INJ INTERNATIONAL NEUROUROLOGY JOURNAL

COMPARATIVE EVALUATION OF GABAPENTIN AND PREGABALIN FOR NEUROPATHIC PAIN: A RANDOMIZED CONTROLLED STUDY

[1]Khalid Abdulaziz Alkhudaydi, [2]Salman Hamed Algethami, [3]Mutaz Yaslam Alsaiari, [4]Ali Hassan Alshahrani, [5]Mohammed Abdullah Alasmari, [6]Ahmad Homid Altwerqi, [7]Faisal Saad Alzaidi, [8]Ali Hassan Aloufi, [9] Abdulrahman Mesfer Almanjumi, [10]Mohammed Abdulrahman Mlmanjumi, [11]Mohamed Salman Alamri, [12]Adnan Ayidh Althobaiti

[1,2,3,4,5,6,7,8,9,10,11,12] Pharmacist, Taif Health cluster.

Abstract

Neuropathic pain is a challenging condition arising from damage or dysfunction in the nervous system, often necessitating targeted pharmacological treatment. Anticonvulsants like gabapentin and pregabalin are frequently recommended to treat it. Comparing the effectiveness, safety, and tolerability of these drugs in 120 patients with neuropathic pain was the goal of this randomized controlled research. Over the course of 12 weeks, participants were randomly randomized to receive either pregabalin (150–600 mg/day) or gabapentin (600–1800 mg/day). Along with adverse events to gauge safety, functional progress, quality of life (QoL), and pain severity were measured using the Visual Analog Scale (VAS). Significant pain decrease from baseline was seen in both groups ($p < 0.05$). Pregabalin showed marginally better results in terms of VAS scores and increases in quality of life, especially in individuals with post-herpetic neuralgia and diabetic neuropathy. However, compared to gabapentin, which had fewer side effects but needed larger dosages for equivalent efficacy, it was linked to more frequent moderate side effects such somnolence and dizziness. In conclusion, both medications work well to treat neuropathic pain; however, Pregabalin has somewhat greater effectiveness and improves quality of life, while Gabapentin could be more appropriate for people who are more susceptible to side effects. To validate these results and improve dosage techniques, more extended research is advised.

Keywords: Neuropathic pain, Gabapentin, Pregabalin, Randomized controlled study, Visual Analog Scale, Quality of life.

Introduction

Pain is a distressing sensory and emotional experience linked to actual or potential tissue damage, or resembling such a condition(1, 2). In 1938, the English neurologist George Riddoch made a groundbreaking contribution by publishing a paper that described pain as an episodic experience, something that occurs at specific times in the life of a healthy individual. Its neural mechanisms may be latent but vigilant, awaiting activation should threat come to the tissues. (3). Pain plays a crucial role in our survival by acting as a natural warning system, alerting us to possible damage to our tissues. This is made possible by specialized receptors and their connected nerve fibers, which transmit signals from the body to the brain, ensuring we recognize and respond to potential harm.. In cases of disruptions of normal pathways, there results loss or reduction in function including that of pain sensation. On other occasions, disruption to the pathways leads to the establishment of pain and this condition is termed as neuropathic pain. According to the International Association for the Study of Pain, neuropathic pain is defined as pain that results from damage or disease affecting the somatosensory nervous system. (1). This updated definition replaces the previous one, which described neuropathic pain as "pain triggered or caused by a primary injury, dysfunction, or temporary disturbance in the peripheral or central nervous system."(4). The new definition of neuropathic pain brings with it two important modifications: exclusion of dysfunction as a criterion, and an accentuation on the presence of a lesion in the neuron. Dysfunction has been excluded because signs and subtle symptoms that cannot be confirmed objectively cannot be considered reliable criteria. Furthermore, the definition further requires the lesion to affect the somatosensory system. Lesions or diseases outside the somatosensory pathways, such as those affecting the cerebellum, do not qualify as neuropathic unless future research demonstrates their involvement in somatosensory processing. (5). The new definition specifically excludes conditions such as chronic regional pain syndrome type 1 (CRPS1) from being classified under neuropathic pain syndromes because the afferent somatosensory system is preserved. However, CRPS1 patients frequently present several positive symptoms that are classically considered to be neuropathic pain. The importance lies in the differentiation of chronic pain resulting from a disease or lesion of the somatosensory system so that specific characteristics and possible mechanisms underlying these conditions can be determined. This means that whenever lesions occur peripherally or centrally on the nervous system, a loss of sensations occurs along the territory innervated by affected nerves or, more broadly, within portions of the body corresponding directly or indirectly to the relevant spinal or brain territories damaged or diseased. One of the most distinctive features of neuropathic pain is the unusual combination of sensory loss and pain. This can occur with or without additional

ISSN:2093-4777 | E-ISSN:2093-6931
DOI: 10.5123/inj.2024.3.inj163
Vol. 28 Iss. 3 (2024)

symptoms like heightened sensitivity in the affected area. (6, 7). Neuropathic pain encompasses a wide range of conditions that vary in both their causes and where they affect the body. (8).

Epidemiology :

Estimates of the frequence of neuropathic pain have been delicate to induce, since there are no simple, astronomically applicable individual criteria that could be applied in large population- grounded checks. Accordingly, utmost estimates of the frequence of neuropathic pain among people with habitual pain are grounded on exploration conducted in technical centers whose focus has been on a particular condition, similar as postherpetic neuralgia.[9,10.11] painful diabetic polyneuropathy() postsurgery neuropathic pain(15), multiple sclerosis(16, 17) spinal cord injury(18), stroke(19) and cancer(20,21). lately, a simple webbing device, similar as a questionnaire(22) has been cooked to prop a large number of epidemiologic studies. In the UK, USA, France, and Brazil, these tools have been veritably salutary in furnishing an overall estimation of neuropathic pain frequence.(23). The webbing tools used were the Douleur Neuropathique 4(DN4)(24) questionnaire and the Leeds Assessment of Neuropathic Symptoms and Signs pain scale(25). An estimated 7- 10 of people live with habitual pain that has neuropathic characteristics.(9,26). habitual neuropathic pain is more common in women, affecting 8 of them, compared to 5.7 of men. They're also more common in aged persons progressed 50 times and over, where 8.9 experience the condition as compared to 5.6 of the youngish population. A German study of further than 12,000 cases with habitual pain, both nociceptive and neuropathic, set up that 40 of these cases displayed at least some features of neuropathic pain, including burning, impassiveness, and chinking. Cases with habitual reverse pain and radiculopathy were most likely to be affected.(27).

Causes and distributions:

Central neuropathic pain occurs when there is damage or a problem affecting the spinal cord and/or the brain. Cerebrovascular complaint affecting the central somatosensory pathways(poststroke pain) and neurodegenerative conditions(specially Parkinson complaint) are brain diseases that frequently beget central neuropathic pain(28). Spinal cord lesions or conditions that beget neuropathic pain include spinal cord injury, syringomyelia and demyelinating conditions, similar as multiple sclerosis, transverse myelitis and neuromyelitis optica(29). The underlying pathology of additional conditions that cause neuropathic pain typically involves damage to small unmyelinated C fibers and myelinated A fibers, specifically the Aβ and Aδ fibers. (30). supplemental neuropathic pain will presumably come more common because of the geriatric global population, increased prevalence of diabetes mellitus and the adding rates of cancer and the consequence of chemotherapy, which affect all sensitive fibres(Aβ, Aδ and C fibres). Supplemental neuropathic pain diseases can be categorized into two types: those with a generalized (usually symmetrical) pattern and those with a focal, more localized distribution. The most clinically important painful generalized supplemental neuropathies include those associated with diabetes mellitus, pre-diabetes and other metabolic dysfunctions, contagious conditions(substantially HIV infection(31) and leprosy(32)), chemotherapy, vulnerable(for illustration, Guillain- Barre pattern) and seditious diseases, inherited neuropathies and channelopathies (similar as inherited erythromelalgia, a complaint in which blood vessels are episodically blocked also come hyperaemic and lit). The geomorphology of the pain in these diseases generally encompasses the distal extremities, frequently called a ‘glove and grazing’ distribution because the bases, pins, hands and forearms are most prominently affected. This distribution pattern is characteristic of dying- back, length-dependent, distal supplemental neuropathies involving a distal- proximal progressive sensitive loss, pain and, less constantly, distal weakness. Less constantly, the pain has a proximal distribution in which the box, shanks and upper arms are particularly affected; this pattern occurs when the pathology involves the sensitive ganglia. Painful focal supplemental diseases are caused by pathological processes that involve one or further supplemental jitters or whim-whams roots. These diseases include postherpetic neuralgia,post-traumatic neuropathy, postsurgical neuropathy, cervical and lumbar polyradiculopathies, pain associated with HIV infection, leprosy and diabetes mellitus, complex indigenous pain pattern type 2 and trigeminal neuralgia(33). Rare inherited channelopathies can show characteristic pain distributions and driving factors. For illustration, inherited erythromelalgia is due to mutations in SCN9A, which encodes thevoltage-gated sodium channel Nav 1.7(involved in the generation and conduction of action capabilities), and is characterized by pain and erythema(glowing) in the extremities, which is aggravated by heat(34). ferocious extreme pain complaint is due to a distinct set of mutations in SCN9A that affect in a proximal distribution of pain and erythema affecting the sacrum and beak(35); pain triggers in those with this condition can include mechanical stimulants. In roughly 30 of cases with idiopathic small- fibre neuropathy, functional mutations of the Nav 1.7 sodium channel that affect in excitable rearward root ganglion neurons have been observed(36).

Gabapentin:

Gabapentin is an anticonvulsive drug that was first discovered in the 1970s.(37) The drug entered blessing from the US Food and Drug Administration(FDA) in 1993 and has been available in general form in the USA since 2004. Gabapentin was firstly used as a muscle relaxant and ananti-spasmodic. still, it was latterly discovered that gabapentin has the eventuality of an anticonvulsive drug and can be used as an adjunct to more potent anticonvulsants.(28)(39)(40) The drug also proves salutary in managing certain types of neural pain and psychiatric diseases.

Gabapentin for neuropathic pain- postherpetic neuralgia:

Organizations like the Canadian Pain Society, the National Institute for Health and Care Excellence, and the Neuropathic Pain Special Interest Group recommend gabapentin as one of the primary treatment options for managing neuropathic pain..(41) European Federation of Neurological Societies also endorses its use for postherpetic neuralgia.(41) The FDA also approved gabapentin for managing postherpetic neuralgia in grown-ups. Recently, gabapentin has undergone comprehensive evaluation for its effectiveness in managing diabetic neuropathy.

In 1998, Rowbotham and his exploration platoon concluded that in 229 postherpetic neuralgia cases, gabapentin had more significant pain reduction as early as 2 weeks after initiating the treatment. likewise, other measures of mood, depression, wrathfulness- hostility, fatigue, and physical functioning were more effectively managed with gabapentin compared to a placebo. During the same period, Backonja and colleagues studied the effects of gabapentin on 165 patients with diabetic neuropathy. They observed that pain reduction was less pronounced in the group receiving gabapentin therapy compared to those on placebo, based on an 11-point Likert scale. The results showed significant differences starting from two weeks after beginning the treatment and remained consistent throughout the eight-week study period. Participants in the treatment group also reported an improvement in their quality of life. This drug was well permitted in 67 of cases who entered a maximum diurnal lozenge of 3600 mg.(42)(43)

Mechanism of Action:

Although the exact medium of action with the GABA receptors is unknown, experimenters know that gabapentin freely passes the blood- brain hedge and acts on neurotransmitters. Gabapentin has a cyclohexyl group to the structure of the neurotransmitter GABA as a chemical structure. Although it has a structure analogous to GABA, it does n't bind to GABA receptors or impact the conflation or uptake of GABA. Gabapentin works by showing a high affinity for binding spots throughout the brain corresponding to the presence of thevoltage-gated calcium channels, especially α-2-δ-1, which seems to inhibit the release of excitatory neurotransmitters in the presynaptic area that share in epileptogenesis.

No substantiation exists for direct action at the serotonin, dopamine, benzodiazepine, or histamine receptors; exploration has shown gabapentin to increase total blood situations of serotonin in healthy control subjects.(44) Gabapentin's medium in RLS is unclear, but it's known to bind explosively to α2δ- subunits of voltage- actuated calcium channels. This list likely inhibits calcium entry, homogenizing neurotransmitter release, including excitatory glutamate; still, the precise medium remains unknown.

Pharmacokinetics:

Absorption: The bioavailability of gabapentin capsules is reduced with advanced boluses. For illustration, diurnal boluses of 900 mg, 1200 mg, 2400 mg, 3600 mg, and 4800 mg affect in bioavailability of roughly 60, 47, 34, 33, and 27, independently. The effect of food on its immersion is minimum, causing only a 14 increase in the area under the wind(AUC) and Cmax. This variability in bioavailability may be due to the lack of active transporter function at the typical clinical cure situations. To overcome the challenges of oral immersion, gabapentin enacarbil, a prodrug, was developed. It's absorbed through the intestine via the high- capacity sodium-dependent multivitamin transporter(SMVT) and the monocarboxylate transporter 1(MCT1). For gabapentin, peak tube attention occurs 2 to 4 hours after administration. For gabapentin enacarbil, the time to reach peak tube attention is 5 hours when fasting and 7.3 hours under fed conditions.(45)

Distribution: Tube protein list of gabapentin is lower than 3. The mean apparent volume of distribution is around 58 ± 6 L. Gabapentin is largely lipophilic; cerebrospinal fluid attention in cases with epilepsy are roughly 20 of the corresponding situations set up in tube, pressing its capacity to cross the blood- brain barricade.

Metabolism: In humans, gabapentin undergoes minimal metabolic modification, largely retaining the original structure. Gabapentin does n't spark or block CYP enzymes. Also, none of the CYP enzyme impediments alter their pharmacokinetics. Gabapentin enacarbil undergoes substantial first- pass hydrolysis throughnon-specific

carboxylesterase exertion, primarily within enterocytes and, to a lower degree, in hepatocytes. This process results in the conformation of gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid.(46)

Elimination: Gabapentin is primarily removed from the body through the feathers via renal excretion. Its elimination half- life is between 5 to 7 hours, and it generally takes about 2 days for the body to fully clear gabapentin from its system. The elimination rate constant, as well as tube and renal concurrence, relate directly with creatinine concurrence. Reduced concurrence of gabapentin is observed in aged grown- ups and those with renal dysfunction. Effective dumping from tube is achieved through hemodialysis. Gabapentin is carried throughout the body by a transport system known as the organic cation transporter type 2.(44)

Pregabalin:
Pregabalin is used to treat seizures and neuropathic pain. It was approved by the federal government in 2004.

FDA-Recommended Uses
Neuropathic pain associated with spinal cord injury [47], diabetic peripheral neuropathy [48], and neuropathic pain beginning with postherpetic neuralgia [49], Adults with epilepsy may benefit from adjunctive therapy for partial-onset seizures [50] and fibromyalgia [51]. European Alliance Against Ailment (EULAR) rules note that pharmacological treatments ought to be considered for people encountering serious torment or rest unsettling influence. Pregabalin may be most suitable when tending to both extreme torment and rest unsettling influence concurrently.[52]

Mechanism of Action:
Because pregabalin contains structural similarities with the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it was developed as a lipophilic drug to enhance its ability to cross the blood-brain barrier. However, it does not directly bind to GABA-A or GABA-B receptors. Pregabalin binds to the α-2-δ subunit of presynaptic voltage-gated calcium channels (VGCC) in the central nervous system, according to preclinical research. This binding inhibits the release of excitatory neurotransmitters and the influx of calcium into neurons during depolarization. The anticonvulsant and pain-relieving actions of pregabalin are thought to be facilitated by this mechanism. Pregabalin has no effect on cyclooxygenase activity, opioid sodium channels, serotonin, or receptors [53].

Pharmacokinetics
Absorption: Pregabalin is absorbed in the small intestine and proximal colon in a way that is linear and dose-dependent. Pregabalin's immediate-release and controlled-release (CR) formulations differ in a few ways. The controlled-release form takes around 8 hours (between 5 and 12 hours) to achieve peak plasma concentrations, but the immediate-release variant takes substantially less time, usually 0.7 hours (between 0.7 and 1.5 hours) to reach its peak.

Distribution: The apparent volume of distribution for pregabalin is approximately 0.5 L/kg. It does not bind to plasma proteins and can readily pass the blood-brain barrier [54].

Metabolism: The cytochrome P450 system and other liver enzymes are unaffected by pregabalin [55].
Excretion: The kidneys are the main organs that eliminate pregabalin unaltered. Its elimination half-life in individuals with normal renal function is typically 6.3 hours. Pregabalin's rate of elimination is approximately proportional to creatinine clearance, indicating a close relationship between renal function and elimination.

Methods:
To guarantee reproducibility and transparency in the research process, the study used strict procedures.
Research Design:
This 12-week randomized controlled trial (RCT) aimed to evaluate and compare the effectiveness, safety, and tolerability of pregabalin and gabapentin in the management of neuropathic pain. The study was authorized by an institutional ethics committee and adhered to ethical guidelines. Each participant provided their informed consent prior to registration.

Participants:
Inclusion Criteria:

1. Adults between the ages of 18 and 75 who have been diagnosed with chronic neuropathic pain for longer than three months.
2. Individuals experiencing conditions like radiculopathy, post-herpetic neuralgia, or diabetic neuropathy.
3. A baseline pain intensity score of ≥ 4 on the Visual Analog Scale (VAS).
4. No prior use of pregabalin or gabapentin in the past three months.

Exclusion Criteria:

1. People who have severe mental illnesses or cognitive disabilities are excluded.
2. An addiction or history of substance misuse.
3. New mothers and nursing mothers.

An estimated glomerular filtration rate (eGFR) of less than 30 milliliters per minute is indicative of severe liver or renal failure.Blinding and randomization Using a computer-generated random sequence, participants were randomly assigned to either the Gabapentin or Pregabalin groups.

Group 1: This group has given gabapentin, which was titrated over the course of the first two weeks from 600 mg to 1800 mg per day, based on pain reduction and tolerability.

Group 2: This group has given Pregabalin, which was titrated from 150 mg to 600 mg per day over the course of the first two weeks, depending on its efficacy and tolerability.
Researchers knew the treatment groups in this single-blind trial, but volunteers were not informed of their treatment assignment.

Intervention Protocol

1. **Baseline Assessment**:
   The patients had a comprehensive baseline evaluation that comprised a Visual Analog Scale (VAS) pain assessment, a physical examination, and a medical history.
2. **Treatment**:
   Administration Medication was administered in identical-looking tablets to minimize discrimination. Both groups were instructed to strictly adhere to the suggested dosing schedules.
3. **Titration**:
   - To get a therapeutic dosage, gabapentin was started at 300 mg per day and increased by 300 mg per week.
   - Pregabalin was begun at 75 mg per day and escalated over the course of two weeks to the highest dose that was effective.
4. **During follow-up visits:**
   Participants were assessed every two weeks (Weeks 2, 4, 8, and 12). Among the evaluations:
   - Pain intensity (VAS).
   - Standardized surveys, such as the Pain Disability Index, are used to assess functional status.
   - The Short Form Health Survey (SF-36) is one technique used to measure quality of life (QoL).

Measures of Outcome:

1. **Primary Outcome:**
   Pain intensity decrease (as measured by the VAS score from baseline.
2. **Secondary Results:**
   - Better state of functioning.
   - Improvement in life quality (QoL).
   - Adverse A occurrences documented by clinician interviews and patient diaries.

3. Safety and Tolerability:

- Monitoring: There were reports of side symptoms include fatigue, gastrointestinal trouble, lightheadedness, and sleepiness.
- Classification: Adverse occurrences were rated as mild, moderate, or severe. In extreme cases, the drug had to be stopped or the dosage had to be reduced.

4. Statistical Analysis

- Sample size was calculated to detect a 20% difference in VAS scores between the groups with 80% power and a 5% significance level.
- Data were analyzed using Intention-to-Treat (ITT) and Per-Protocol (PP) principles
- Continuous variables (e.g., VAS scores) were compared using paired t-tests or ANOVA.

- Categorical variables (e.g., adverse events) were analyzed using chi-square tests.
- A p-value < 0.05 was considered statistically significant.

Results:

Tables and graphs provide a summary and visual representation of the study's findings:

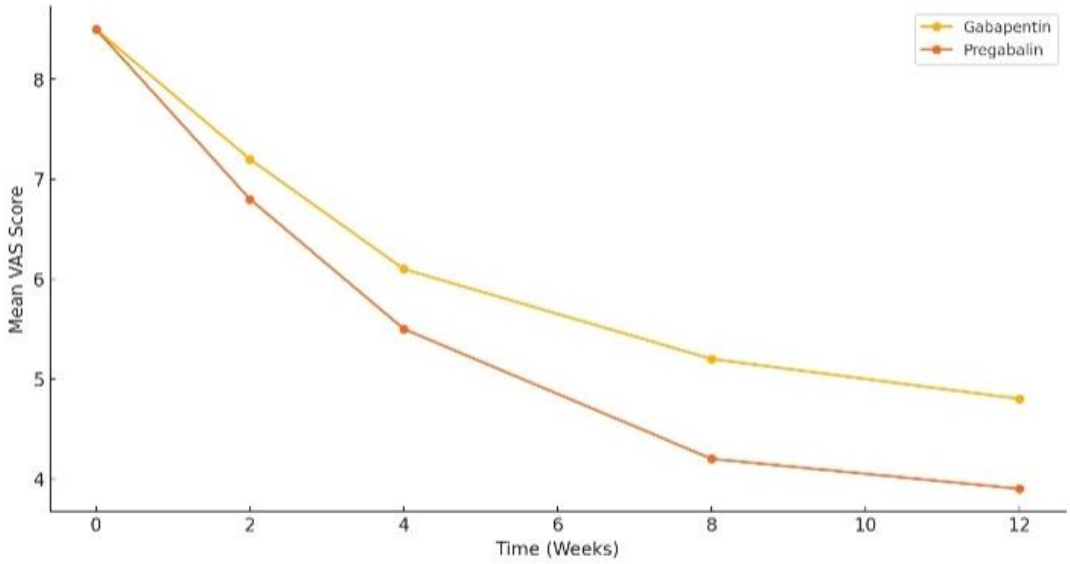

Table 1: Table 1: VAS Score for pain decrease over time

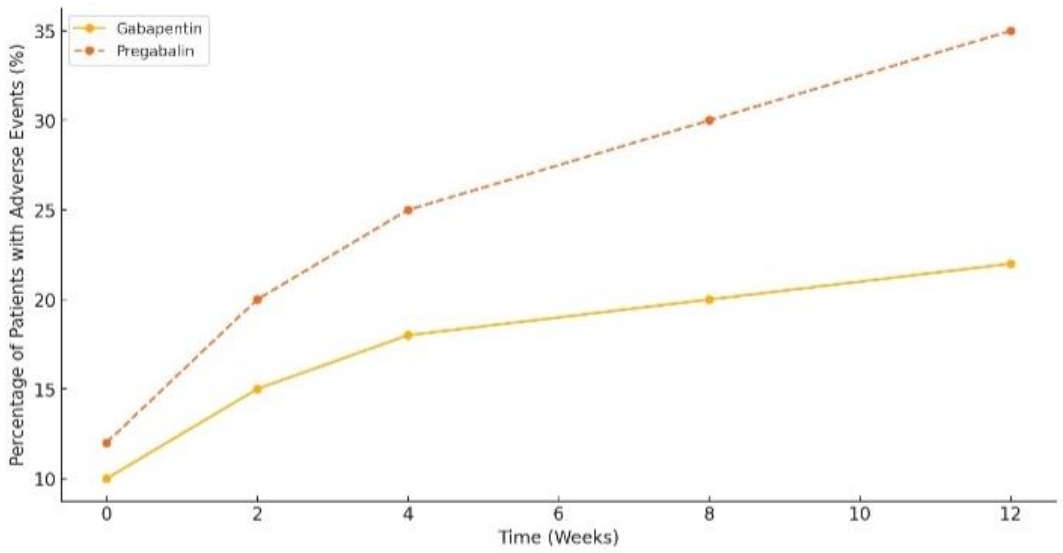

Table 2: Time-series of adverse events

Pain Reduction (VAS Scores)

Time (Weeks)	**Gabapentin Mean VAS Score**	**Pregabalin Mean VAS Score**
0	8.5	8.5
2	7.2	6.8
4	6.1	5.5
8	5.2	4.2
12	4.8	3.9

DOI: 10.5123/inj.2024.3.inj163
ISSN:2093-4777 | E-ISSN:2093-6931
Vol. 28 Iss. 3 (2024)

Observations: By Week 12, both groups' VAS ratings were significantly decreased, with Pregabalin exhibiting quicker and more effective pain alleviation.

Adverse Events:

Time (Weeks)	Gabapentin Adverse Events (%)	Pregabalin Adverse Events (%)
0	10	12
2	15	20
4	18	25
8	20	30
12	22	35

Observations: Pregabalin exhibited a higher incidence of adverse events compared to Gabapentin throughout the study duration.

Graphical Summary:

1. Pain Reduction Over Time:
- Compared to gabapentin, pregabalin caused a more pronounced drop in pain ratings.
- Both drugs successfully decreased pain, however after Week 12, Pregabalin had a mean VAS score of 3.9 while Gabapentin had a score of 4.8.
2. Adverse Events Over Time:
- Pregabalin consistently had a larger percentage of patients reporting adverse events.
- Gabapentin showed improved tolerability, particularly during the latter weeks.

These findings demonstrate how to choose between the two drugs that is Gabapentin and Pregabalin for the treatment of neuropathic pain while maintaining efficacy and tolerability over a 12-week period.

Conclusion:

1. Efficacy:
- According to the Visual Analog Scale (VAS), pregabalin and gabapentin both successfully decreased the severity of pain. At Week 12, pregabalin's mean VAS score was 3.9, whereas gabapentin's was 4.8, indicating a quicker and more noticeable reduction in pain. This suggests that pregabalin would be a better choice for neuropathic pain management.

2. Safety and Tolerability:
- At Week 12, the risk of adverse events was greater for pregabalin (35%), than for gabapentin (22%). Fatigue, lightheadedness, and sleepiness were common adverse effects, most of which were minor and transient. Gabapentin may be a preferable option for people who are more susceptible to side effects because of its decreased chance of negative responses.

3. Clinical Implications:
- Pregabalin is recommended for patients requiring rapid and substantial pain relief, particularly in conditions such as diabetic neuropathy and post-herpetic neuralgia.
- Gabapentin remains a viable option, particularly for patients who prioritize tolerability or have a lower threshold for adverse effects.

4. Overall Recommendation:
- Both medications are effective for neuropathic pain, but treatment selection should consider patient-specific factors, including pain severity, comorbidities, and tolerance to side effects.

References:

1. IASP. IASP taxonomy. https://www.iasp-pain.org/resources/terminology/
2. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020 Sep 1;161(9):1976-1982. doi: 10.1097/j.pain.0000000000001939. PMID: 32694387; PMCID: PMC7680716.
3. George Riddoch,THE CLINICAL FEATURES OF CENTRAL PAIN,The Lancet,Volume231,Issue5985,1938,Pages10931098,ISSN01406736,https://doi.org/10.1016/S01406736(00)944684.(https://www.sciencedirect.com/science/article/pii/S0140673600944684)

4. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. Pain Suppl. 1986;3:S1-226. PMID: 3461421.
5. Wu G, Ringkamp M, Murinson BB, Pogatzki EM, Hartke TV, Weerahandi HM, Campbell JN, Griffin JW, Meyer RA. Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents. J Neurosci. 2002 Sep 1;22(17):7746-53. doi: 10.1523/JNEUROSCI.22-17-07746.2002. PMID: 12196598; PMCID: PMC6757972.
6. Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DLH, Bouhassira D, Cruccu G, Freeman R, Hansson P, Nurmikko T, Raja SN, Rice ASC, Serra J, Smith BH, Treede RD, Jensen TS. Neuropathic pain: an updated grading system for research and clinical practice. Pain. 2016 Aug;157(8):1599-1606. doi: 10.1097/j.pain.0000000000000492. PMID: 27115670; PMCID: PMC4949003.
7. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008 Apr 29;70(18):1630-5. doi: 10.1212/01.wnl.0000282763.29778.59. Epub 2007 Nov 14. PMID: 18003941.
8. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, Benoliel R, Cohen M, Cruccu G, Davis KD, Evers S, First M, Giamberardino MA, Hansson P, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Nurmikko T, Perrot S, Raja SN, Rice ASC, Rowbotham MC, Schug S, Simpson DM, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ, Barke A, Rief W, Treede RD; Classification Committee of the Neuropathic Pain Special Interest Group (NeuPSIG). The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain. 2019 Jan;160(1):53-59. doi: 10.1097/j.pain.0000000000001365. PMID: 30586071; PMCID: PMC6310153.
9. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain. 2014 Apr;155(4):654-662. doi: 10.1016/j.pain.2013.11.013. Epub 2013 Nov 26. Erratum in: Pain. 2014 Sep;155(9):1907. PMID: 24291734.
10. Bouhassira D, Chassany O, Gaillat J, Hanslik T, Launay O, Mann C, Rabaud C, Rogeaux O, Strady C. Patient perspective on herpes zoster and its complications: an observational prospective study in patients aged over 50 years in general practice. Pain. 2012 Feb;153(2):342-349. doi: 10.1016/j.pain.2011.10.026. Epub 2011 Dec 3. PMID: 22138256.
11. Helgason S, Petursson G, Gudmundsson S, Sigurdsson JA. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. BMJ. 2000 Sep 30;321(7264):794-6. doi: 10.1136/bmj.321.7264.794. PMID: 11009518; PMCID: PMC27491.
12. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care. 2011 Oct;34(10):2220-4. doi: 10.2337/dc11-1108. Epub 2011 Aug 18. PMID: 21852677; PMCID: PMC3177727.
13. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabet Med. 2004 Sep;21(9):976-82. doi: 10.1111/j.1464-5491.2004.01271.x. PMID: 15317601.
14. Bouhassira D, Letanoux M, Hartemann A. Chronic pain with neuropathic characteristics in diabetic patients: a French cross-sectional study. PLoS One. 2013 Sep 13;8(9):e74195. doi: 10.1371/journal.pone.0074195. PMID: 24058527; PMCID: PMC3772849.
15. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology. 2007 Apr 10;68(15):1178-82. doi: 10.1212/01.wnl.0000259085.61898.9e. PMID: 17420400.
16. Solaro C, Brichetto G, Amato MP, Cocco E, Colombo B, D'Aleo G, Gasperini C, Ghezzi A, Martinelli V, Milanese C, Patti F, Trojano M, Verdun E, Mancardi GL; PaIMS Study Group. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. Neurology. 2004 Sep 14;63(5):919-21. doi: 10.1212/01.wnl.0000137047.85868.d6. PMID: 15365151.
17. Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis--prevalence and clinical characteristics. Eur J Pain. 2005 Oct;9(5):531-42. doi: 10.1016/j.ejpain.2004.11.005. Epub 2004 Dec 22. PMID: 16139182.
18. Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. Pain. 2003 Jun;103(3):249-257. doi: 10.1016/S0304-3959(02)00452-9. PMID: 12791431.
19. Klit H, Finnerup NB, Andersen G, Jensen TS. Central poststroke pain: a population-based study. Pain. 2011 Apr;152(4):818-824. doi: 10.1016/j.pain.2010.12.030. Epub 2011 Jan 26. PMID: 21272999.

20. Rayment C, Hjermstad MJ, Aass N, Kaasa S, Caraceni A, Strasser F, Heitzer E, Fainsinger R, Bennett MI; European Palliative Care Research Collaborative (EPCRC). Neuropathic cancer pain: prevalence, severity, analgesics and impact from the European Palliative Care Research Collaborative-Computerised Symptom Assessment study. Palliat Med. 2013 Sep;27(8):714-21. doi: 10.1177/0269216312464408. Epub 2012 Nov 21. PMID: 23175513.
21. Bennett MI, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain. 2012 Feb;153(2):359-365. doi: 10.1016/j.pain.2011.10.028. Epub 2011 Nov 23. PMID: 22115921.
22. Bouhassira D, Attal N. Diagnosis and assessment of neuropathic pain: the saga of clinical tools. Pain. 2011 Mar;152(3 Suppl):S74-S83. doi: 10.1016/j.pain.2010.11.027. Epub 2010 Dec 23. PMID: 21185120.
23. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain. 2006 Apr;7(4):281-9. doi: 10.1016/j.jpain.2005.11.008. PMID: 16618472.
24. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lantéri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005 Mar;114(1-2):29-36. doi: 10.1016/j.pain.2004.12.010. Epub 2005 Jan 26. PMID: 15733628.
25. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain. 2001 May;92(1-2):147-57. doi: 10.1016/s0304-3959(00)00482-6. PMID: 11323136.
26. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain. 2008 Jun;136(3):380-387. doi: 10.1016/j.pain.2007.08.013. Epub 2007 Sep 20. PMID: 17888574.
27. Freynhagen R, Baron R, Tölle T, Stemmler E, Gockel U, Stevens M, Maier C. Screening of neuropathic pain components in patients with chronic back pain associated with nerve root compression: a prospective observational pilot study (MIPORT). Curr Med Res Opin. 2006 Mar;22(3):529-37. doi: 10.1185/030079906X89874. PMID: 16574036.
28. Borsook D. Neurological diseases and pain. Brain. 2012 Feb;135(Pt 2):320-44. doi: 10.1093/brain/awr271. Epub 2011 Nov 8. PMID: 22067541; PMCID: PMC3281476.
29. Watson JC, Sandroni P. Central Neuropathic Pain Syndromes. Mayo Clin Proc. 2016 Mar;91(3):372-85. doi: 10.1016/j.mayocp.2016.01.017. PMID: 26944242.
30. Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DLH, Bouhassira D, Cruccu G, Freeman R, Hansson P, Nurmikko T, Raja SN, Rice ASC, Serra J, Smith BH, Treede RD, Jensen TS. Neuropathic pain: an updated grading system for research and clinical practice. Pain. 2016 Aug;157(8):1599-1606. doi: 10.1097/j.pain.0000000000000492. PMID: 27115670; PMCID: PMC4949003.
31. Stavros K, Simpson DM. Understanding the etiology and management of HIV-associated peripheral neuropathy. Curr HIV/AIDS Rep. 2014 Sep;11(3):195-201. doi: 10.1007/s11904-014-0211-2. PMID: 24969360.
32. Stavros K, Simpson DM. Understanding the etiology and management of HIV-associated peripheral neuropathy. Curr HIV/AIDS Rep. 2014 Sep;11(3):195-201. doi: 10.1007/s11904-014-0211-2. PMID: 24969360.
33. Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. Curr Diab Rep. 2009 Dec;9(6):423-31. doi: 10.1007/s11892-009-0069-7. PMID: 19954686.
34. Yang Y, Wang Y, Li S, Xu Z, Li H, Ma L, Fan J, Bu D, Liu B, Fan Z, Wu G, Jin J, Ding B, Zhu X, Shen Y. Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. J Med Genet. 2004 Mar;41(3):171-4. doi: 10.1136/jmg.2003.012153. PMID: 14985375; PMCID: PMC1735695.
35. Fertleman CR, Baker MD, Parker KA, Moffatt S, Elmslie FV, Abrahamsen B, Ostman J, Klugbauer N, Wood JN, Gardiner RM, Rees M. SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. Neuron. 2006 Dec 7;52(5):767-74. doi: 10.1016/j.neuron.2006.10.006. PMID: 17145499.
36. Faber CG, Hoeijmakers JG, Ahn HS, Cheng X, Han C, Choi JS, Estacion M, Lauria G, Vanhoutte EK, Gerrits MM, Dib-Hajj S, Drenth JP, Waxman SG, Merkies IS. Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol. 2012 Jan;71(1):26-39. doi: 10.1002/ana.22485. Epub 2011 Jun 22. PMID: 21698661.
37. Lumsden DE, Crowe B, Basu A, Amin S, Devlin A, DeAlwis Y, Kumar R, Lodh R, Lundy CT, Mordekar SR, Smith M, Cadwgan J. Pharmacological management of abnormal tone and movement in cerebral palsy. Arch Dis Child. 2019 Aug;104(8):775-780. doi: 10.1136/archdischild-2018-316309. Epub 2019 Apr 4. PMID: 30948360.

38. Rocha S, Ferraz R, Prudêncio C, Fernandes MH, Costa-Rodrigues J. Differential effects of antiepileptic drugs on human bone cells. J Cell Physiol. 2019 Nov;234(11):19691-19701. doi: 10.1002/jcp.28569. Epub 2019 Apr 2. PMID: 30941778.
39. Chin KK, Carroll I, Desai K, Asch S, Seto T, McDonald KM, Curtin C, Hernandez-Boussard T. Integrating Adjuvant Analgesics into Perioperative Pain Practice: Results from an Academic Medical Center. Pain Med. 2020 Jan 1;21(1):161-170. doi: 10.1093/pm/pnz053. PMID: 30933284; PMCID: PMC10147384.
40. Viniol A, Ploner T, Hickstein L, Haasenritter J, Klein KM, Walker J, Donner-Banzhoff N, Becker A. Prescribing practice of pregabalin/gabapentin in pain therapy: an evaluation of German claim data. BMJ Open. 2019 Mar 30;9(3):e021535. doi: 10.1136/bmjopen-2018-021535. PMID: 30928920; PMCID: PMC6475154.
41. Cruccu G, Truini A. A review of Neuropathic Pain: From Guidelines to Clinical Practice. Pain Ther. 2017 Dec;6(Suppl 1):35-42. doi: 10.1007/s40122-017-0087-0. Epub 2017 Nov 24. PMID: 29178033; PMCID: PMC5701894.
42. Kneib CJ, Sibbett SH, Carrougher GJ, Muffley LA, Gibran NS, Mandell SP. The Effects of Early Neuropathic Pain Control With Gabapentin on Long-Term Chronic Pain and Itch in Burn Patients. J Burn Care Res. 2019 Jun 21;40(4):457-463. doi: 10.1093/jbcr/irz036. PMID: 30893433.
43. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998 Dec 2;280(21):1831-6. doi: 10.1001/jama.280.21.1831. PMID: 9846777.
44. Chincholkar M. Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice. Br J Pain. 2020 May;14(2):104-114. doi: 10.1177/2049463720912496. Epub 2020 Mar 13. PMID: 32537149; PMCID: PMC7265598.
45. Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE Jr, Welge JA, Bishop F, Stanford KE, Hess EV, Hudson JI. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum. 2007 Apr;56(4):1336-44. doi: 10.1002/art.22457. PMID: 17393438.
46. Kume A. Gabapentin enacarbil for the treatment of moderate to severe primary restless legs syndrome (Willis-Ekbom disease): 600 or 1,200 mg dose? Neuropsychiatr Dis Treat. 2014 Feb 3;10:249-62. doi: 10.2147/NDT.S30160. PMID: 24523590; PMCID: PMC3921090.
47. Tong C, Zhengyao Z, Mei L, Dongpo S, Qian H, Fengqun M. Pregabalin and Gabapentin in Patients with Spinal Cord Injury-Related Neuropathic Pain: A Network Meta-Analysis. Pain Ther. 2021 Dec;10(2):1497-1509. doi: 10.1007/s40122-021-00302-8. Epub 2021 Sep 7. PMID: 34491542; PMCID: PMC8586377.
48. Bragg S, Marrison ST, Haley S. Diabetic Peripheral Neuropathy: Prevention and Treatment. Am Fam Physician. 2024 Mar;109(3):226-232. PMID: 38574212.
49. Argoff CE. Review of current guidelines on the care of postherpetic neuralgia. Postgrad Med. 2011 Sep;123(5):134-42. doi: 10.3810/pgm.2011.09.2469. PMID: 21904096.
50. French J, Kwan P, Fakhoury T, Pitman V, DuBrava S, Knapp L, Yurkewicz L. Pregabalin monotherapy in patients with partial-onset seizures: a historical-controlled trial. Neurology. 2014 Feb 18;82(7):590-7. doi: 10.1212/WNL.0000000000000119. Epub 2014 Jan 10. PMID: 24415567; PMCID: PMC3963419.
51. Bidari A, Moazen-Zadeh E, Ghavidel-Parsa B, Rahmani S, Hosseini S, Hassankhani A. Comparing duloxetine and pregabalin for treatment of pain and depression in women with fibromyalgia: an open-label randomized clinical trial. Daru. 2019 Jun;27(1):149-158. doi: 10.1007/s40199-019-00257-4. Epub 2019 Mar 14. PMID: 30877484; PMCID: PMC6593027.
52. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, Choy E, Kosek E, Amris K, Branco J, Dincer F, Leino-Arjas P, Longley K, McCarthy GM, Makri S, Perrot S, Sarzi-Puttini P, Taylor A, Jones GT. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017 Feb;76(2):318-328.
53. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res. 2007 Feb;73(2):137-50. doi: 10.1016/j.eplepsyres.2006.09.008. Epub 2006 Nov 28. PMID: 17126531.
54. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia. 2004;45 Suppl 6:13-8. doi: 10.1111/j.0013-9580.2004.455003.x. PMID: 15315511.
55. Keller DA, Bassan A, Amberg A, Burns Naas LA, Chambers J, Cross K, Hall F, Jahnke GD, Luniwal A, Manganelli S, Mestres J, Mihalchik-Burhans AL, Woolley D, Tice RR. *In silico* approaches in carcinogenicity hazard assessment: case study of pregabalin, a nongenotoxic mouse carcinogen. Front

Toxicol. 2023 Nov 13;5:1234498. doi: 10.3389/ftox.2023.1234498. PMID: 38026843; PMCID: PMC10679394.