A REVIEW BASED ON PREGABALIN POTENTIAL IN THE MANAGEMENT OF NEUROPATHIC PAIN

Shamim[1*], Amjad Khan Pathan[2], Rizwan Ahmad[3]

Abstract

Neuropathic pain is a distressing sensory and emotional behaviour which traced back to real or imagined tissue injury. In a seminal study published in 1938, English neurologist George Riddoch said that pain is experienced only intermittently in the life of the healthy, its neural mechanisms lying dormant, but vigilant, ready to be awakened if the tissues of the body are threatened. The present review was based on the literature survey of pregabalin's effectiveness in different types of neuropathic pain. In some countries, like the UK, France, and Austria, the rates are as high as 8%, 6.9%, and 3.3%, respectively. Pregabalin (3-(aminomethyl)-5-methylhexanoic acid) is another synthetic atom and an underlying structure of the inhibitory junction (neurons) γ-aminobutyric corrosive. It is a α2- δ ligand having pain relieving, anti-convulsant, anxiolytic, and rest adjusting exercises. Pregabalin exhibits inhibitory effect on the release of Sub-P, CGRP and glutamate thus subsides neuropathic pain perception. Strong opioids, non-gabapentinoid antiepileptic medications, and cannabinoids are frequently prescribed as third- and fourth-line medications. In general, bigger doses of pregabalin lead to worse poisonings. Below 20mg/kg, most people (83%) only have slight poisoning if they take less than 20mg/kg. It concluded that pregabalin has been extensively utilized as effective drug against neuropathic pain generated due to various medical conditions including chronic diabetes, cancer neuropathy, fibromyalgia, trigeminal neuralgia, post-herpetic neuralgia and spine diseases or damages. It is also regarded as safe moiety for the treatment of neuropathic pain.

Keywords: pregabalin, neuropathic pain, calcium channel, GABA, toxicity

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INTRODUCTION

Neuropathic pain is a distressing sensory and emotional behaviour which traced back to real or imagined tissue injury. In a seminal study published in 1938, English neurologist George Riddoch said that pain is experienced only intermittently in the life of the healthy, its neural mechanisms lying dormant, but vigilant, ready to be awakened if the tissues of the body are threatened (Luana et al. 2017). Pain that "begins in, or is triggered by, a primary lesion, dysfunction, or transient perturbation of the peripheral or central nervous system" is no longer considered to be neuropathic pain according to this definition. Important shifts in this revised definition include the inclusion of "dysfunction" and "the neuronal lesion" (Derry et al. 2019). Since the afferent neural system works, this type of pain is called neuropathic pain syndrome. A review of all studies published since 2000 says that the total number of cases is 7%. In the UK, France, and Austria, for example, the numbers are as high as 8%, 6.9%, and 3.3%, respectively (Cavalli et al., 2019).

Most of the time, the cause of nerve damage is used to describe neuropathic pain. Major causes of neuropathic pain include as follows-

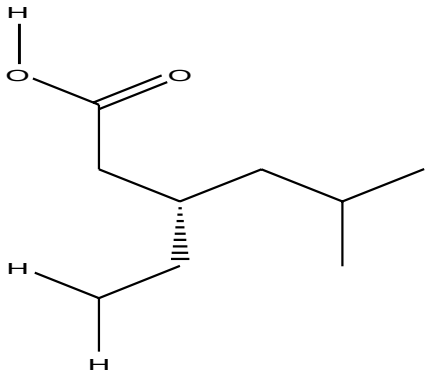
- Painful diabetic neuropathy
- Postherpetic neuralgia
- Amputation stump and phantom limb pain
- Trauma
- Stroke/damage to the spinal cord
- Trigeminal neuralgia
- HIV infection

Most people with neuropathic pain report they have pain that comes and goes and doesn't seem to have a cause. Like an electric shock, paroxysms of pain can happen on their own or in addition to the constant pain that happens on its own. Damage to the nervous system could lead to strange feelings that aren't painful. Both dysesthesia and paresthesia are examples of unusual feelings, but while dysesthesia is uncomfortable, paresthesia is not.

Both can happen on their own or in response to something. You can have evoked pain instead of or in addition to random pain. Patients usually feel pain when they are touched or when they are exposed to cold. Allodynia might not be picked up by the tests, or the signs might be too quick to notice during a regular check-up. Depending on whether certain nerve fibres are still there or not, pain can be triggered (Baba et al. 2012).

Pregabalin

Pregabalin (3-(aminomethyl)-5-methylhexanoic acid) is another synthetic atom and an underlying structure of the inhibitory junction (neurons) γ-aminobutyric corrosive (Yada et al. 2007). It is a α2- δ ligand having pain relieving, anti-convulsant, anxiolytic, and rest adjusting exercises (Li et al. 2006). Pregabalin ties strongly to α2- δ subunit of Ca^{2+} channels, bringing about a decrease in the arrival of a few synapses, including Nor-Adrenaline, 5-HT, Dopamine, & substance-P.



Pregabalin

Fig 1. Pregabalin's structure

Planned as a lipophilic-GABA simple substituted at the third position to work with diffusion across the Blood Brain Barrier (Gong et al., 2006). Soares et al. (2000) say that opening KATP channels has anti-nociceptive effects because it makes neurons less active and stops the release of many chemicals, like substance P in the spinal cord.

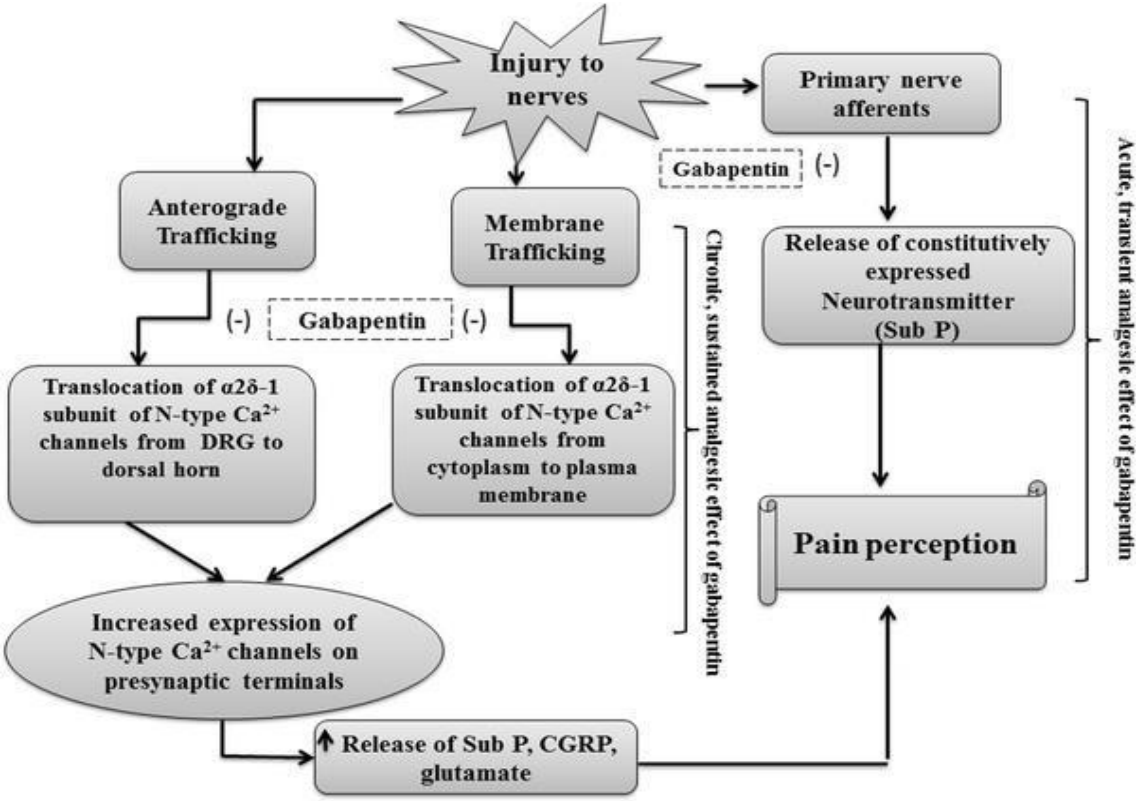


Fig 2. Pregabalin exhibiting inhibitory effect on the release of Sub-P, CGRP and glutamate thus subsides neuropathic pain perception

In spinal cord sensitivity caused by inflammation, pregabalin changes the way sensory neuropeptides like substance P and CGRP are released (Fehrenbacher et al., 2003). The beneficial effect of pregabalin is likely caused by its anti-inflammatory effect. This is shown by the fact that it stops lipid peroxidation, reduces the number of microglial cells, and slows the death of cells, especially in oligodendrocytes (Ha et al., 2008).

In different models of neuropathic pain, pregabalin has been used to study different molecular targets and signaling systems, such as the release of neurotransmitters through Ca2+ channels, the activation of excitatory amino acid transporters, potassium channels, and the blocking of pathways that involve inflammatory mediators (Verma et al., 2014).

Various studies have shown for effectiveness of pregabalin in different neuropathic pain as enumerated below-

Spine Diseases/ damages

Toshihiko et al. (2021) determined how well pregabalin works to treat chronic pain with a NeP component in people with spine diseases who get regular primary care. We put together the results of two 8-week prospective observational cohort studies done in Japan on people with chronic low back pain and lower limb pain (NeP component)

and people with chronic neck pain and upper limb radiating pain. In both studies, patients were treated for 8 weeks with either pregabalin (alone or with other painkillers) or with standard painkillers like nonsteroidal anti-inflammatory drugs as part of standard care. Changes in pain numerical rating scale (NRS), Pain-Related Sleep Interference Scale, and EuroQol 5-dimension 5-level (EQ-5D-5L) scores from baseline to week 8 were summed up and compared between the pregabalin and usual care groups, as well as for subgroups of main diagnosis. In the pregabalin group, bad things that happened were used to figure out how safe it was. There were 700 people in the pooled data set: 302 in the pregabalin group and 398 in the normal care group. All patient-reported outcomes scores improved more in the pregabalin group than in the usual care group from the start of the study to week 8. Overall, the pregabalin group did better on all three PRO measures than the normal care group, no matter what the main diagnosis was. 36.1% of the pregabalin group reported side effects. This study showed that treatment with pregabalin is effective from the patient's point of view in a "real-world" setting for all patients with chronic NeP from different spine diseases. Siddall et al. (2006) to test how well pregabalin works for people with central

neuropathic pain caused by a spinal cord injury. A 12-week, multicenter study with patients who were given either flexible-dose pregabalin 150 to 600 mg/day (n=70) or a placebo (n=67), given BID. Patients were allowed to keep using pain treatments that worked well for them. The main measure of effectiveness was the endpoint mean pain score, which was based on the patients' daily pain diary notes from the last 7 days. The SF-MPQ, sleep disturbance, mood, and the patient's global measure of change were all important secondary outcomes. In the pregabalin group, the mean pain score at the start was 6.54, and in the control group, it was 6.73. The average pain score at the end of the study was lower in the pregabalin group (4.62 vs. 6.27) than in the placebo group (6.27). This effect was seen as early as week 1 and lasted for the whole study. After 3 weeks of getting used to the drug, the usual dose of pregabalin was 460 mg/day. In the endpoint ratings of the SF-MPQ, pregabalin was much better than placebo. With pregabalin, the rates of 30% and 50% pain responders were higher than with control. Pregabalin was linked to better sleep and less worry, and at the endpoint, more patients in the pregabalin group said they felt better overall. The most common side effects were mild or moderate sleepiness and confusion that usually went away quickly. Spinal cord injury patients who took 150 to 600 mg of pregabalin per day had less central neuropathic pain, better sleep, less anxiety, and a better general health.

Diabetic neuropathy

Brett et al. (2008) Neuropathic pain caused by postherpetic neuralgia (PHN) and painful diabetic peripheral neuropathy (DPN) can be persistent and may not respond to common treatments like tricyclic antidepressants (TCAs) and opioids. This long-term, open-label study was a first look at how well pregabalin worked for people with neuropathic pain whose pain didn't respond to other medicines. Patients had already taken pregabalin in DPN and PHN in randomised, double-blind, placebo-controlled studies. Even though they were taking gabapentin, a TCA, and a third drug (such as other anticonvulsants, opioids, selective serotonin reuptake inhibitors, or tramadol), they still had mild to severe neuropathy pain. Flexible-dose pregabalin (150-600mg/day) was given for three months, followed by "drug holidays" of 3-28 days without pregabalin. This was done for up to 15 months, or five treatment rounds. The Short-Form McGill Pain Questionnaire's visual analogue scale was used to measure how bad the pain was. In this study, there were a total of 81 patients. During each treatment cycle, taking 150–600 mg/day of Pregabalin was linked to a decrease in pain that was clinically significant and lasted. During "drug holidays" from pregabalin, the pain quickly went back to where it was before. When pregabalin was given again, the pain went down again. These results show that pregabalin might be helpful for people with neuropathic pain who haven't gotten good results from other treatments. Rosenstock et al. (2004*)* A three randomised, double-blind, multicentre studies of 5-8 weeks in length involving patients with painful diabetic peripheral neuropathy, pregabalin at fixed dosages of 300 and 600 mg/day (three times daily) is reported to be superior to placebo in reducing pain and improving pain-related sleep interference. Richter et al. (2005) In a 6-week multicenter study, taking 600 mg of pregabalin every day lowered the average pain score by a lot and increased the number of patients whose pain was 50% less than at the start (39 percent vs. 15 percent for a placebo). Devi et al. (2012) A 12-week study comparing pregabalin (75-300 mg/day), duloxetine (20-120 mg/day), and gabapentin (300-1800 mg/day) for the treatment of diabetic neuropathy found that pregabalin monotherapy was superior in terms of the rate at which pain was reduced. Biyik et al. (2012) Patients with painful diabetic neuropathy treated with pregabalin or gabapentin for 6 weeks experienced similar reductions in pain intensity and improvements in sleep quality. De Salas-Cansado et al. (2012) Pregabalin has been shown to be more cost-effective in the management of refractory diabetic neuropathy than existing treatments (antidepressants, opioids, anticonvulsants other than pregabalin, and/or analgesics), in addition to having better pain-relieving effects. Various other researches have also backed up the usefulness of pregabalin in treating different types of neuropathic pain.

Cancer neuropathy

Baba and Gomyo, (2012) Pregabalin has shown promise in the treatment of neuropathic pain, including that caused by cancer and by the chemotherapy drugs used to treat it. In a retrospective study involving Japanese patients, high-dose pregabalin treatment for neuropathic cancer pain was found to be effective. Pregabalin and oxycodone were more successful at reducing neuropathic pain in patients with non-small cell lung cancer who had undergone chemoradiation therapy than a combination of the transdermal fentanyl patch, oxycodone, and gabapentin.

Post-herpetic Neuralgia

Sabatowski et al. (2004) In two multi-center, double-blind, placebo-controlled studies with 370 and 238 PHN patients for 13 weeks and 8 weeks,

respectively, 150, 300, and 600 mg/day of pregabalin worked within a week of treatment. Mild to moderate side effects included sleepiness, peripheral edema, headache, dry mouth, and ataxia. A meta-analysis using the MEDLINE and AMBASE databases showed that pregabalin is good at reducing the intensity of pain in people with PHN-related neuropathic pain.

Fibromyalgia

Crofford et al. (2005) Randomized, double-blind, multi-center clinical study that lasted eight weeks showed that different doses of pregabalin (150, 300, and 450 mg/day) helped 529 people with fibromyalgia feel less pain. Pregabalin was shown to improve health-related quality of life by a lot, but it had low to moderate side effects that were easy to deal with. The most common ones were sleepiness and dizziness. It was also shown to make pain less severe on average. At the end of the study, more patients (29 percent compared to 13 percent in the control group) had pain that was better by more than or equal to 50 percent.

Trigeminal neuralgia

Obermann et al. (2008) Patients with trigeminal neuralgia who take 150–600 mg of pregabalin per day have less pain intensity and frequency (>50%) after 8 weeks, whether or not they also have facial pain. This is according to an open-label, one-year follow-up study that looked at the effectiveness of pregabalin treatment in these patients. Trigeminal neuralgia may be best treated with pregabalin because the pain relief stayed for a long time and kept going even after a year.

Pre/ post operative pain

Kim et al. (2008) Pregabalin was shown to be effective and safe in reducing both acute post-operative pain (up to 48 hours after surgery) and chronic pain (measured as hypoesthesia in the anterior chest after 3 months of surgery) in patients after robot-assisted endoscopic thyroidectomy when administered preoperatively (1 hour prior surgery) (initial dose 150 mg, followed by Pregabalin was mostly beneficial in lowering early postoperative pain, but not chronic pain, as evidenced by the lack of a significant difference between two groups in regards to chronic pain and chest hypoesthesia after three months following surgery.

Seventer et al. (2010) Pregabalin works well to treat both central and peripheral neuropathic pain. This study looked at how well pregabalin works for treating post-trauma peripheral neuropathic pain, which includes pain after surgery. Patients with a pain score of 4 (0–10 scale) were given either flexible-dose pregabalin 150–600 mg/day (n = 127) or a placebo (n=127) for 8 weeks. This was followed by a 2-week run-in with the placebo. When compared to the placebo, the mean end-point pain score went down more with pregabalin than with the placebo. The mean treatment difference was 0.62 (95% CI: 1.09 to 0.15). At the end point, the usual dose of pregabalin was about 326 mg per day. Pain that kept people from sleeping, as well as the Medical Outcomes Study sleep scale's sleep troubles index and sleep disturbance subscale, all got better after taking pregabalin. In the group of all patients, pregabalin was linked to a statistically significant improvement in the worry subscale of the Hospital worry and Depression Scale. In total, 29% of patients had moderate or serious anxiety at the start. Treatment with pregabalin did not help anxiety much in this group. At the end point, more people who took pregabalin (68%) than those who took a placebo (43%) said they felt better generally. Because of side effects, 20% of people taking pregabalin and 7% of people taking placebo stopped taking them. In the pregabalin group, the most common side effects were mild or moderate confusion and sleepiness. Flexible-dose pregabalin (150-600mg/day) helped patients with post-traumatic peripheral neuropathic pain feel less pain, sleep better, and feel better overall.

As third- and fourth-line treatments, strong opioids, non-gabapentinoid antiepileptic drugs, and cannabinoids are routinely administered. Consensus is that carbamazepine is an effective treatment for trigeminal neuralgia. Topical combinations of capsaicin and lidocaine are recommended for localized neuropathic pain (NICE, 2013).

Pregabalin: effective in neuropathic pain and disease conditions

Pregabalin is not limited to neuropathic pain only, moreover it has shown its effectiveness in other disease conditions. The following table 1. Shows the use of pregabalin in different disease conditions with different dose (Derry et al. 2019; Pregabalin 2023)-

Table 1. Pregabalin: effective in neuropathic pain and disease conditions

Drug	Dosage form	Dose	Disease
Pregabalin	Capsule	Initial: 50mg/day Maintenance: 100-300mg/day	Diabetic Peripheral Neuropathic Pain
Pregabalin	Extended-release tablets	Initial: 165mg/day Maintenance: Up to 330mg/day	Diabetic Peripheral Neuropathic Pain
Pregabalin	Capsule	Initial: 150-300 mg/day Maintenance: Up to 300mg/day	Postherpetic Neuralgia
Pregabalin	Extended-release tablets	Initial: 165mg/day Maintenance: Up to 330mg/day	Postherpetic Neuralgia
Pregabalin	Capsule/oral solution	Initial: 50-150mg/day Maintenance: 300-400mg/day	Fibromyalgia
Pregabalin	Capsule	Initial: 150mg/day Maintenance: Up to 600mg/day	Partial Onset Seizures
Pregabalin	Capsule/ oral solution	Initial: 150-300mg/day Maintenance: Up to 600mg/day	Neuropathic Pain with Spinal Cord Injury

Toxicity of pregabalin

The dose-toxicity data of individual pregabalin poisonings came from (1) a prospective study done by the Dutch Poisons Information Centre (4 April 2014 to 4 October 2016) and (2) case reports and case series found in the literature. The Poisoning Severity Score (PSS) was used to grade poisonings, and the link between dose (mg/kg) and PSS was looked at. In our study of 21 people, the most common signs were sleepiness (62%), confusion (29%), and lack of interest (24%). In three (14%), there was no PSS, in 15 (71%), it was minor, and in three (14%), it was mild. Most case studies also said that most poisonings (69–100%) had a PSS of none to mild. We had detailed information on dose and clinical course for 34 patients (21 from our study and 13 from the literature) so we could look at the link between dose and toxicity. The median dose was much lower in the PSS noneminor group ("benign") (8.6 mg/kg, interquartile range (IQ25–75): 5.0–17.6 mg kg1) than in the PSS moderate–severe group ("significant toxicity") (46.7mg/kg, IQ25–75: 21.3–64.3mg/kg); the median difference was estimated to be 27.3mg/kg (95% confidence interval [CI]: 10–48.6). In general, bigger doses of pregabalin lead to worse poisonings. Below 20mg/kg, most people (83%) only have slight poisoning if they take less than 20mg/kg. But the way pregabalin makes people sick varies a lot from person to person. So, pre-hospital triage should look at more than just the amount of pregabalin a person is taking. It should also look at underlying illnesses, co-exposures, and stated symptoms (Saskia et al. 2022). Pregabalin is an anticonvulsant that has only one known way of working. It is most often used to treat nerve pain. With evidence-based results for pregabalin's clinical use in mind, the bad side effects of this drug from controlled, randomised, and open studies as well as long-term, open studies are explained. Pregabalin is a drug that is mostly well tolerated and is used to treat nerve pain and other diseases. Pregabalin use is linked to harmless effects on the central nervous system and the body as a whole. There are also very few metabolic, unique, or teratogenic side effects. It is important for both the doctor treating the patient and the person being treated to know about these side effects. Sedation, dizziness, swelling around the edges of the body, and dry mouth are the most common side effects in all clinical groups (Toth, 2012).

CONCLUSION

Most likely, pregabalin works by blocking voltage-gated Ca2+ channels. This makes less excitatory neurotransmitters and slows down synaptic signalling. According to both preclinical and clinical studies, pregabalin is likely to be very safe and a very good treatment for neuropathic pain. It concluded that pregabalin has been extensively utilized as effective drug against neuropathic pain generated due to various medical conditions including chronic diabetes, cancer neuropathy, fibromyalgia, trigeminal neuralgia, post-herpetic neuralgia and spine diseases or damages. It is also regarded as safe moiety for the treatment of neuropathic pain.

Other possible ways it could relieve pain are by reducing inflammation, regulating excitatory amino acid transporters, and changing the conductance of K+ channels. Still, more research needs to be done to figure out how it works.

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CONFLICT OF INTEREST
Authors have declared for 'none' conflict of interest.

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