

Versatile Therapeutic Potential Of Gabapentin

Mohit Yadav^{1*}, Dr. Silky Sethy², Dr. Farah Deeba³

^{1,2*,3}SGT College of Pharmacy, SGT University, Gurgaon, Haryana, India

*Corresponding Author: Dr. Silky Sethy

^{*}Department of Pharmaceutical Chemistry, SGT University, Gurugram, Haryana, 122505, SGT College of Pharmacy, SGT University, Gurgaon, Haryana, India

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Abstract

In the current era seizures and epilepsy are the most common and incapacitating neurological conditions that affect all ages. Surprisingly, more than 65 million individuals (about 3.2m of the world population) suffer from epilepsy and seizures. Gabapentin is the most widely used drug to treat seizures and epilepsy and also has some other dominant purposes. It was introduced in 1993 as an anticonvulsant for the treatment of seizures, but recently it's thought to be convenient for chronic perioperative prophylaxis, chronic post-operative pain, postoperative nausea and vomiting, and alcohol disorder. It acts on the brain by inhibiting the alpha-2delta-1 receptor and ligand-gated ion channel (GABA) present in the brain which inhibit or decrease the production of excitatory neurotransmitters. This article evaluates the therapeutic potential of gabapentin, dosage, and pharmacodynamics with the goal of providing referable aspects.

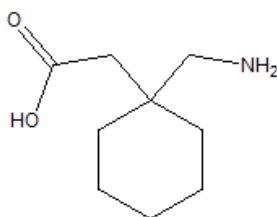
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INTRODUCTION

Gabapentin is a prescribed drug commonly used to treat epilepsy and seizures, as it comes under the class of anticonvulsants works by decreasing the abnormal excitatory hormones released by the brain. Previously, it was used as a muscle relaxant and anti-spasmodic drug but later on, in 1970 it came across to know that it has the potential of anticonvulsant medication. Gabapentin gets FDA approved in 1993 and has been available as a prescribed drug of patients' use since 2004.⁽¹⁸⁾ Lately, gabapentin seems to treat many other disorders which are nerve pain caused by diabetes and shingles infection, restless leg syndrome, relieves postherpetic neuralgia. Lately, newer research explained nonprescriptive uses of gabapentin such as to treat acute symptoms of anxiety, alcohol withdrawal, postoperative surgical pain, and hot flashes which are common in females. The major advantage of gabapentin is that there's limited drug-drug interaction and because of this gabapentin shows bare minimum side effects, also it's safe to use, effective and convenient.⁽¹⁾⁽²⁾⁽⁶⁾

Molecular chemistry:

Gabapentin is [1-(Amino methyl) cyclohexane acetic acid] is a gamma-amino acid i.e.; cyclohexane replaced at position 1 by amino methyl and carboxymethyl. It's structurally similar to gamma-aminobutyric acid (GABA) which is a neurotransmitter that acts on CNS by reducing neuronal excitability by inhibiting nerve transmission.⁽¹³⁾⁽²⁰⁾



Appearance: white crystalline solid

Molecular formula: C₉H₁₇NO₂

Molecular mass: 171.237g/mol

Density: 1.058g/cm³

PH value: 7.4

Pharmacokinetics

Mechanism of action:

Gabapentin acts in alpha-2 delta calcium channels subunits that disrupts the regulatory and protein binding activity of alpha-2 delta. Which inhibits or slow down the calcium channel influx into the cell membrane which reduces the activity of

alpha-2 delta channels and facilitates GABA receptor activity, decreases the release of neurotransmitters and blocks the activity of neural GABA receptor activity which leads to inhibition the release of excitatory hormones thus reduces the spread of seizure.(6)(8)(20)

Absorption:

Gabapentin is only available in oral dosage form. It's absorbed in the gut by active transport process which is mediated by amino acid transporter and half of the metabolites are absorbed by kidneys. It gets absorbed slowly until with maximum plasma level concentration which is attained within 3-4 hrs.(5)(8)

Oral bioavailability:

According to studies bioavailability of is approximately ranges from 60%, 47%, 34%, 33%, and 27% as per the following dose 900, 1200, 2400, 3600, 4800 mg/day divided into 3 doses. Oral bioavailability increases with those drugs which increase the transit time of gabapentin in small intestine such as oral morphine.(14)(20)

Elimination:

Gabapentin is eliminated from the body through urine as unchanged particles. The t-half of gabapentin in a normal person is approximately 5-7 hrs. In patients who have a high creatinine clearance rate, the t-half or the rate of elimination of gabapentin is found to be less than is about 52 hrs.(5)(8)

Therapeutic effects of Gabapentin:

Gabapentin for neuropathic pain syndrome:

The most important use of gabapentin is in neuropathic pain like post-herpetic neuralgia, diabetic neuropathy, Trigeminal neuralgia, HIV-associated neuralgia, and stroke (4)(11). Previously to treat neuropathic pain AEDs like carbamazepine, phenytoin, and valproate were seemed to be used although each has shown serious side effects on patients, therefore, to treat these painful conditions gabapentin was chosen over these drugs because it shows bare minimum side effects. Here gabapentin acts as an anti-analgesic it works by inhibiting the voltage-gated calcium channels which decreases the amount of calcium in the neural cleft and therefore decreases the release of neurotransmitters from the hyper-excited neuron .(3)(2)(6)

Gabapentin dosage for adults: starts with a single dose of 300 mg/day for day 1, for day 2 total of 600mg/day (300mg twice a day). Studies show dose can be increased up to 1800mg/day (600mg thrice a day) as needed for pain relief by the patient.(4)(12)

Gabapentin dosage for pediatric patients: Recommended initial dose is 2mg/kg/day, the maximum range of dose can reach up to 8 to 35mg/kg/day divided into 3 times in a day. (12)

Sist et al. described the effect of gabapentin in neuropathic pain on two patients. Gabapentin given dose to the patient was given 900mg/day for a week. The patient reported progress in pain paroxysms for trigeminal neuralgia pain started to decrease and the patient was kept followed up for 6 months and gabapentin was still effective.(12)(11)

Wiffin pj et al. described effect of gabapentin for diabetic neuropathy and HIV. Out of 10, 6 patients shows reduction in neuropathic pain caused by diabetes and HIV associated neuropathic pain. Given dose of gabapentin to patients was 1800mg/day to 3600mg/day. The outcome of clinical study shows 60% reduction of pain after continuing gabapentin for at least a week and there was no relative side effects shown by patients. Clinical studies was done on different age groups and in different type of neuropathic pain have shown it to be the most effective drug either given as immunotherapy or combined with any other drug.(12)(16)

Gabapentin for psychiatric disorders:

Gabapentin analyses to use in many psychiatric conditions such as anxiety, depression, alcohol withdrawal, and bipolar disorder. But its notably effective in bipolar disorder and in alcohol withdrawal. Gabapentin is the safe alternative option for those people who have shown partial results towards benzodiazepines for acute anxiety disorder. Studies have shown that gabapentin helps in psychiatric disorders as it has the ability to calm the excitatory response of neurons.(1)(4)

Adult dosage of Gabapentin: starts with 600mg/day (300 mg twice a day) or 2400mg/day (800mg thrice a day or 600mg four times a day) depending on patient condition and response .dose can increase up to 3600mg/day.(15)(18)

Pediatric dosage of Gabapentin: 300mg/day once daily, dose can increase up to 900 to 1200mg/day.(15)

Bennett et al. evaluated the response of 5 patients with bipolar disorder (3) and acute anxiety disorder(2). Patients had a history of intolerance and unresponsiveness toward other medications. on hospitalization, patients received the dose of gabapentin 600-2400mg/day for one month along with their mood stabilizing medications. The patient experienced marked improvement and told to have less anxiety after having gabapentin.(21)

Stanton et al. described a 40 yrs. old was hospitalized because of bipolar disorder and alcohol dependency. The patient

was suffering from abnormal liver function, thrombocytopenia, and prolonged thrombin count so the patient refused to get treated with valproate and carbamazepine gabapentin immunotherapy was given to the patient at a dose of 900mg/day for 3 days and dose was increased to 3600mg/day by day 4. After 10 days of therapy gabapentin patient shows marked improvement, previous symptoms of irritability, insomnia, anxiety, and hallucinations all are improved.(18)(20)
Here studies show that gabapentin is effective in many psychiatric disorders and shows very less side effects.

Gabapentin for movement disorders:

Studies show that gabapentin is efficacious in many movement disorders such as tremors, restless leg syndrome, parkinsonism, amyotrophic lateral sclerosis (ALS), and periodic limb movement of sleep.(2)(21)

Adult dosage of Gabapentin: Starts with 300mg/day (100mg thrice a day) two hours before the regular onset of symptoms. Dosage can be increased in every few days as per required, maximum dose limit can reach up to 1800mg to 2400mg/day(19)

Pediatric dosage of Gabapentin: Starts with 100mg/day (once or twice) one to two hours before the regular onset of symptoms. The maximum dose limit can reach up to 900-1200mg/day.(19)

Pahwa et al. investigate the efficacy of gabapentin for the treatment of tremors compared with placebo for first 14 days patients was treated with 1800mg of gabapentin per day, and the patient shows no response compared to the placebo. The research was carried out again and this time patient received 3600mg of gabapentin for six weeks in contrast to placebo. The patient shows marked improvement in self-report scores for tremors, observed tremors score and daily activity was improved.(21)

Restless leg syndrome is a disorder characterized by the uncontrolled urge of leg movement because of sensory and motor symptoms. About 2-10% of people are suffering from restless leg syndrome. Patient was previously treated with benzodiazepines, dopaminergic drugs, and opiates; but the patient didn't seem to achieve any positive results. Recent studies show that restless leg syndrome can get successfully treated with gabapentin therapy.(13)

Adler et al. conducted an open lab study to demonstrate the efficacy of gabapentin toward restless leg syndrome. Eight patients suffering from restless leg syndrome received 300-2400mg dose of gabapentin per day. Out of 8 patients, 4 patients shows proper improvement and decrease in symptoms, 3 patients shows 76% effectiveness and improvement in symptoms, and 1 patient discontinued the dose. Positive results were shown by patients after gabapentin therapy.(21)

Gabapentin for alcohol disorder:

Globally, alcohol abuse ranks sixth in terms of risk factors for early mortality and disability. as gabapentin doesn't metabolized in liver and have shown no impact on liver cells, gabapentin has been used to treat alcohol dependency. It works by reducing the amplitudes of inhibitory post synaptic currents (IPSCs) In the central nucleus of the amygdala (CeA), which is mediated by GABA receptors and reduced dependence-induced alcohol consumption.(22)

Bonnet et al. conducted the study on 37 patients who was suffering from severe alcohol withdrawal disorder. Each patient received a dose of 800mg of gabapentin 3 times a day for 3 months, some patients have shown early improvement in their symptoms and some have shown late response with mild side effects like insomnia and anxiety.

So, conducted researches have shown that gabapentin at a dose of 2,400mg-3,200mg is effective for the treatment of severe alcohol withdrawal.(9,22)

Additional uses of Gabapentin:

Some newer researches shows evidence of gabapentin for the treatment of migraine, cocaine dependence, posttraumatic stress syndrome (PTSD).(1)(9)(21)

Markowitz et al. explained a case history of a patient who was suffering from cocaine dependency. Patient starts using gabapentin at a dose of 600-1500mg/day after she observed the symptoms of cocaine withdrawal (irritability, agitation, insomnia, depression and cravings). she continued the dose of gabapentin for 3 months and reported that gabapentin helps with the cravings and relaxed her. She also reported gabapentin helps her to overcome cocaine dependency.(20)(21)

Mathew and Lucker evaluate the effect of gabapentin for the prophylaxis of migraine headaches in their study. Patients were suffering from migraine headaches some with aura and some without aura. They noticed that there is reduction in the frequency and severity of migraine when patients was given gabapentin therapy at a dose of 900-1800mg/day.(21)

Stein et al. purposed the study on 48 patients suffering from PTSD. 17 patients was treated with propranolol at a dose of 60-120mg/day, 17 patients received placebo after 48 hours of PTSD trauma and rest 14 patients was given gabapentin at a dose of 900-1200mg/day. There were no significant response from first 17 patients who received a treatment of propranolol, however about 30 patients who received gabapentin shows marked reduction in symptoms, improved sleep

and shows decreased frequency of nightmares.(18)

Dosage forms and strength of Gabapentin available: Gabapentin tablet: available as 300 mg, 600mg and 800mg
Gabapentin oral solution: Available as 250mg
Gabapentin capsule: Available as 100mg, 300mg and 400mg gelatin capsule Gabapentin enacarbil: Available as 300 mg and 600mg extended release tablet.

Available brand names for gabapentin

- Neurontin
- Horizant
- Gralise
- Fusepaq fanatrex

What are the Contraindications/precautions for the use of Gabapentin?

Gabapentin is contraindicated in those who have shown hypersensitivity to it or any other components.(4)(20)
Patients who's suffering from:

☐ **Depression or suicidal tendency**

Patient on Gabapentin therapy tends to show behavioral and mood changes that can worsen the signs of depression and patients' tendency of suicide by unintentional overdose(4)

☐ **Kidney disease**

As Gabapentin is excreted by kidneys, in patients suffering from kidney diseases such as renal impairment, or renal failure, dialysis-increased doses of Gabapentin can worsen the symptoms(4)(20).

☐ **Withdrawal of dosage**

The person who tends to abruptly stop or discontinue the dose given of gabapentin has the possibility of an increase in the frequency of seizures and some withdrawal symptoms such as tremors, slow heart rate, excessive sweating, and insomnia(20)

☐ **Drug dependency**

People who abuse gabapentin for higher sedation and former opioids. Gabapentin can boost the effect or decrease the effect because this patient can experience severe anxiety (20)

☐ **Respiratory distress**

Patient with underlying respiratory problem such as COPD tends to develop serious respiratory suppression which can be seriously fatal.(4)(20)

☐ **Pregnancy**

As such there's no evidence that gabapentin should be avoided during pregnancy, but females suffering from epilepsy should be more closely monitoring the fetus. Development during the first and third trimesters. (4)

What are the Side effects associated with gabapentin?

Common side effects:

- ☐ Feeling sleepy tired or dizzy
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhoea
- ☐ Mood changes
- ☐ Swelling
- ☐ Blurred vision
- ☐ Xerostomia
- ☐ Constipation
- ☐ Head ache
- ☐ Weight gain
- ☐ Ataxia

☐ Peripheral oedema
Serious side effects:

- Suicidal thoughts
- Persistent fever
- Continuous stomach pain
- Swollen gland
- Muscle pain

- Hallucinations
- Anaphylaxis
- Angioedema

Drug interaction

Drug interaction can change the action of the drug, can disturb how medicine works, and can affect the bioavailability of gabapentin which can lead to serious side effects. Here are some drugs that should be avoided while taking gabapentin; antihistamines such as cetirizine, and phhenhydramine, drugs for sleep and anxiety such as alprazolam, diazepam, zolpidem, musclerelaxants, narcotic pain relievers such as codeine, morphine, products that cause drowsiness such as alcohol, cold and cough medications, antacids such as aluminum hydroxide, magnesium hydroxide, probenecid .(7)(19)

CONCLUSION

Gabapentin is a novel antiepileptic/ anticonvulsant drug with secondary generalization. Nowadays it is widely prescribed by primary health care providers, neurologists, and orthopedic surgeons for mental health disorders, Because of its fewer side effect and minimum drug interaction properties the effectiveness of gabapentin has been exemplified in various conditions namely neuropathic pain syndrome, alcohol withdrawal, bipolar syndromes, cocaine dependency, migraine, post-traumatic stress syndrome, tremors, restless leg syndrome. This article reviewed various studies on gabapentin and those studies suggest that gabapentin can show a significant improvement in symptoms of various disorders. Also gabapentin appeared to be perfectly accepted by patients. There are still many researches going on for the further advancement in treatment and more trials are being conducted to explore the versatility in therapeutic potential of gabapentin.

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