrome, post-traumatic stress disorder, stuttering, tics, vestibular disorders, Ménière's disease, dizziness, for the prevention of traveling or motion sickness, and for the prevention of anxiety before or after surgical procedures or painful diagnostic tests.[11]

## HISTORY

Phenibut was synthesized at the A. I. Herzen Leningrad Pedagogical Institute (USSR) by Professor Vsevolod Perekalin's team and tested at the Institute of Experimental Medicine, USSR Academy of Medical Sciences. It was introduced into clinical use in Russia in 1960.[12]

### Structure and Analogs

Phenibut is a derivative of the inhibitory neurotransmitter GABA. Hence, it is a GABA analog. Phenibut is specifically the analog of GABA with a phenyl ring substituted in the β-position. As such, its chemical name is β-phenyl-GABA, which can be abbreviated as β-phenyl-GABA. The presence of the phenyl ring allows phenibut to cross the blood–brain barrier significantly, unlike the case of GABA. Phenibut also contains the trace amine PEA in its structure.[13]

Phenibut is closely related to a variety of other GABA analogs including baclofen (β-(4-chlorophenyl)-GABA), 4-fluorophenibut (β-(4-fluorophenyl)-GABA), tolibut (β-(4-methylphenyl)-GABA), pregabalin ((*S*)-β-isobutyl-GABA), gabapentin (1-(aminomethyl) cyclohexane acetic acid), and GABOB (β-hydroxy-GABA). It has almost the same chemical structure as baclofen, differing from it only in having a hydrogen atom instead of a chlorine atom at the different position in the phenyl ring. Phenibut is also close in structure to pregabalin, which has an isobutyl group at the β-position instead of phenibut's phenyl ring.[14]

## MECHANISM OF ACTION

### Pharmacodynamics

Phenibut, as being the full agonist of the $GABA_B$ receptor, has between 30-- and 68-fold lower affinity for the $GABA_B$ receptor than baclofen, which, in a manner of confirming with, is used at far lower doses in comparison. (*R*)-Phenibut has more than 100-fold higher affinity for the $GABA_B$ receptor than does (*S*)-phenibut; hence, (*R*)-phenibut is an active enantiomer at the $GABA_B$ receptor. In very high concentrations, phenibut has been told that it acts as an agonist of the $GABA_A$ receptor, which is the receptor responsible for the actions of the benzodiazepines, barbiturates, and alcohol.[15]

Phenibut also combines with the subunits and blocks $\alpha_2\delta$ subunit-containing VDCCs, same as the gabapentin and pregabalin and therefore is a gabapentinoid. Both (*R*)-phenibut and (*S*)-phenibut

give this action with similar affinity of $K_i$=23 and 39 μM, respectively. Moreover, (*R*)-phenibut possesses 4-fold greater affinity for this site than for the $GABA_B$ receptor which is $K_i$=92 μM, while (*S*)-phenibut does not bind significantly to the $GABA_B$ receptor which is $K_i$> 1 mM. Hence, based on the results of this study, phenibut would appear to have much greater potential in its interactions with $\alpha_2\delta$ subunit-containing VDCCs rather than with the $GABA_B$ receptor which is in between 5- and 10-fold. For this reason, the actions of phenibut as an $\alpha_2\delta$ subunit-containing voltage-gated calcium channel blocker or gabapentinoid may be its true primary mechanism of action, and this may explain the differences between phenibut and its close relative baclofen, which, in option, has essentially insignificant activity as a gabapentinoid; $K_i$=6 μM for the $GABA_B$ receptor and $K_i$=156 μM for $\alpha_2\delta$ subunit-containing VDCCs, or a 26-fold difference in affinity.[16]

(*R*)-Phenibut and (*S*)-phenibut have been assayed at 85 binding sites at a concentration of 100 μM, where it has no activity to have < 20% inhibition of binding observed except at the $\alpha_2\delta$ VDCC subunit and the $GABA_B$ receptor. In this study, (*R*)-phenibut and (*S*)-phenibut showed $IC_{50}$ values for inhibition of gabapentin binding of 87.1 μM and 91.0 μM ($K_i$=60 μM), respectively. The $IC_{50}$ for gabapentin under the same conditions was 0.09 μM. The researchers also assessed phenibut at the $GABA_B$ receptor and found a $K_i$ value of 57 μM for (*R*)-phenibut, which would be about twice that concentration (~114 μM) with racemic phenibut.[17]

### Pharmacokinetics

Very little information has been published on the clinical pharmacokinetics of phenibut. The drug is reported to be well-absorbed. It distributes widely throughout the body and across the blood–brain barrier. Approximately 0.1% of an administered dose of phenibut reportedly penetrates into the brain, with this said to occur to a much greater extent in young people and the elderly. Following a single 250 mg dose in healthy volunteers, its elimination half-life was approximately 5.3 h, and the drug was largely (63%) excreted in the urine unchanged. In animals, the absolute bioavailability of phenibut was 64% after oral and intravenous administration, it appeared to undergo minimal or no metabolism in multiple species, and it crossed the blood–brain barrier to a significantly greater extent than GABA. The metabolites of phenibut are reported to be inactive.[18]

Some limited information has been described on the pharmacokinetics of phenibut in recreational users taking much higher doses (e.g., 1–3 g) than typical clinical doses. In these individuals, the onset of the action of phenibut has been reported to be 2-4 h orally and 20–30 min rectally, the peak effects are described as occurring 4–6 h following oral ingestion, and the total duration for the oral route has been reported to be 15–24 h or approximately 3– 5 terminal half-lives.[19]

## FUNCTIONS

Phenibut comes with few number of powerful benefits. It has been clinically shown to both improve a person's mood and enhance cognitive functionality in various ways.

### Brain Function

There is also some limited evidence that phenibut may increase cognitive abilities and mental performance. According to several trials, taking phenibut led to improved brain function, especially in regard to communication between the hemispheres of the brain.[20]

### Mood Boosting

The main benefit of phenibut is its mood-boosting properties. It is very effective for boosting mood and its effects are similar to ingesting a hearty dosage of piracetam mixed with the mood uplift and anxiety block of a low dose of codeine.[21]

Phenibut is an excellent choice of drug for the following benefits too.

### Stress level of a Person

Phenibut is a powerful anxiolytic compound, which reduces the stress levels of a person. It actively reduces anxiety within your brain. It does this by targeting the person's GABA receptors, which promotes a feeling of mental calmness while also reducing stress.[14] Anyone who has been stressed knows that they cannot simply "turn off" being stressed. However, phenibut's anti-stress effects may be the closest; they will ever get to finding that coveted "anti-stress" button.[22]

### Learning and Cognition

It has better problem-solving skills and more creative thought. Phenibut may further support better memory and learning.

Phenibut can also help to improve cognition. Many people do not consider phenibut to be a nootropic drug. Although it has been shown to improve cognition, it has not been shown to greatly improve cognition, when compared to racetams, smart drugs, and other more powerful nootropics. That being said, phenibut has demonstrated some cognitive benefits in various studies, and it may facilitate communication between two brain hemispheres while also enhancing problem-solving skills.[15,23]

### Insomnia

To help the person's having problems in sleeping, phenibut can be the drug of choice. It improves the

sleeping quality and the person tends to fell asleep more easily. If a person is having in trouble falling asleep and feeling rested, then phenibut may be his or her new best friend. Phenibut is prized for its ability to encourage a deep, well-rested sleep.[24]

### Neuroprotection

Phenibut also increases neuroprotection. Phenibut protects the person's neuron cells from being damaged. When we are stressed, we often do irreversible damage to our neuron cells. Phenibut helps prevent this damage. Interestingly enough, this same stress can also strain a person's heart's ventricles, which means phenibut can help improve the overall cardiovascular health.[25]

### Positive and Controlled Mood

Other than that phenibut can also help in promoting a positive and controlled mood. If the person tends to feel irritable or angry on a regular basis, it may be due to a chemical imbalance in his or her brain. These chemical imbalances are caused by external factors which are by the stress. Phenibut increases dopamine, neutralizing the effects of these chemicals and balancing the person's mood. This has also been attributed to higher levels of motivation.[26]

Phenibut has a few more effects that are particularly relevant for bodybuilders.

### Post-exercise Growth Hormone Secretion

Phenibut can increase resting and post-exercise growth hormone secretion. In a study of weight training men, GABA supplementation increased resting growth hormone concentrations by 375%. Post-exercise growth hormone concentration rose by 175%.[27] Baclofen, which works almost exactly the same as phenibut, also increases growth hormone synthesis. Phenibut is antihypoxic. When you train a muscle intensely, it cannot get enough oxygen anymore and become hypoxic. This metabolic stress mediates muscle hypertrophy. Phenibut may thus increase your tolerance to metabolic stress and allow you to train harder. Phenibut is neuroprotective and augments cell energy potential, again possibly allowing you to train harder.[28]

## CONTRAINDICATION

The use of phenibut is contraindicated in some cases which include intolerance to phenibut, ulcerative lesions, or gastrointestinal problems. Phenibut is also not be prescribed to pregnant women or breastfeeding mothers. It is also contraindicated to patients with liver function insufficiency or liver failure. Age of the patient plays an important role in prescribing phenibut. Patients who are younger than 2 years old are not advised to take phenibut.[29]

## INTERACTION

Phenibut may mutually potentiate and extend the duration of the effects of other central nervous system depressants including anxiolytics, antipsychotics, sedatives, opioids, anticonvulsants, and alcohol.

## OPTIMAL DOSAGE

The vast majority of studies have only researched dosages up to 3 g a day. At these dosages, no psychological side effects are found. However, many people take much higher dosages for longer periods of time. This is the same more is better fallacy that leads people to drastically overestimate how much protein they need per day and become addicted to caffeine. Like caffeine, phenibut feels great and seems harmless, so people consume high amounts of it on a regular basis. The result is addiction: Tolerance to the good effects and withdrawal when ceasing supplementation. Moreover, they pay the price. Phenibut withdrawal is hell. When coming off 20 g a day, you can literally become psychotic for a while. Tapering off the dose will minimize withdrawal symptoms, but my recommendation is to avoid becoming addicted in the first place.[29]

## SIDE EFFECTS

Phenibut is generally well-tolerated. Possible side effects may include sedation, somnolence, nausea, irritability, agitation, anxiety, dizziness, headache, and allergic reactions such as skin rash and itching. At high doses, motor incoordination, loss of balance, and hangovers may occur. Tolerance develops to phenibut with repeated use. Withdrawal symptoms may occur on discontinuation, and, in recreational users taking high doses, have been reported to include severe rebound anxiety, insomnia, anger, irritability, agitation, visual and auditory hallucinations, and acute psychosis. Due to its central nervous system depressant effects, people taking phenibut should refrain from potentially dangerous activities such as operating heavy machinery. With prolonged use of phenibut, particularly at high doses, the liver and blood should be monitored, due to risk of fatty liver disease and eosinophilia.[30]

## OVERDOSE

In overdose, phenibut can cause severe drowsiness, nausea, vomiting, eosinophilia, lowered blood pressure, renal impairment, and, above 7 g, fatty liver degeneration. There are no specific antidotes for phenibut overdose. Lethargy, somnolence, agitation, delirium, tonic–clonic seizures, reduced consciousness or unconsciousness, and unresponsiveness have been reported in recreational users who have overdosed. The management of phenibut overdose includes activated

charcoal, gastric lavage, induction of vomiting, and symptom-based treatment. Unlike certain other related central nervous system depressants such as baclofen and GHB, there have been no reports of death in association with phenibut overdose.[31]

## CONCLUSION

Ultimately, phenibut is the first and foremost a mood booster. With marked nootropic benefits, it helps in dealing with anxiety. It can also be used to induce sleep in patients suffering from chronic insomniac disorders. It can be used in the treatment of anxiety, depression, asthenia, post-traumatic stress disorder, stuttering, and vestibular disorders.

## REFERENCES


1. Khaunina RA, Maslova MN. The pharmacologic activity and cerebral permeability of gamma-aminobutyric acid and its derivatives. Vopr Psikhiatr Nevropatol 1968;13:583-91.
2. Lapin I. Phenibut (beta-phenyl-GABA): A tranquilizer and nootropic drug. CNS Drug Rev 2001;7:471-81.
3. Sytinsky IA, Soldatenkov AT, Lajtha A. Neurochemical basis of the therapeutic effect of gamma-aminobutyric acid and its derivatives. Prog Neurobiol 1978;10:89-133.
4. Neumyvakin IP, Krupina TN, Polevoĭ LG, Semeĭkina LA. Principles for making up pharmaceutical kits to supply cosmonauts with drug packs. Kosm Biol Aviakosm Med 1978;12:27-31.
5. Powers M. GABA supplementation and growth hormone response. Med Sport Sci 2012;59:36-46.
6. Downes MA, Berling IL, Mostafa A, Grice J, Roberts MS, Isbister GK, *et al.* Acute behavioural disturbance associated with phenibut purchased via an internet supplier. Clin Toxicol (Phila) 2015;53:636-8.
7. Samokhvalov AV, Paton-Gay CL, Balchand K, Rehm J. Phenibut dependence. BMJ Case Rep 2013;2013:bcr2012008381.
8. Powers ME, Yarrow JF, McCoy SC, Borst SE. Growth hormone isoform responses to GABA ingestion at rest and after exercise. Med Sci Sports Exerc 2008;40:104-10.
9. Cavagnini F, Benetti G, Invitti C, Ramella G, Pinto M, Lazza M, *et al.* Effect of gamma-aminobutyric acid on growth hormone and prolactin secretion in man: Influence of pimozide and domperidone. J Clin Endocrinol Metab 1980;51:789-92.
10. Frati P, Kyriakou C, Del Rio A, Marinelli E, Vergallo GM, Zaami S, *et al.* Smart drugs and synthetic androgens for cognitive and physical enhancement: Revolving doors of cosmetic neurology. Curr Neuropharmacol 2015;13:5-11.
11. Lanni C, Lenzken SC, Pascale A, Del Vecchio I, Racchi M, Pistoia F, *et al.* Cognition enhancers between treating and doping the mind. Pharmacol Res 2008;57:196-213.
12. Cavagnini F, Invitti C, Pinto M, Maraschini C, Di Landro A, Dubini A, *et al.* Effect of acute and repeated administration of gamma aminobutyric acid (GABA) on growth hormone and prolactin secretion in man. Acta Endocrinol (Copenh) 1980;93:149-54.
13. Lapin IP, Slepokurov MV. The anxiogenic activity of phenylethylamine in the social isolation test on mice. Farmakol Toksikol 1991;54:9-11.
14. Chutko LS, Surushkina SY, Anisimova TI. Anxiety and fear in children and adolescents. Zh Nevrol Psikhiatr Im S S Korsakova 2016;116:99-103.
15. Owen DR, Wood DM, Archer JR, Dargan PI. Phenibut (4-amino-3-phenyl-butyric acid): Availability, prevalence of use, desired effects and acute toxicity. Drug Alcohol Rev 2016;35:591-6.
16. Lapin IP, Khaunina RA. Pharmacology and clinical use of gamma-aminobutyric acid and its derivatives. In: Role of Gamma-aminobutyric Acid in the Activity of the Nervous System. Leningrad: Izd. LGU; 1964. p. 101-15.
17. Lee JY, Choi JW, Kim H. Determination of body surface area and formulas to estimate body surface area using the alginate method. J Physiol Anthropol 2008;27:71-82.
18. Verbraecken J, Van de Heyning P, De Backer W, Van Gaal L. Body surface area in normal-weight, overweight, and obese adults. A comparison study. Metabolism 2006;55:515-24.
19. Perfilova VN, Sadikova NV, Berestovitskaia VM, Vasileva OS. Cardioprotective properties of new glutamic acid derivative under stress conditions. Eksp Klin Farmakol 2014;77:13-7.
20. Högberg L, Szabó I, Ruusa J. Psychotic symptoms during phenibut (beta-phenyl-gamma-aminobutyric acid) withdrawal. J Subst Use 2013;18:335-8.
21. Riago LK, Sarv KhA, Allikmets LKh. Effect of multiple daily administration of fenibut and diazepam on GABA and benzodiazepine receptors in the mouse brain. Biull Eksp Biol Med 1983;96:49-50.
22. Gusel' VA, Smirnov DP. Peripheral mechanism of the phenomenon of fenibut habituation. Farmakol Toksikol 1980;43:431-3.
23. Samotrueva MA, Tiurenkov IN, Teplyĭ DL, Kuleshevskaia NR, Khlebtsova EV. Immune-regulating effect of phenibut under lipopolysaccharide-induced immune stress conditions. Eksp Klin Farmakol 2010;73:30-2.
24. Shulgina GI. On neurotransmitter mechanisms of reinforcement and internal inhibition. Pavlov J Biol Sci 1986;21:129-40.
25. Dambrova M, Zvejniece L, Liepinsh E, Cirule H, Zharkova O, Veinberg G, *et al.* Comparative pharmacological activity of optical isomers of phenibut. Eur J Pharmacol 2008;583:128-34.
26. Nelson, LS. Phenibut withdrawal a novel nutritional supplement. ClinToxicol 2008;46:605.
27. Group DW. Encyclopedia of Mind Enhancing Foods, Drugs and Nutritional Substances. 2nd ed. McFarland: Wiley-Blackwell; 2015. p. 186.
28. Kovaleva EL. Comparative characteristics of the nootropic action of fenibut and fepiron. Farmakol Toksikol 1984;47:20-3.
29. Sytinskiĭ IA, Kopelevich VM, Nikitina ZS, Polevoĭ LG. Alcoholic intoxication and the gamma-aminobutyric acid system of the brain in exposure to pantogam and fenibut. Farmakol Toksikol 1986;49:79-82.
30. Merchan C, Morgan R, Papadopoulos J, Fridman D. Phenibut overdose in combination with fasoracetam: Emerging drugs of abuse. J Clin Intensive Care Med 2016;1:1-4.
31. Li C, Sundararajan K. An uncommon case of phenibut toxicity in an intensive care unit. Int J Med Pharm Case Rep 2015;5:1-6.


Source of support: Nil; Conflict of interest: None Declared