American Journal of Emergency Medicine 37 (2019) 2066–2071

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Phenibut exposures and clinical effects reported to a regional poison center

Daniel J. McCabe, MD [a,b,*], Stacey A. Bangh, PharmD [b], Ann M. Arens, MD [b,c], Jon B. Cole, MD [b,c]

[a] Department of Emergency Medicine, Regions Hospital, St Paul, MN, United States of America
[b] Minnesota Poison Control System, MN, United States of America
[c] Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, MN, United States of America

ARTICLE INFO

Article history:
Received 17 January 2019
Received in revised form 25 February 2019
Accepted 28 February 2019

ABSTRACT

Background: Phenibut is a synthetically produced central nervous system (CNS) depressant that is structurally similar to the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Phenibut has been identified as a drug of abuse with numerous clinical effects in overdose and a withdrawal syndrome with chronic use. The purpose of this study is to report the incidence of exposure calls regarding phenibut to a poison center, describe the reasons for its use and clinical effects.
Methods: Study subjects were identified using Toxicall®, the electronic medical record utilized by the Minnesota Poison Control System. All phenibut exposure calls from January 2000 through December 2018 were included. Analysis was performed on incidence of exposure calls, reported reasons for use, signs and symptoms, coingestants, and outcome.
Results: There were 56 exposure calls over 19 years with 48 (85.7%) calls within the past five years. Over 50% of patients had CNS effects and 10.7% had withdrawal concerns. Twenty-seven patients (48%) had abuse as the reason for use and 13 (23%) used phenibut to treat anxiety. There were documented coingestants in 35.7% of patients. No patients died due to reported phenibut use, though 11 patients (19.6%) were intubated.
Conclusion: Exposure calls to a regional poison center regarding phenibut have increased over the past five years. CNS depression was common, and associated with significant clinical outcomes including respiratory failure requiring intubation. As phenibut is easily attainable and exposures appear to be increasing, physicians should be aware of phenibut-associated CNS and respiratory depression and be prepared to manage airways appropriately.

1. Introduction

Phenibut (β-Phenyl-γ-Aminobutyric Acid HCl) is a synthetically produced central nervous system (CNS) depressant that is structurally similar to the inhibitory neurotransmitter γ-aminobutyric acid (GABA) [1]. Introduced in Russia in the 1960s, phenibut is marketed as a dietary supplement for anxiolysis, depression, and neurocognitive enhancement [1,2]. Manifestations of acute phenibut intoxication can produce a broad spectrum of effects from severe agitation to lethargy [3-11]. The varied response may be the result of individual metabolism, purity of the product, or the amount consumed [3,4]. Additionally, phenibut has been shown to have sedative, euphoric, and anxiolytic effects similar to xenobiotics of similar chemical structure (Fig. 1) [1,2,12-17]. There are studies demonstrating phenibut's effects on multiple receptors including GABA-A receptors, GABA-B receptors, and voltage-dependent calcium channels (VDCCs) without a clear, anticipated clinical course [1,12,14]. Additionally, phenibut may produce anxiolysis by antagonizing the effects of endogenous phenethylamine and dopamine ("anxiogenics") [1] These characteristics produce a complex presentation for a physician to interpret, especially an emergency physician that may need to treat a patient with incomplete data.

1.1. Illustrative case report

The primary author (DM) provided an inpatient consultation for a unique case of acute phenibut intoxication in a 27-year-old man. Prior to presentation, the patient was admitted to an inpatient chemical dependency unit for two months due to kratom and phenibut dependence, which previously required intubation for phenibut overdose. He was started on baclofen (10 mg every 8 h) during this time period to treat phenibut dependence. The day prior to hospital arrival, the patient had been transferred to a facility with less direct supervision. On the day of presentation, he purchased 100 g (g) of phenibut at a local head shop and ingested 30 g of phenibut powder

* Corresponding author at: Regions Hospital, Department of Emergency Medicine, 640 Jackson St, St Paul, MN 55101, United States of America.
E-mail address: djmccabe429@gmail.com (D.J. McCabe).

https://doi.org/10.1016/j.ajem.2019.02.044
0735-6757/

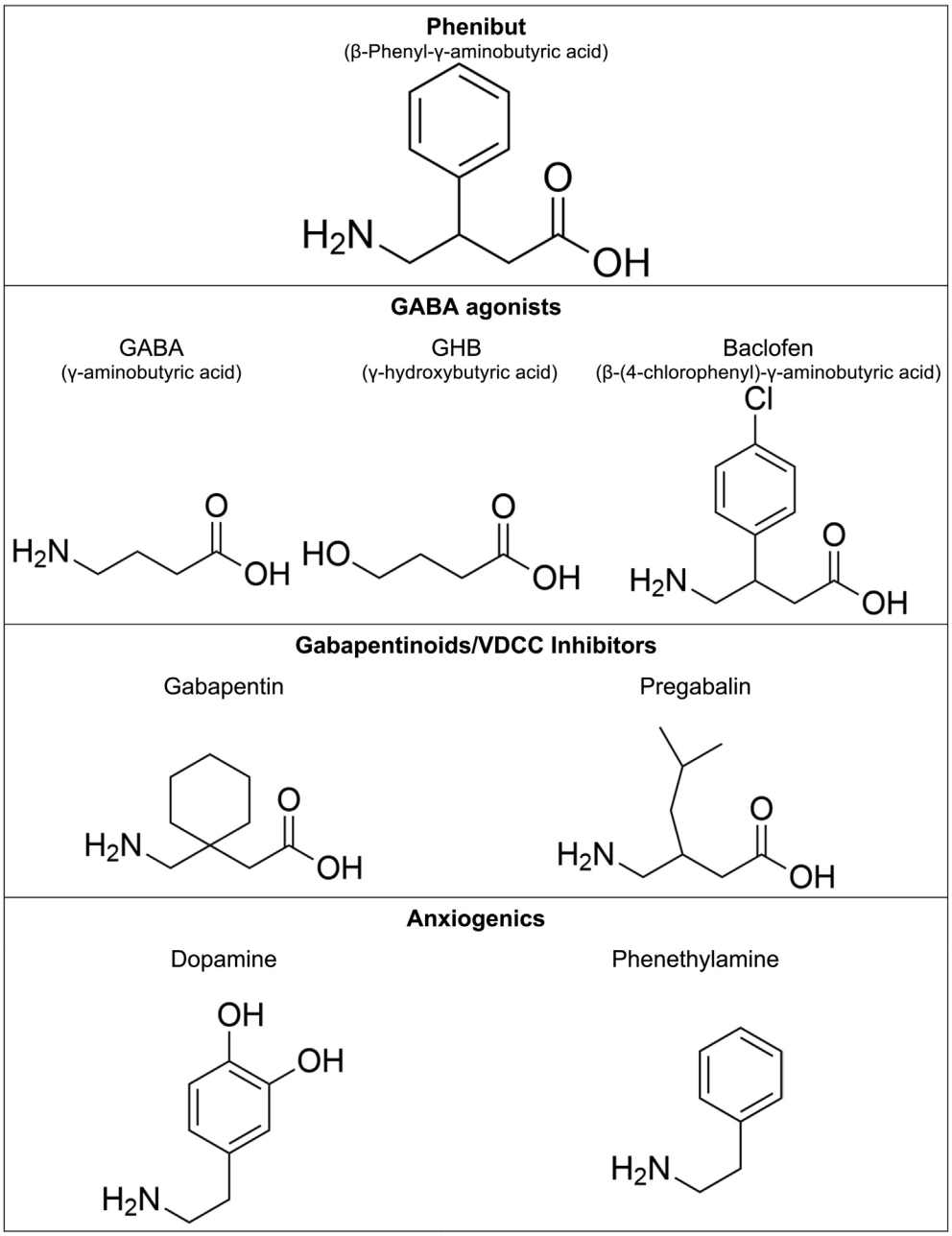

Fig. 1. Structural similarity of common γ-aminobutyric acid (GABA) receptor agonists, gabapentinoids/voltage dependent calcium channel (VDCC) inhibitors, and known anxiogenic biogenic amines.

in an attempt to decrease anxiety and experience disinhibition. He became extremely agitated and started to hit his head against a sink when emergency medical services (EMS) were called. He was agitated for EMS but was not given sedatives. By the time he arrived at the emergency department, he was completely unresponsive with a Glasgow Coma Scale score of 3 and was intubated. In the subsequent days (days 1–3), the patient developed severe agitation, tachycardia, and hypertension requiring high continuous infusions of opioids (fentanyl) and benzodiazepines (midazolam) in addition to increasing his baclofen dose (20 mg every 8 h) and continuation of his home valproic acid. He developed hyperthermia, rigidity, and myoclonus on day three of this regimen. Fentanyl was discontinued and he was started on phenobarbital (5 mg/kg every 12 h) for three days with improvement of serotoninergic signs. During this time, he developed ventilator-associated pneumonia. During the following days [7-12], the patient was weaned from the ventilator using a combination of benzodiazepines, hydromorphone, baclofen, gabapentin, olanzapine, dexmedetomidine, clonidine, and methadone. On day 13, the patient was extubated and aggressively weaned from benzodiazepines (4 days) opioids (7–10 days), and baclofen (12 days). He was continued on gabapentin chronically.

The patient described his use of phenibut and confirmed that he had only used phenibut without any coingestants on the day of admission. Prior to abstention, he previously had ramped up his daily doses from around 1 g to 20–30 g as he developed tolerance over two months. He remembered the initial "rush" and the subsequent "out-of-body" experience with extreme hallucinations on the day of admission.

This case report highlights the numerous clinical effects from a large ingestion of phenibut including initial euphoria and agitation, subsequent loss of consciousness, and withdrawal state. The patient provided consent to have his data published.

1.2. Importance

There is little description in the medical literature regarding the incidence, reasons for use, and clinical effects of phenibut use [2]. The medical literature on phenibut intoxication is limited to case reports describing adverse effects from phenibut use, which may signify the need for an increased awareness regarding the prevalence and effects of this emerging drug [3,4,8,9,18-20].

1.3. Goals of this investigation

The purpose of this study is to report the incidence of calls relating to phenibut exposure for one poison control center (PC), describe the clinical effects, reported reasons for use, coingestant use, and outcomes.

2. Methods

2.1. Study design and setting

This is a retrospective observational study. Subjects were identified using Toxicall®, the electronic medical record utilized by the Minnesota Poison Control System (PC). This center is an American Associate of Poison Control Centers (AAPCC) accredited regional poison center covering three U.S. states. This PC follows patients longitudinally until the patient is asymptomatic or until symptoms are determined to be unrelated. The human subjects research committee at the Hennepin Healthcare Research Institute approved this study.

2.2. Selection of participants

All exposure calls from January 2000 through December 2018 were included with stated concerns for phenibut ingestion; this search was completed by the primary author. Data collection was performed in a manner similar to a prior study which included three of our authors [21]. A search was completed for the following terms: "phenibut" and "4-amino-phenylbutyrate." Several products reported to contain phenibut were searched without any cases found, including: "phenitropic", "maxzzzz", "somadrol", "chill pill", "somabien", "SNS", "Happy Hippo Herbals", "PrimaForce", "PeakNootropics", "DNA Anabolics", "EST", "HoltraCeuticals". Each case in Toxicall® consists of categorical data (demographics, route of exposure, clinical effects) as well as free text case notes. The entire Toxicall® record was reviewed, the data was extracted from both sources, and all documented effects were included for analysis. Information-only calls were excluded. If a patient had fluctuating clinical effects, all effects were listed. If a coingestant was documented, each clinical effect was included.

2.3. Measurements

The following data were collected: date of call, age and gender of patient, relationship of caller to patient, the reason for ingestion, coingestants, any signs and/or symptoms present, and documented Toxicall® medical outcomes as defined by the American Association of Poison Control Centers' National poison Data System [22,23]. If the caller specifically reported withdrawal concerns, this was recorded as a clinical effect in addition to the other reported signs and symptoms.

2.4. Intubation sub-group analysis

All patients with a recorded intubation were reviewed by the primary investigator to determine the indication for intubation.

Table 1
Patient demographic data, documented outcomes, and reasons for patient use of phenibut.[a, b]

All patients (n = 56)		n (%)
Age (years)	27 (median) 19–93 (range)	
Gender		
Male		42 (75)
Female		13 (23.2)
Unknown		1 (1.8)
Identity of caller		
Healthcare professional		49 (87.5)
Patient		4 (7.1)
Family/friend		3 (5.4)
Poison control medical outcome[a]		
No effect		2 (3.6)
Minor		17 (30.4)
Moderate		16 (28.6)
Major		7 (12.5)
Other		14 (25)
Reason for use		
Abuse		27(48.2)
Anxiety/mood enhancer		13(23.2)
Unknown/other[b]		16(28.6)

No Effect: "The patient developed no symptoms as a result of the exposure."
Minor effect: "The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient".
Moderate effect: "The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement."
Major effect: "The patient has exhibited symptoms as a result of the exposure which were life threatening or resulted in significant residual disability or disfigurement."
"Other" includes the following coded effects: "Not followed, judged as nontoxic exposure (clinical effects not expected)," "Not followed, minimal clinical effects possible (no more than minor effect possible)," "Unable to follow, judged as a potentially toxic exposure," or "Unrelated effect, the exposure was probably not responsible for the effect(s)."
[a] Definitions from NPDS Coding Users Manual [23].
[b] Reason for use was labeled as unknown if no explicit reason was documented. Other included the following reasons for use: provider recommended [2], restless leg syndrome [1], weight loss [1], self harm [1].

3. Results

3.1. Characteristics of study subjects

There were 56 PC exposure calls during the study time period. Demographic data, the identity of caller, medical outcome, and reasons for use are presented in Table 1. Two information-only calls were excluded.

3.2. Main results

Fig. 2 illustrates the incidence of PC calls with concerns about phenibut during the study period. Thirty-one (55.4%) patients were reported in the last two years and 48 patients (85.7%) in the past five years. The reported clinical effects are shown in Table 2. The most common effects were CNS (depressive or stimulatory) and cardiovascular effects (tachycardia or bradycardia). Twenty (35.7%) cases had documented coingestants. Withdrawal was a stated concern in six (10.7%) patients; five of these patients did not have listed coingestants. There were no reported deaths.

Of the 56 total exposure patients, six (10.7%) were managed at home, 22 (39.3%) were evaluated and treated in an emergency department, and 26 (46.4%) required admission to the hospital. Two patients were referred to a hospital but follow-up data was not attained.

Twenty-seven patients (48%) had abuse as reason for use and 13 patients (23%) consumed phenibut to treat anxiety (Table 1). Forty-

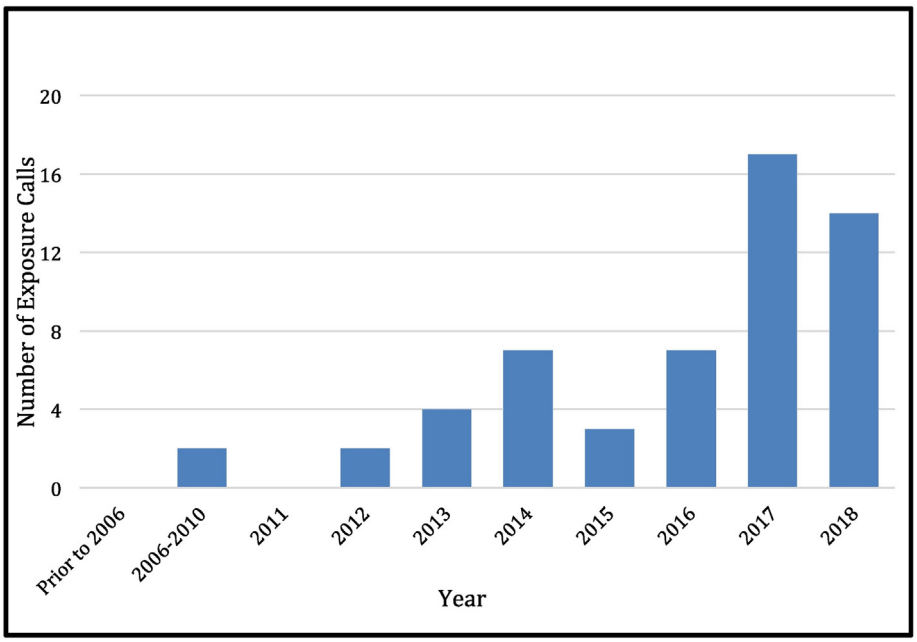

Fig. 2. Incidence of poison center calls after phenibut exposure.

nine (87.5%) phone calls were made by healthcare professionals and seven (12.5%) by non-healthcare professionals.

3.3. Intubated patients

Eleven (19.6%) patients were intubated. Table 3 provides a description of these patients. Ten (90.9%) of these patients were intubated due to depressive CNS symptoms. One patient was intubated for severe agitation after initial presentation of depressive CNS effects. Five (45.4%) of these patients had coingestants.

4. Discussion

4.1. Increasing incidence of exposure calls

We present all of the cases reported to one poison center regarding phenibut exposure over a 19-year study period. There appears to be an increasing incidence of calls to our PC during this time. This may be due to an increase in recognition and reporting of phenibut exposure. There could be increasing use in the community due to a growing awareness of its effects in the laypublic [10] and easy attainability on the internet and in stores; though this study is unable to confirm this hypothesis.

4.2. Clinical effects of intoxication

Phenibut has been used for a myriad of reasons including to manage anxiety, enhance cognition, and to assist with chemical dependence involving other substances [1,2,10,19,24]. Phenibut is easily attainable in many products, inexpensive, has an increasing popularity in "drug discussion forums" on the internet as a means to decrease social anxiety or to attain a state of euphoria [2]. The majority of medical literature pertaining to phenibut intoxication or withdrawal is contained in case reports and very small case series [3-9,11,18-20]. Comparable to ethanol, phenibut appears to have an anxiolytic effect at lower doses with increased aggression and decreased motor coordination associated with more moderate doses, and profound respiratory depression at very high doses [1,2]. Due to an inadequate description of the clinical effects associated with this drug and the multi-receptor effects, it is difficult to predict a reliable toxidrome in these patients. In this study, we found a large percentage of patients had both depressive and stimulatory CNS effects. There were significant clinical effects associated with this drug including a noteworthy number of patients requiring intubation.

As healthcare professionals made the majority (87.5%) of calls, we found calls from non-healthcare professionals to be particularly interesting. These calls provided a better narrative regarding reason for use and associated symptoms. Two callers were family members of the user; both of these patients were elderly (ages 80 and 93). One had an unknown reason for use despite using chronically and had symptoms of dizziness. The other had an accidental consumption with symptoms of nausea and vomiting. Four callers were the patients themselves. One patient was taking phenibut for anxiety and was calling for information regarding the product they were using. A second patient was using it for abuse potential and complained about vision changes and anxiety symptoms with consumption. A third patient took high doses of phenibut daily for three days for anxiolysis and stopped taking it a few days prior to calling the poison center. This patient suspected they were experiencing withdrawal symptoms with irritation and anxiety after experiencing a panic attack. A fourth patient took their usual dose of phenibut and wanted to know if they should refrain from taking their prescribed risperidone.

4.3. Clinical effects of withdrawal

There is minimal description regarding the withdrawal symptoms after cessation of phenibut [7,9,10,18-20]. With chronic administration, phenibut has been shown to have a high affinity to benzodiazepine receptors without anticonvulsant properties [1]. Tolerance has been observed within one to two weeks of consistent use [1,10,20]. This combination of properties is concerning due to a possibility of down regulation at the benzodiazepine receptor. One patient in this study admitted to using phenibut to treat her benzodiazepine withdrawal symptoms. She ran out of her clonazepam and attempted to treat subsequent withdrawal symptoms with phenibut for two days. She presented anxious and agitated with a rapid change in clinical status to bradycardia and drowsiness after intravenous administration of diazepam (10 mg). As some people use phenibut to wean from chemical dependence on other substances [19], this could subsequently place them at a higher risk for severe withdrawal symptoms. In

Table 2
Description of clinical effects after phenibut exposure. *Depressive CNS effects* include confusion, decreased level of consciousness (LOC), drowsiness, obtundation, unresponsive mental status, sedation, somnolence, lethargy, disorientation, nonverbal, slurred speech and being "found down." *Stimulated CNS effects* include agitation, irritation, anxiousness, and restlessness. CNS: Central nervous system, IV: intravenous. If a coingestant was reported, it was listed with all the reported effects for each patient.

Signs/symptoms	All Patients n = 56(100)	Phenibut Only n = 36(100)	Phenibut + Coingestants n = 20 (100)	Listed coingestants
	n(%)	n(%)	n(%)	
CNS				
Depressive CNS effects	38(67.9)	24(66.7)	14(70)	Dextroamphetamine, diazepam(IV), ephedra, ethanol, insulin, kratom, marijuana, methamphetamine, psilocybin, saffron, valerian root
Stimulated CNS effects	29(51.8)	20(55.6)	9(45)	Buprenorphine, caffeine, dextroamphetamine, ephedrine/guaifenesin, escitalopram, ethanol, kratom, marijuana, tramadol
Tremulousness/ Shakiness	4(7.1)	2(5.6)	2(10)	Buprenorphine, etizolam
Ataxia	2(3.6)	1(2.8)	1(5)	Methamphetamine
Psychiatric				
Hallucinations	4(7.1)	1(2.8)	3(15)	Etizolam, marijuana, psilocybin, saffron, valerian root
Insomnia	3(5.4)	2(5.6)	1(5)	Caffeine, ephedrine/guaifenesin
Cardiovascular				
Tachycardia (HR > 100)	10(17.9)	2(5.6)	8(40)	Buprenorphine, ephedra, ethanol, etizolam kratom, marijuana, methamphetamine, psilocybin
Bradycardia (HR < 60)	8(14.3)	4(11.1)	4(20)	Diazepam(IV), ethanol, escitalopram, kratom
Pulmonary				
Decreased respiration	3(5.4)	2(5.6)	1(5)	Ethanol
Gastrointestinal				
Nausea, vomiting	7(12.5)	4(11.1)	3(15)	Ethanol, etizolam, saffron, valerian root
Other				
Verbalized "withdrawal" concern	6(10.7)	5(13.9)	1(5)	Etizolam
Diaphoresis	3(5.4)	3(8.3)	0(0)	

Table 3
Description of patients requiring intubation. LOC = level of consciousness.

Patient	Age/Gender	Indication for intubation	Listed coingestants	Reason for Use
1	31/M	Decreased LOC, airway protection		Abuse
2	30/M	Fluctuating mental status (somnolence, agitation)	Ethanol	Abuse
3	22/M	Initial verbalized concern for "withdrawal", hallucinations, anxiety Subsequent CNS depression and aspiration		Abuse
4	21/M	Unresponsive mental status		Abuse
5	31/M	Unresponsive mental status	Ephedra	Unknown/Chronic
6	20/F	Unresponsive mental status	Ethanol	Unknown
7	20/M	Initial depressive CNS effects Subsequent severe agitation requiring intubation	Kratom	Abuse
8	25/M	Unresponsive mental status		Abuse
9	31/M	Apneic episodes		Abuse
10	49/M	Unresponsive mental status	Ethanol	Abuse
11	27/M	Unresponsive mental status		Abuse

this study, we were unable to differentiate acute phenibut disinhibition from a withdrawal state unless the caller specifically reported withdrawal concerns. Despite multiple patients with concern for withdrawal symptoms, there were no seizures reported in our case series nor did we find a case of seizures related to phenibut withdrawal in the medical literature.

4.4. Reason for use/receptor effects

There are numerous xenobiotics with a similar chemical structure, which could explain the diverse clinical effects of phenibut. It is a synthetically produced compound that is structurally similar to GABA and produces clinical effects associated with other GABA agonists in addition to inhibition of the $\alpha_2\delta$ subunit of VDCC [1,2,12-17].

A considerable percentage (48%) of patients were consuming phenibut for its abuse potential. There are multiple receptor effects that could contribute to this. The structure and apparent mechanism of action of phenibut is similar to baclofen, another β-phenyl derivative of GABA with GABA-B agonism [1,2,13-15,17]. Additionally there is evidence supporting an increase in presynaptic GABA release due to phenibut [1,16]. These properties could contribute to GABAergic effects with decreased CNS effects compared to baclofen.

We found 27% of the patients in this study used phenibut to treat anxiety. Despite evidence that GABA-B receptors are agonized more than GABA-A receptors, phenibut has been associated with density changes of GABA-A and benzodiazepine receptors [1,2]. Phenibut also has been shown to have some of the anxiolytic and tranquilizing effects produced by diazepam; despite diazepam being a known GABA-A agonist [1,2]. Additionally, phenibut has been shown to bind to the $\alpha_2\delta$ subunit of VDCC and exerts gabapentin-like anti-nociceptive effects [12]. Phenethylamine is a known endogenous (and exogenous) anxiogenic with a similar structure to phenibut, amphetamines, and cathinones (Fig. 1).

There are studies relating this structural similarity to the anxiolytic effects of phenibut through phenethylamine antagonism [1]. Additionally, phenibut's structural similarity to dopamine has been theorized to contribute to dopaminergic effects of phenibut [1,2]. To date there does not appear to be a complete description of the different effects phenibut has on these receptors which creates uncertainty when attempting to determine the expected clinical effects.

As phenibut is an unregulated xenobiotic with a diverse clinical profile, we found it noteworthy that healthcare providers recommended a patient initiate phenibut use. Two patients were introduced to phenibut by a provider (one physician and one chiropractor). One patient presented to the emergency department with nausea, vertigo, and bradycardia (44 beats/min). A second patient had symptoms of restlessness and anxiety after abrupt cessation after chronic use of phenibut.

4.5. Potentiation/synergism with coingestants

Previous studies have shown phenibut potentiates the CNS depressant effects when combined with other depressants and phenibut's behavioral effects on socialization were increased with the addition of diazepam or ethanol [1,2]. In our study, ethanol was a coingestant in three of the intubated patients. This cannot be confirmed, but the need for intubation may have been due to a synergistic respiratory depression from both phenibut and ethanol. There were no known coingestants in 64% of all patients and 55% of intubated patients; which is concerning that phenibut may have produced severe effects as a single agent.

4.6. Outcomes

Consistent with prior studies, our study did not identify a phenibut-caused death. Despite this, there were multiple negative consequences from phenibut use including intubation, CNS effects, and withdrawal concerns.

4.7. Limitations

As this is a retrospective chart review using only poison center data, there is a limit to the accuracy and thoroughness of clinical data and confirmatory testing was not available [25,26]. It was not feasible to objectively differentiate acute phenibut disinhibition from a withdrawal state from this data set. This makes it difficult to determine if initial or subsequent effects were due to disinhibitory or withdrawal effects. We hope that continued description of the phenibut intoxication and withdrawal effects will allow objective differentiation in the future.

The incidence of phenibut use is likely higher than the calls to a single regional poison center. We hypothesize this would create a bias towards more symptomatic patients seeking healthcare. Presumably it would also be rare for a healthcare professional to report an asymptomatic patient. In addition, our ability to perform an accurate search of a poison center database is limited by the reported name of the ingestion, the documentation of the ingestion by poison center staff, and our knowledge of the phenibut-containing products.

4.8. Conclusion

Phenibut is an emerging drug of abuse with complex clinical effects. This study suggests the number of phenibut exposures is increasing with associated serious clinical consequences, including CNS depression and acute respiratory failure. As this drug is touted for multiple acute and chronic indications, there may be a vast array of clinical presentations based on dosage, tolerance, dependence, and coingestants. Further elucidation of the expected effects from phenibut use may eventually be achieved through continued reporting of cases, a clarification of the receptor effects, and possible development of diagnostic testing.

Funding

There was no funding used for this study.

IRB

This study was approved by the Institutional Review Board at Hennepin Healthcare Research Institute.

Conflicts of interest

The authors report no declarations of interest.

Acknowledgements

Chemical structures created using ChemDraw® JS 17.1.

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