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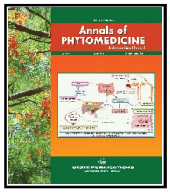

Review Article : Open Access

A comprehensive review on pregabalin as a drug for different neurological disorders

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Abstract

Lyrica, the brand name for pregabalin, is a versatile medication that offers a wide array of therapeutic uses. Its IUPAC name is (S)-3-(amidomethyl)-5-methylhexanoic acid. It falls under the category of medications referred to as anticonvulsants or antiepileptics. This drug is used to treat multiple medical conditions. Pregabalin is primarily indicated for neuropathic pain conditions, including neuropathic pain associated with spinal cord injury, diabetic neuropathy, fibromyalgia and postherpetic-neuralgia. It is also used as an adjunct therapy for partial onset seizures in epilepsy and the management of generalized anxiety disorder (GAD). In the brain, pregabalin attaches to calcium channels within the central nervous system, thereby diminishing the secretion of neurotransmitters like glutamate, norepinephrine, and substance P. This modulation of neurotransmitter release leads to a dampening of abnormal electrical activity. In general, pregabalin is widely regarded as a versatile medication because of its effectiveness in treating neuropathic pain, seizures and generalized anxiety disorder. It offers relief to numerous patients suffering from these conditions. Pregabalin is utilized more frequently by women than men, and the regular implementation of therapeutic drug monitoring (TDM) is most prevalent among patients diagnosed with epilepsy.

1 Introduction

Pregabalin is a naturally occurring transmitter of GABA (gamma-aminobutyric acid) (Ryvlin *et al.,* 2008). Pregabalin is used for the management of partial epilepsy, neuropsychiatric disease and treatment. Pregabalin has proven to be a very successful and well-tolerated adjuvant medication in clinical studies for treating people with partial seizures (Vinod Gahlot *et al.,* 2021). whether they have secondary generalization (French *et al.,* 2003). It was first demonstrated to be useful in the treatment of diabetic peripheral neuropathy neuralgia and neuropathic pain. In June 2005 saw the approval of adjuvant therapy for seizure sufferers whether a secondary generalization is present or not (Tassone *et al.,* 2007). Pregabalin is categorized as a class 1 substance in the biopharmaceutics classification system (BCS). It also has anticonvulsant, oxidant and inflammatory properties (Ayman Geddawy *et al*., 2023: Kumar *et al*., 2022). Pregabalin taken orally is absorbed more quickly, reaching maximum plasma concentrations in about an hour. First-order linear absorption results in plasma concentrations rising in direct proportion to dosage (Jack *et al*., 2008).

Furthermore, extensive clinical studies have provided evidence of the efficacy and varying impact of pregabalin based on dosage. When used alone or in case conjunction with analgesics for the management of the condition pain and associated symptoms (Shibahara *et al*., 2011; Shibahara *et al*., 2012). Despite its structural similarity to GABA, pregabalin does not exhibit any activity at GABA receptors and does not seem to imitate GABA's physiological effects. This paper aims to examine the chemical and pharmacokinetic characteristics of pregabalin, as well as delve into its historical background (Ryvlin *et al*., 2008).

2. History overview

In July 2004, the European Commission granted approval for the use of pregabalin in the treatment of peripheral neuropathic pain and as an adjuvant therapy for partial seizures in patients with epilepsy. This decision was made after evaluating the outcomes of ten clinical trials that involved a total of over nine thousand patients. In December 2004, the United States Food and Drug Administration (USFDA) approved pregabalin to be used in the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and postherpetic-neuralgia. Similarly, in March 2006, the European Commission also authorized the use of pregabalin for the treatment of generalized anxiety disorder. Later in 2005, the medication received approval for its supplementary use in treating partial-onset epilepsy in adults. Following reports of heightened mood in carefully monitored clinical trials, the occurrence of negative effects upon sudden discontinuation of pregabalin and findings from a limited study involving fifteen recreational drug users who were not dependent on the drug, the Drug Enforcement Administration has categorized pregabalin as a Schedule V substance under the Controlled Substances Act (Drug Enforcement Administration, 2005).

3. Structure activity relationship

Pregabalin binds strongly to the α2-δ subunit of voltage-gated calcium channels and is also transported by the system L neutral amino acid transporter. Researchers prepared and tested analogs of pregabalin to understand their binding affinity to α2-δ subunits and their ability to inhibit system L transporter function. In preclinical studies, these

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compounds were evaluated for their efficacy in promoting anxiolytic, analgesic and anti-convulsant effects. The results indicate that different structural characteristics affect the binding to α2-δ subunits and the inhibition of system L transport, but both interactions contribute to the compounds overall *in vivo* effects (Belliotti Thomas *et al.*, 2005).

Pregabalin does not seem to physiologically replicate GABA and is not active at a number of GABA receptors. Preclinical models have demonstrated its efficacy in various analgesia models, such as rat models of surgical pain, a model of thermal hyperalgesia and models of hyperalgesia induced by formalin and carrageenan. In rodent studies, it also prevents both static and dynamic allodynia. Analgesics for both neuropathic and non-neuropathic chronic pain are being developed, including pregabalin (Hill *et al.*, 2001). Pregabalin is a lipophilic derivative of GABA; its exact mechanisms of action as an analgesic and anti-convulsant are unknown (Errante and Petroff, 2003). It is well known that the c-amino acid pregabalin binds to the gabapentin binding site on the α2-δ subunit of the central nervous system's voltage-sensitive calcium channels. Pregabalin's binding to the α2-δ protein is thought to modify the functional effects that these proteins have on enhanced neurotransmitter release and calcium currents in activated neurons. The anticonvulsant, anxiolytic and analgesic actions of these substances are believed to be caused by reduced release of excitatory neurotransmitters and peptide neuromodulators, particularly in situations of hyperexcitability. In placebo-controlled trials, pregabalin has been demonstrated to lessen the frequency of partial seizures, the pain associated with diabetic peripheral neuropathy and postherpetic-neuralgia and the symptoms of generalized anxiety disorder (Schelkun *et al.*, 2006).

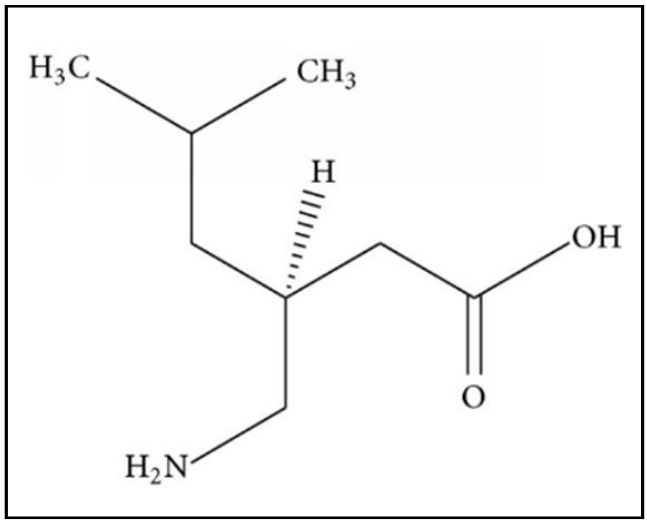

Figure 1: Structure of pregabalin.

4. Dosage

The maximum suggested dose of pregabalin for uncomfortable DPN is 100 mg thrice a day. The starting dosage should be 50 mg three times a day (150 mg/day); based on tolerability with impaired renal function should have their dosage modified. Despite being evaluated at a less well-tolerated dose of 600 mg/day, pregabalin does not appear to offer any further substantial benefits. Treating DPN patients with doses greater than 300 mg/day is not advised due to the dose-dependent side effects (Gajraj, 2007).

Table 1: Dosage regimen for different indications (Manjushree *et al.*, 2015)

Type of pain	Dose and duration
Diabetic painful neuropathy	150-600 mg/kg, 4-14 weeks
Chemotherapy-induced neuropathic pain	75-300 mg/day, 2-8 weeks
Postherpetic-neuralgia (PHN)	150-600 mg/day, 8-13 weeks
Fibromyalgia	150-600 mg/day, 4-12 weeks
Trigeminal neuralgia	150-600 mg/kg, 8 weeks
Post-operative pain	300-600 mg/day, pre/post-operatively

5. Mechanism of action

Pregabalin hinders the VGCC (voltage gated calcium channel), leading to a decrease in Ca^{2+} influx. Consequently, synapses release glutamate and sensory neuropeptides (substance P and CGRP). Additionally, pregabalin enhances the functioning of excitatory amino acid transporters (EAATs), thereby decreasing the synaptic availability of glutamate. The neurotransmitters will not enter (Palla Anil Kumar *et al.*, 2022). Reduced glutamate concentrations additionally prevented the reduction in neural activity and NMDA activation. Pregabalin also helps the suppression of neuronal excitation by activating the K^{+}-ATP channels. In diverse neuropathic pain situations, pregabalin finally provides significant pain relief through all these pathways (Martin *et al.*, 2002).

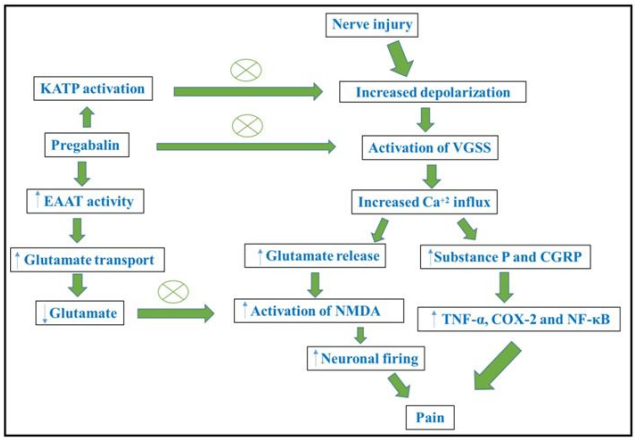

Figure 2: Schematic representation of mechanism of action.

6. Pharmacokinetics

Pregabalin is a pharmaceutical drug that falls under the category of antiepileptic medications. It is primarily prescribed to alleviate a range of medical conditions, such as neuropathic pain and seizures. However, they differ in their absorption, metabolism and elimination processes (Stewart *et al.*, 1993).

6.1 Absorption

Pregabalin exhibits a linear pharmacokinetic profile due to the absence of saturable absorption (Bockbrader *et al.*, 2010; Su *et al.*, 2005). Within an hour of administration, peak blood concentrations are reached due to its rapid absorption (Ben-Menachem, 2004).

6.2 Bioavailability

Pregabalin has a dose-independent average bioavailability of over 90%. This predictability could result in a more consistent reaction from the patient (Piyapolrungroj *et al.*, 2001; Busch *et al.*, 1999).

6.3 Metabolism and elimination

Pregabalin does not bind to plasma proteins and undergoes no metabolic changes in the liver. The majority of the absorbed dose, approximately 98% is excreted unchanged in the urine, indicating that renal elimination is the primary route of elimination. The amount of pregabalin removed is almost equal to the amount of creatinine cleared (Randinitis *et al.*, 2003).

6.4 Dosage adjustments

Pregabalin clearance is decreased in those with compromised kidney function. As a result, patients with a creatinine clearance between 30 and 60 ml/min should receive a 50% decrease in their daily dosage, in contrast to patients whose clearance is above 60 ml/min.

6.5 Drug interactions

Formal interaction studies have not revealed any pharmacokinetic drug-drug interactions for pregabalin. They do not interact, based on their pharmacokinetic profiles (Brodie *et al.*, 2005; Perucca, 2006).

7. Pregabalin in fibromyalgia

Fibromyalgia, a chronic pain syndrome, is characterized by allodynia, hyperalgesia, and widespread musculoskeletal pain, without any identifiable cause. This condition is predominantly found in older adults and has a higher prevalence among women (Derry *et al.*, 2016). Pregabalin is among the recommended medications in the present therapeutic approaches, which encompass non-pharmacological techniques as well. Pregabalin is thought to alleviate fibromyalgia pain by inhibiting the release of neurotransmitters and calcium channels in the ascending pain pathway. Furthermore, it effectively reduces the concentrations of glutamate and glutamine in the posterior insula, impeding its capacity to interact with the default mode network (DFN) (Clauw, 2014). Patients with fibromyalgia demonstrate heightened activity in the DFN, a brain network commonly associated with introspective thinking and the recollection of personal memories. It is still unknown if the fibromyalgia-related neuropathy is the cause or the effect of the increased DFN activity (Fitzcharles *et al.,* 2013).

Table 2: Recommended dosage according to age in fibromyalgia

Age	Initial dosage	Maximum dosage	Administration frequency
Pediatric patients (30 kg or more)	3.5 mg/day	Must be determined by the doctor	3 divided doses
Adults (17 and older)	300-450 mg/day	450 mg/day (do not exceed)	2 or 3 divided doses

8. Pregabalin in diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) is a common consequence of type 2 diabetes mellitus, resulting from nerve impairment due to consistently elevated blood sugar levels. Primarily impacting the lower limbs, indications encompass numbness, tingling, burning sensations, intense discomfort and impaired equilibrium. Opioids, topical capsaicin patches, and tricyclic antidepressants are among the treatment options available for DPN (Fashner and Bell, 2011). Pregabalin is recommended to be taken in daily doses ranging from 300 mg to 600 mg. Its mechanism of action involves suppressing the excitatory primary afferent fibers that transmit nociceptive information to the spinal dorsal horn. Patients commonly experience these effects within a short period, suggesting a mechanism of action that could potentially involve synaptic plasticity and a decrease in pro-nociceptive proteins (Woolf and Mannion, 1999).

Table 3: Recommended dosage according to age in diabetic peripheral neuropathy

Age	Initial dosage	Maximum dosage	Administration frequency
Pediatric patients (below 12)	75 mg/day	150 mg/day	2 divided doses
Adults (17 and above)	150-300 mg/day	300 mg/day	2 or 3 divided doses

Table 4: Recommended dosage according to age in postherpetic (Herpes Zoster) neuralgia

Age	Initial dosage	Maximum dosage	Administration frequency
Pediatric patients (30 kg or more)	2.5 mg/day	10 mg/day(not to exceed 600 mg/day)	2 or 3 divided doses
Pediatric patients (less than 30 kg)	3.5 mg/day	14 mg/day	Less than 4 years of age divided doses4 years of age and older: 2 or 3 divided doses
Adults (17 and older)	150 mg/day	600 mg/day	2 or 3 divided doses

9. Postherpetic (Herpes Zoster) neuralgia

Postherpetic-neuralgia (PHN) is a distressing ailment that can endure for an extended period, ranging from months to even years, after an outbreak of herpes zoster (shingles). This condition arises when the varicellar zoster virus, responsible for causing chicken pox, reawakens from its dormant phase (Van Nooten *et al.*, 2017). PHN can present itself as either constant or intermittent pain without any external trigger, or as hyperalgesia. There are several treatment options available for PHN, including tricyclic antidepressants and topical analgesics such as lidocaine and gabapentinoids. Pregabalin, which is typically prescribed at doses ranging from 150 mg to 600 mg per day, consistently improves pain scores in patients with PHN. It has been found to have similar effectiveness as gabapentin and when used in combination

with topical lidocaine, it can significantly reduce pain, even in patients who did not respond to either medication individually (Patel *et al*., 2000). It is worth noting that PHN is less commonly observed in pediatric epileptic patients (Hindmarch *et al*., 2005).

10. Adverse effects

Pregabalin has temporary, dose-dependent mild to moderate side effects that are often well tolerated. The most commonly reported symptoms are somnolence and dizziness (22-29%). Less common adverse reactions include xerostomia, peripheral swelling, visual impairment, increased body weight and diminished ability to focus.

A thorough examination of 38 studies with 6,588 participants revealed that major adverse events (AEs) were documented in 21 of them or 55% of the total. Of them, 2,206 received a placebo and 4,382 were randomly assigned to receive pregabalin. There was no discernible difference in risk between the two groups, as indicated by the relaive risk (RR) of 1.02 (with a 95% confidence interval of 0.77 to 1.36) for having a serious adverse event (AE) when taking pregabalin as opposed to placebo.

Serious adverse events (AEs) associated with pregabalin were as follows: sleeplessness, ataxia, peripheral edema, ventricular extrasystoles, falls or unintentional injuries, spasticity from drug withdrawal, heightened anxiety, arm fracture from a fall, chest pain, subacute myocardial infarction, hypotension, momentary unconsciousness, asthenia and encephalopathy. One patient also had decreased platelet count, hypervolemia and edema. For patients on placebo, serious AEs considered related to treatment included coronary artery disorder, ventricular extrasystoles, attack of unconsciousness, manic reaction and prostate cancer (Adiga *et al*., 2023).

Table 5: Adverse effects significantly associated with pregabalin (Gaetano Zaccara *et al*., 2011)

Adverse effect	150 mg/day	300 mg/day	450 mg/day	600 mg/day
Dizziness	0.008	0.21	0.29	0.30
vertigo	0.002	0.005	0.003	0.06
Incoordination	0.00	0.003	0.007	0.07
Blurred vision	0.02	0.04	0.06	0.07
Thinking abnormal	0.02	0.04	0.06	0.08
Dry mouth	0.04	0.05	0.08	0.07
Constipation	0.02	0.03	0.04	0.04

11. Conclusion

Here is an overview of the drug pregabalin which includes the history, mechanism of action and pharmacokinetic profile. Pregabalin is mainly used to treat epilepsy, neuropathic pain and general anxiety disorder. The mechanism reduces the release of certain neurotransmitters involved in pain signaling, by alleviating pain symptoms. It also has some common side effects which can be treated.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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