



Review about Gabapentin Misuse, Interactions, Contraindications and Side Effects

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ABSTRACT

The present review aims to examine the potential for gabapentin abuse, clinically significant drug interactions, adverse effects, and contraindications associated with its use. A total of 99 references published between 1983 and 2016 were included in the review. A literature search of PubMed was conducted for publications published between January 1983 and December 2016. Relevant review articles, case reports, clinical studies, and animal studies addressing gabapentin abuse, drug interactions, adverse effects, and contraindications were considered. The search was performed using the keywords “gabapentin,” “anticonvulsant,” and “antiepileptic.” The findings indicate that gabapentin has considerable potential for misuse and abuse, particularly in individuals with a history of substance use. Reports of prescription misuse, recreational use, elevated self-administered doses, and gabapentin-associated fatalities highlight important safety concerns. The major factors contributing to gabapentin misuse include its potential to produce euphoric effects, alleviate symptoms associated with opioid withdrawal, and enhance the effects of other psychoactive substances. Therefore, careful prescribing, appropriate patient selection, monitoring for misuse, and awareness of potential drug interactions are essential to minimize the risks associated with gabapentin therapy.

Keywords: Gabapentin, Misuse, Interactions, Contraindications, Side Effects.

INTRODUCTION

The pharmacological medication gabapentin has a white solid (tiny crystals) physical look. Gabapentin's chemical formula is $C_9H_{17}NO_2$, and the formula for it is 171.23678 g/mol in weight. Its brand names are varied and include Gralise, Neurontin, Horizant (National Centre for Biotechnology Information) and Fanatrex. Gabapentin is available commercially in a variety of dosages as pills or capsules. (100, 300, and 400 mg capsules; 300, 600, and 800 mg tablets; United States website) States National Library of Medicine). The pharmacokinetic and pharmacodynamic characteristics of gabapentin are diverse. One Gabapentin is more effective than pregabalin is absorbed slowly following oral administration, and it has an maximum amount in plasma in three to four hours. In addition, oral Gabapentin treatment results in saturable absorption (a nonlinear procedure, zero order). One Additionally, the

plasma Gabapentin levels do not rise in proportion if its Increased dosages are used; gabapentin does not bind to plasma proteins [1]. Neither inhibits nor metabolises gabapentin liver enzymes; moreover, gabapentin can be eliminated by the renal system, and it takes around six hours for it to be excreted.

Mechanisms of action of gabapentin

An anticonvulsant medication called gabapentin decreases presynaptic voltage-gated Ca^{2+} and Na^{+} , which in turn decreases synaptic transmission. Additionally, gabapentin decreases exocytosis through channels [2–4] and neurotransmitter release from presynaptic synapses [5, 6]. However, a different research line revealed that gabapentin acts on the $\alpha 2\text{-}\delta 1$ subunit of calcium channels to reduce the development of excitatory synapses [7, 8]. Additionally, supplementary studies revealed that gabapentin possesses particular affinity for the $\alpha 2\text{-}\delta 1$ subunit, but

less affinity for non-affinity for $\alpha 2$ - $\delta 3$ subunits and $\alpha 2$ - $\delta 2$ subunit. Studies on gabapentin's impact on levels of the neurotransmitter gamma-aminobutyric acid (GABA) have revealed inconsistent outcomes, such as elevated GABA levels based on human research [10], but no in vitro effects have been documented Research [11]. Gabapentin also influences GABA(A), although not Responses of GABA(B) receptors, based on in vitro studies. According to human tests, gabapentin did not alter the amount of the neurotransmitter glutamate, according to another study [10]. Additionally, research has revealed the Gabapentin's antagonistic effects on N-methyl-d-aspartate Protein kinase C and (NMDA) glutamatergic receptors [13] PKC-ERK1/2, or extracellular signal-regulated kinase 1/2 routes [14]. Lastly, it has also been noted that gabapentin has no effect on glycine receptor activity and GIRK stands for G-protein-coupled inwardly rectifying potassium. Channels

Gabapentin uses in experimentation

For the past few decades, gabapentin has been used in both scientific and clinical research [15–18]. At first, research was concentrated on epilepsy treatment. It was later investigated for treating other conditions like behaviour control issues and mental health conditions, amyotrophic lateral sclerosis, pain alleviation, nerve pain, and restlessness legs syndrome, bipolar disorder, and other conditions. But it's important to keep in mind that the research regarding the reduction of behavioural dysregulation following the application of A case study (n=1) that served as the basis for gabapentin revealed a lad of thirteen, and the dependability was restricted due to due to the limited sample size Additionally, a clinical trial involving four participants served as the basis for the study about the decrease in pain following gabapentin use, and the majority of these participants (three out of four) were between the ages of 50 and 82; 25 Lastly, another clinical investigation about the reduction of neuralgia following the use Including a relatively small sample size (n=1) of gabapentin, a 78-year-old lady). Given these tiny sample sizes, it's critical to take into account the reliability's constraints and the constrained age ranges. The current work's primary goal is to provide an updated analysis of gabapentin-related issues abuse, adverse effects, drug interactions, and usage contraindications.

Problems related to misuse, abuse or dependence on gabapentin

Large group studies and case clinical research indicate that gabapentin abuse may result in health issues.32–37 In particular, a Smith *et al.*, 37 investigation revealed that gabapentin has been abused (for non-medical purposes) in a sample of adults from the Kentucky's Appalachia (n=503). In particular, it was said 15% of the participants took gabapentin to get high in the preceding six months; this figure amounted to 165% rise in contrast to a comparable survey conducted the year before. In Furthermore, the subjects mentioned

using gabapentin as an 25 days on average from the 30 days prior. Additionally, Physicians were the two main sources of gabapentin (52%). and narcotics traffickers (36%), while street expenses were documented to be under \$1.00 USD each tablet. Generally speaking, the approach of this study was sound (additional information is provided in another article by the same group38); qualified personnel evaluated the mental health components, including substance abuse, employing the Mini International Neuropsychiatric Examination The Diagnostic and Statistical Manual (version 5.0) DSM IV criteria for mental disorders were applied to the the classification's objective. However, the validity of the clinical research by Regarding gabapentin dependence being distinct, Kruszewski *et al.*, due to the extremely tiny sample size (n=1) on which it was based. a 38-year-old man); moreover, the study's patient acquired an off-label prescription for gabapentin. Conversely, However, the human study that documented the misuse of gabapentin included a limited number of men (n=5), with a range of they were prisoners between the ages of 29 and 45, and they sniffed powdered gabapentin from capsules. Therefore, there are restrictions on how far these results can be applied. To a larger demographic due to the limited sample size and Inmates were the unique group that reported. In order to investigate gabapentinoids, Baird *et al.*, conducted a study in Scotland using a questionnaire-based survey with 129 participants. (pregabalin and gabapentin) as well as other drug misuse. The According to the investigation, 22% of participants (29/129) demonstrated misuse of gabapentinoid. Additionally, a sizable percentage of these participants (38%, 11/29), misused gabapentinoids for increasing the methadone dosage. An examination of the Approximately one-fifth of the individuals (25, 19%) used gabapentin without a prescription, according to the data. One of the study's limitations was the absence of confirmation of the questionnaire employed.

- Gabapentin has powerful sedative and psychedelic effects.
- Gabapentin was sold on the web without the need of a medical prescription.
- It is a very complete pharmaceutical substance, and its effects are like super amphetamine rush.
- Gabapentin can induce dissociations such as those found on dextromethorphan (only on head and hands).
- Gabapentin helps in becoming very active, friendly, talkative and disinhibited.
- Gabapentin can be combined with other drugs such as baclofen, cannabis, alcohol, selective serotonin reuptake inhibitors, lysergic acid diethylamide, amphetamine and gamma-hydroxybutyric acid.

Side effects caused by gabapentin

The limited sample size, 61,62 and the use of several medications (medical polydrug regimen) in the

investigations on gabapentin and teratogenicity have been some of the studies' drawbacks. studies; these elements restrict how far the findings may be applied.⁶² Additionally, in my view, the teratogenic effects can be seen not just during pregnancy or the first few months after delivery, but additionally at later phases (such as adolescence), and these later Future studies should examine phases. For reference, A review referenced a study on how cognitive function changed after early postpartum period brought on by gabapentin However, a recent assessment by Verrotti *et al.*,⁶¹ shown a significant difference in teratogenicity between new and ancient antiepileptic medications: novel antiepileptic drugs (like such as gabapentin) are minimal risk. of significant birth defects in contrast to antiepileptic medications from the past. According to a different analysis of gabapentin clinical trials, the most frequent adverse effects were fatigue (11%), ataxia (13%), dizziness (18%), and somnolence (20%).⁶³ Additionally, another sizable trial that employed gabapentin as supplemental treatment for seizure management revealed that the The most frequent adverse effects were asthenia (6.0%), dizziness (10.9%), and somnolence (15.2%). Lastly, some experts believe that gabapentin adverse effects can be avoided even at greater dosages;⁶⁵ The differences in gabapentin's effects may rely more on on the administrative route.

The interactions between gabapentin and other drugs

According to several research studies, gabapentin may interact with other medications or not. Generally speaking, research has indicated that gabapentin is an antiepileptic medication with a minimal history of interactions with other substances. In particular, a general review found that Gabapentin does not interact with plasma or hepatic enzymes proteins and other medications; these elements make gabapentin appropriate for senior citizens with hepatic disorders. Additionally, a study of medication combinations for treating According to epilepsy, gabapentin did exhibit a low profile of interactions between pharmacokinetic and pharmacodynamic further antiepileptic medications Gabapentin has a better pharmacokinetic profile, according to another analysis of medication combinations for treating epilepsy, but it is not entirely immune to interactions with additional medications. Additionally, these writers also determined that gabapentin may be beneficial for a specific patient. Such as individuals undergoing anticoagulant therapy, HIV infection, cancer patients, and transplant recipients.⁷⁰ and lastly, one more review about medication combinations to treat epilepsy came to a conclusion. That there aren't many interactions with gabapentin because Gabapentin's pharmacokinetic properties include low blood albumin binding, renal excretion, or metabolism (by either uridine glucuronyl transferases or noncytochrome P450). However, a study on mice revealed that the combinations of gabapentin and antidiuretic medications (such Hydrochlorothiazide and ethacrynic acid) don't change the Gabapentin's

anticonvulsant properties Furthermore, another experimental research revealed no pharmacokinetic interactions between gabapentin and antiepileptic medications (valproate, carbamazepine⁷⁴, and phenobarbitone⁷⁵) or contraceptive medications (norethindrone acetate and ethinylestradiol). An additional investigation verified that Despite having no pharmacokinetic interaction, gabapentin exhibits connection between the antiepileptic medication and pharmacodynamics Topiramate Lastly, research on how gabapentin interacts with and morphine reported varying outcomes. In particular, a There were no pharmacokinetic interactions found in the rodent study, However, pharmacodynamic interactions (behavioural synergism) were found in other rodent experiments. But other Human studies revealed that gabapentin and morphine interacted pharmacokinetically and pharmacodynamically.

Remarkable interactions between gabapentin and other drugs

The interactions between gabapentin and other medications were examined in several studies. For example, a study on mice revealed that the interactions between losartan and gabapentin resulted in motor impairment.⁸⁰ Another study on mice revealed interference with motor function (based on the chimney test) due to the way gabapentin interacts with The diuretic medication ethacrynic acid However, a different mouse study revealed that A beta-adreno receptor antagonist called carvedilol can also enhance the anticonvulsive effects of gabapentin action;⁸² This implies a possible beneficial combination for managing epilepsy. The other research on mice showed a decrease in in the anticonvulsant effectiveness of gabapentin with the combination with sertraline, an antidepressant medication other research has demonstrated that gabapentin's interactions with other medications can help reduce pain. For example, combining smaller dosages of Tramadol and gabapentin can work together to reduce the pain perception; moreover, this analgesic effect is dose dependent whether given orally, spinally, or locally.⁸³ This combination effectively reverses formalin-induced nociception, which may be helpful in the clinical management of pain from inflammation.⁸³ Another study on rats discovered a synergistic interaction between metamizol and gabapentin in rats formalin test, in particular, the oral delivery of both medications that reduced flinching behaviour in a dose-dependent manner during the formalin test's second phase; this implies investigating Moreover, the combination of metamizol and gabapentin for reducing inflammatory pain in humans Lastly, sevelamer⁹⁴, a medication that lowers serum uric acid levels in haemodialysis patients⁹⁵, and naproxen⁹², a nonselective nonsteroidal anti-inflammatory⁹³, are additional medications that interact with gabapentin. As a rule of thumb, sevelamer and gabapentin have a moderate interaction, with the primary effect being a decrease in gabapentin impacts.

Some contraindications for gabapentin use in patients with muscular problems

Gabapentin use in individuals with myoclonus or myasthenia gravis has been cautioned against in several cases. In particular, a clinical research found symptoms that were comparable to those in myasthenia gravis (weakness in the eyes, weariness, masticatory weakness, facial weakness, and increased serum level of antibodies against the cholinergic receptor following 400 mg/day of gabapentin therapy. Additionally, the patient's health improved with pyridostigmine treatment and withdrawing from gabapentin. According to this, gabapentin may exacerbate myasthenia gravis patients' symptoms. In a trial with rats, the animals received experimental autoimmune Gabapentin (150 mg/kg) was administered to patients with myasthenia gravis or control therapies. Following treatment with gabapentin, the rats of the decreased electrophysiological responses in the experimental group. reactions (amplitude ratio upon repeated stimulation of the nerves) in contrast to rats used as controls Another human investigation found that 1.9% of patients experienced deterioration or the start of myoclonus following gabapentin medication. In particular, myoclonus developed or worsened in these patients within two weeks after beginning gabapentin therapy. The dosages associated with these issues varied from 600–1800 mg. Following the withdrawal of gabapentin or clonazepam treatment, the myoclonus stopped with no significant repercussions.

CONCLUSION

Both large sample studies and individual clinical trials have shown that gabapentin can lead to general health issues when it is overused or misused. Various causes of an insufficient the following are ways that gabapentin is used: inspiration to get "high," reducing the symptoms of opioid withdrawal and increasing A high from methadone. A robust correlation between opioid usage and Dysfunction and overuse of gabapentin have been documented (a research in former prisoners). 43 Issues pertaining to the insufficient application of Death and poisoning are possible outcomes of gabapentin use (Finnish study).

The frequency of issues associated with gabapentin use reported in various research fall between 1.1 and 19%: 1.1% lifelong abuse (online study conducted in the UK), 44 4.8% abuse or dependence (EudraVigilance database), 42 15% abuse (Kentucky Appalachian study), and 37 16% abuse (previous prisoners).43 and 19% use without a prescription. Teratogenicity, hypoventilation, respiratory failure, visual field impairments, myopathy, suicidal or self-harming behaviour, mitochondrial toxicity, somnolence, dizziness, and asthenia are a few of the adverse effects associated with gabapentin. One important consideration is the method of administering gabapentin impacting adverse consequences.

However, more research has revealed the lack

of gabapentin's teratogenic effects; further it is essential to conduct studies with bigger sample sizes and test for teratogenic effects at later developmental stages. (for instance, following early postnatal development). Additionally, it is required to carry out more research using bigger sample sizes on the Gabapentin's effects on visual field defects, potential for abuse, Suicidal behaviour, self-harm, and myopathy: the relevant research have mostly used tiny sample sizes thus far. The findings of the investigations on gabapentin interactions were not all the same. According to various research, gabapentin has a low profile of interactions with hepatic enzymes and other medications as well as plasma proteins. Furthermore, gabapentin is advised for specific populations, such as elderly people who are suffering from cancer patients, people with liver disorders, and others. However, many investigations have revealed that gabapentin may interact with other medications. Such as ethacrynic acid and losartan, can cause motor impairment (research on mice). Furthermore, gabapentin can combine with caffeine and lessen its anticonvulsant properties (Research on mice). For pain relief, gabapentin can work in concert with metamizol or tramadol.

In Furthermore, gabapentin and antiepileptic medications may interact. (mefloquine and phenytoin), antacids (magnesium oxide, Cimetidine, a nonsteroidal anti-inflammatory drug that is not selective medications (naproxen), which lower serum uric acid The findings of the investigations on gabapentin interactions were not all the same. According to various research, gabapentin has a low profile of interactions with hepatic enzymes and other medications as well as plasma proteins. Furthermore, gabapentin is advised for specific populations, such as elderly people who are suffering from cancer patients, people with liver disorders, and others. However, many investigations have revealed that gabapentin may interact with other medications. Such as ethacrynic acid and losartan, can cause motor impairment (research on mice). Furthermore, gabapentin can combine with caffeine and lessen its anticonvulsant properties (Research on mice). For pain relief, gabapentin can work in concert with metamizol or tramadol. In Furthermore, gabapentin and antiepileptic medications may interact. (mefloquine and phenytoin), antacids (magnesium oxide, Cimetidine, a nonsteroidal anti-inflammatory drug that is not selective medications (naproxen), which lower serum uric acid.

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The main reasons for gabapentin misuse are getting “high”, alleviating opioid withdrawal and potentiating methadone. The prevalence of problems related to gabapentin use ranges from 1.1% to 19%. Gabapentin inadequate use can lead to toxicity and mortality. Gabapentin can induce diverse side effects such as teratogenicity, hypoventilation, respiratory failure, deficits in visual field, myopathy, self-harm behavior, suicidal behavior, mitochondrial toxicity, somnolence, dizziness and asthenia; these can be related to the route of administration. However, it seems necessary to conduct more studies with larger sample sizes for confirming these effects. Gabapentin can interact with losartan, ethacrynic acid, caffeine, phenytoin, mefloquine, magnesium oxide, cimetidine, naproxen, sevelamer and morphine. Gabapentin use is contraindicated in patients with myasthenia gravis or myoclonus.

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