# Gabapentin as a Novel Drug

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**ABSTRACT**
**Background:** *Gabapentin is an antiepileptic and analgesic drug. There is an urge for reliable scientific evidence to support its ongoing widespread use for treatment of a number of other conditions as well.*
**Objective:** *Critical appraisal of the available literature on pharmacological basis of approved and off-label uses of gabapentin to assess the scope for its new roles in therapeutics.*
**Data Source:** *A systematic review of literature was made to study history, pharmacology, approved uses and off-label uses of gabapentin.*
**Conclusion:** *Gabapentin use has extended into the management of a variety of disorders besides epilepsy, neuropathic pain and restless leg syndrome. A large number of clinical trials are conducted to establish its role in a wide spectrum of clinical situations. While tremendous scientific speculations are surrounding the drug; there is a need to know more about this novel drug including its mechanism of action and adverse effect profile.*

**Key words:** *Gabapentin, off-label, anticonvulsant*

## INTRODUCTION

Gabapentin was introduced in 1993 as an anticonvulsant and later was found effective in chronic neuropathic pain as well. The US Food and Drug Administration (USFDA) has approved gabapentin as an adjuvant anticonvulsant drug for the treatment of refractory partial seizures, post-herpetic neuralgia and restless leg syndrome (RLS) only but the drug is enjoying significant off-label uses. Scientific evidence of clinical efficacy supports many of these off-label uses if not all of them. According to a survey in the USA, gabapentin had highest proportion of off-label prescription (87%) followed by amitriptyline hydrochloride (81%) among 160 commonly prescribed drugs[1]. There is a need to understand the pharmacological rationale for its diverse indications and adverse effects in order to evaluate whether or not there can be any theoretically specific indicators to suggest its yet newer indications that merit scientific scrutiny in the form of well-designed clinical trials to generate credible evidence.

### Pharmacology

Gabapentin is a structural analogue of the inhibitory neurotransmitter gamma amino butyric acid; described as 1-(aminomethyl) cyclohexane acetic acid with molecular formula of $C_9 11_{17} NO_2$. It is water soluble and absorption in gastrointestinal tract occurs via the amino acid transport system in the proximal small bowel. This transportation is capacity limited, thus gabapentin bioavailability decreases at high doses. Plasma concentrations are proportional with dose up to 1800mg daily and then plateau at approximately 3600mg daily. After ingestion of a single 300mg capsule, peak plasma concentrations of 2.7µg/ml are achieved within 2 to 3 hours. Gabapentin is neither plasma protein bound nor does it induce hepatic enzymes. In humans, it is not metabolized and is eliminated unchanged in urine; elimination half-life is between 4.8 and 8.7 hours. Dose adjustment should be made in patients with compromised renal function. Drug-drug interactions of gabapentin are few; cimetidine decreases its renal clearance and antacids reduce its bioavailability in healthy individuals. The drug is well tolerated; the most common adverse effects include somnolence (15.2%), dizziness (10.9%), asthenia (6%), headache (4.8%), nausea (3.2%), ataxia (2.6%), weight gain (2.6%) and amblyopia (2.1%) [4]. Peripheral edema and sexual dysfunction is also reported. 1n 2009 the USFDA issued a warning of increased risk of depression and suicide associated with gabapentin use, along with other anticonvulsants.

Although a GABA analogue, yet gabapentin does not bind to $GABA_A$ or $GABA_B$ receptor. Its high affinity for auxiliary $\alpha_2\delta$ subunit of voltage gated $Ca^{2+}$(Ca(V)) channels[2] was known but only recently and unexpectedly this binding was proposed to be responsible for its mechanism of action; previously the subunit was not speculated to be a therapeutic target. Evidence is accumulating that neuronal role of $\alpha_2\delta$ subunit include channel trafficking, calcium current

modulation and synaptogenesis. Gabapentin binds to $\alpha_2\delta$ and reduces influx of calcium through presynaptic voltage-gated calcium channels thereby reducing neurotransmitter release bestowing analgesic, antiepileptic and sedative properties. A study performed in mice and in cell culture suggested that gabapentin halts the formation of new synapses in the brain[3]. Nevertheless, additional molecular targets and other mechanisms of action cannot be ruled out.

**Indications**

Gabapentin was approved by the USFDA in December 1993 as an adjuvant anticonvulsant drug for the treatment of refractory partial seizures, with or without secondary generalization in patients over the age of 12years. In October 2000, it was approved as adjunctive therapy for partial seizures in patients aged 3-12 years. Then again in 2002, gabapentin got approval by the USFDA for treatment of post-herpetic neuralgia. Gabapentin enacarbil extended-release tablet formulation was approved for treatment of moderate to severe primary restless leg syndrome (RLG) in adults in April, 2011. In the UK, it is approved for treatment of all types of neuropathic pain.

**Off-label uses**

Off-label use of a drug though different from its formal regulatory agreement is generally legal. However, marketing of off-label uses of a drug is illegal. Gabapentin has significant number of non-FDA approved uses. In fact, the drug was widely used for the off-label treatment of pain and psychiatric conditions following its advent in the market making it a remarkable financial success. Subsequently, its manufacturer was investigated and convicted for inappropriate marketing and illegal promotion of the agent for its off-label uses[5,6].

Gabapentin has been used to treat variety of chronic pain conditions, including post-herpetic neuralgia, diabetic neuropathy, complex regional pain syndrome, inflammatory pain, central pain, malignant pain, trigeminal neuralgia, HIV-related neuropathy, headaches, and multiple sclerosis. In a double-blind, double dummy, cross over trial involving patients with diabetic polyneuropathy or post-herpetic neuralgia with daily pain score of at least 4 (scale 0–10), combined gabapentin and nortriptyline was found to be more efficacious than either drug given alone for neuropathic pain[7].Pain with combination treatment was significantly lower than with gabapentin (−0·9, 95% CI −1·4 to −0·3, p=0·001) or nortriptyline alone (−0·6, 95% CI −1·1 to −0·1, p=0·02). Gabapentin has been evaluated as multimodal perioperative drug in some good quality studies[8-10]. Most of these studies have shown that either single preoperative or repeated doses of gabapentin decrease acute postoperative pain and/or need for postoperative opioids. In the study by Pandey *et al,* patients in the gabapentin group had significantly lower pain scores at all-time intervals (2.65 +/- 3.00, 1.99 +/- 1.48, 1.40 +/- 0.95, 0.65 +/- 0.61) in comparison to tramadol (2.97 +/- 2.35, 2.37 +/- 1.45, 1.89 +/- 1.16, 0.87 +/- 0.50) and placebo (5.53 +/- 2.22, 3.33 +/- 1.37, 2.41 +/- 1.19, 1.19 +/- 0.56). Other such studies involved surgical procedures like abdominal and vaginal hysterectomy, breast surgery for cancer, lumbar discectomy and spinal fusion, laparoscopic cholecystectomy, orthopedic surgery and ENT surgery.

The drug has been shown useful in chemotherapy induced nausea and vomiting[11]. Many studies have reported gabapentin as a potential antiemetic in perioperative setting. In the study of Pandey *et al* (2000) gabapentin as premedication effectively suppresses nausea and vomiting and postoperative rescue analgesic requirement in patients of laparoscopic cholecystectomy[12]. Incidence of post-operative nausea and vomiting within 24 hrs after laparoscopic cholecystectomy was significantly lower in gabapentin group (46/125) than in the placebo group (75/125) (37.8% vs. 60%; P =0.04). Saeed Khademi *et al*, in 2010, demonstrated that gabapentin decreased postoperative nausea and vomiting (PONV) and additional postoperative analgesics after open cholecystectomy[13]. Antiemetic and analgesic effect of gabapentin was also shown by Srivastava *et al* after minilap open cholecystectomy[14]. It is interesting that a single drug may have multimodal perioperative effects.

Gabapentin is used for a variety of mental health conditions. In the treatment of bipolar disorder it has advantages like a wide therapeutic index, lack of need to follow serum levels and relative ease while changing doses[15]. In 1997 Stanton and colleagues[16] first reported the successful use of gabapentin as monotherapy in acute mania. Several open and retrospective studies report good responses with gabapentin in the treatment of bipolar disorder[17] but it has failed to show clear antimanic efficacy in randomized trials. Nevertheless, gabapentin may be clinically useful as an add-on agent in refractory and co-morbid patients[18]. Gabapentin has been used in patients with anxiety disorder, panic disorder, social phobia, aggressive behavior, posttraumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD)[19]. Other clinical uses of gabapentin have been in the treatment of substance abuse disorders and in the treatment of agitation and disruptive behavior in Alzheimer's disease[20].

Gabapentin has been shown to reduce hot flash frequency and severity in postmenopausal women. Anecdotal experience with gabapentin, as a non-hormonal option for hot flashes, was reported in 2002[21]. The first report of a prospective pilot trial appeared in 2002[22]. In 2003 the first results of a randomized, double blind, placebo controlled trial were published[23]. Pandya

*et al*, in 2005, enrolled 420 women with breast cancer who were having two or more hot flashes per day[24]. Patients were randomly assigned placebo, gabapentin 300 mg/day, or gabapentin 900 mg/day by mouth in three divided doses for 8 weeks. The percentage decreases in hot-flash severity score between baseline and weeks 4 and 8, respectively were: 21% (95% CI 12 to 30) and 15% (1 to 29) in the placebo group; 33% (23 to 43) and 31% (16 to 46) in the group assigned gabapentin 300 mg; and 49% (42 to 56) and 46% (34 to 58) in the group assigned gabapentin 900 mg. The differences between the groups were significant (p=0.0001 at 4 weeks and p=0.007 at 8 weeks by ANCOVA for overall treatment effect). Subsequently, reports from other studies became available[25]. The studies are few but all have shown gabapentin to be safe and effective in treatment of hot flashes.

A number of reliable clinical trials have found gabapentin well tolerated and effective in prophylaxis of migraine[26]. Gabapentin is cost-effective in migraine prophylaxis but further evaluation may be required. In a randomized, double blind, placebo-controlled trial, gabapentin reduced alcohol consumption and craving[27]. A 12-week, randomized dose-ranging trial of 150 men and women over 18 years of age with current alcohol dependence was conducted. The abstinence rate was 4.1% (95% CI, 1.1 to 13.7) in the placebo group, 11.1% (95% CI, 5.2 to 22.2) in the 900 mg group, and 17.0% (95% CI, 8.9 to 30.1) in the 1800 mg group (p = 0.04 for linear dose effect, NNT = 8 for 1800 mg). Further studies are required to determine the utility and safety of the drug in treatment of alcoholism. A randomized placebo-controlled double-blind trial shows that gabapentin is safe and effective for treating uremic pruritus in hemodialysis patients[28].

## CONCLUSION

Gabapentin is in widespread use both for approved as well as unapproved indications; it has a favorable side effect profile. The drug binds to $\alpha_2\delta$ subunit of voltage gated $Ca^{2+}$ (Ca(V)) channels and modulates neuronal function at synapses making it effective for various painful conditions as well as epilepsy. But gabapentin displays a broad spectrum of other pharmacological effects giving rise to the possibility of its additional mechanisms of action that need to be studied. Furthermore, as of now the only other drug known to be $\alpha_2\delta$ ligand is pregabalin. Considering $\alpha_2\delta$ subunit as a potential drug target in therapeutics, the search for more such ligands and their evaluation and clinical utility becomes inevitable. Gabapentin may be a safe and well tolerated treatment for a number of clinical situations if supported by enough scientific evidence. Future clinical trials are essential to furnish the insight into the pharmacology of this multimodal drug in order to further delineate its role in treatment of diverse disorders.

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