Incidence of Neuropsychiatric Adverse Effects Following the Initiation of Gabapentin or Pregabalin for the Treatment of Neuropathic Pain

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ABSTRACT

Neuropathic pain is a challenging condition to manage clinically, with symptoms that have a significant impact on patients' quality of life. Gabapentin and pregabalin are two of the primary options, demonstrating good efficacy and tolerability. Psycho-behavioral side effects of gabapentinoids are relatively well-documented, although they are observed more frequently in the context of epilepsy, highlighting the importance of careful monitoring for these adverse effects in the management of neuropathic pain. We conducted a retrospective chart review of adult patients with neuropathic pain treated with gabapentin or pregabalin at a neurology outpatient center in Jeddah, Saudi Arabia, between May 2023 and May 2024. Patients with at least two follow-up visits over six months were included. Data on demographics, diagnosis, treatment, and neuropsychiatric adverse effects were collected and analyzed using descriptive statistics and chi-square tests. A total of 110 patients were included in the study, with 54.5% being male and 50.9% aged 60 years or older. Polyneuropathy was the primary diagnosis in 45% of patients, and 30.9% had experienced neuropathic pain for more than 12 months. Gabapentin was administered to 74 patients, while 36 patients received pregabalin. 94.5% of patients did not report any psycho-behavioral adverse effects. Six patients experienced mild to moderate symptoms. Three patients complained of sleep disturbances, two of apathy, and one of anxiety. Noticeably, five of these six patients were over the age of 50. No patients discontinued their medication due to these adverse effects. Gabapentin and pregabalin demonstrate an admirable safety profile for neuropathic pain, supporting high compliance and improved quality of life. Gabapentinoids appear to present a lower risk of psychiatric side effects when used for neuropathic pain compared to epilepsy, making them a preferred first-line option for symptom control in neuropathic pain management.

Keywords: Gabapentin, Pregabalin, Neuropsychiatric, Adverse effects, Neuropathic pain

INTRODUCTION

Neuropathic pain is a complex condition, usually arising from an insult to a nerve, which is particularly challenging to manage clinically even today. The etiology generally develops in abnormal neural activity, in which symptoms of burning, tingling, and shooting pains can seriously reduce a patient's quality of life[1,2,3]. In general, neuropathic pain is treated with multiple modalities. A combination of pharmacological and non-pharmacological interventional approaches secures maximum benefit whenever possible. Of the many well-recognized pharmacological medications used in treating neuropathic pain, gabapentinoids (gabapentin and pregabalin) are two of the most well-recognized options. Both have established their efficacy, with a very encouraging profile in terms of tolerability[4].

Although it was developed for the treatment of epilepsy, gabapentin was also repurposed for use in most forms of neuropathic pain, such as restless leg syndrome, postherpetic neuralgia, diabetic neuropathy, and fibromyalgia. This wide usage in painful conditions speaks for its versatility and broad effectiveness against the complexities of neuropathic pain[5,6,7].

Pregabalin, which is considered the second-generation successor to gabapentin, was approved for painful conditions such as diabetic peripheral neuropathy, postherpetic neuralgia, and neuropathic pain associated with spinal cord injury[8,9,10,11]. In fact, in many studies, it was found that pregabalin was highly effective at reducing the intensity of pain and at improving quality of life[12]. Additionally, pregabalin's ability to alleviate anxiety, a common comorbidity in chronic pain patients, further broadens its therapeutic value[13,14].

Overall, safety appears to be good for both gabapentin and pregabalin; however, some common adverse effects like dizziness, somnolence, peripheral edema, and psycho-behavioral manifestations may potentially impact the patient's adherence. Psycho-behavioral side effects are relatively well described for gabapentinoids in the setting of epilepsy and stress the importance of their careful monitoring and therapy individualization[15,16].

This review discusses the incidence of these symptoms and their impact on treatment adherence in neuropathic pain management.

METHODS

A retrospective chart review was conducted at a neurology outpatient center in Jeddah, Saudi Arabia, covering the period from May 2023 to May 2024. The study targeted adult patients (aged ≥18 years) who were diagnosed with neuropathic pain and received either gabapentin or pregabalin.

Sampling Method: A non-probability consecutive sampling technique was used. All eligible patients seen during the study period and who met the inclusion criteria were enrolled until the desired sample size was reached.

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Sample Size: A total of 110 patients were included. While no formal sample size calculation was performed, this number represents all patients who met the inclusion criteria within the study period and had completed at least two follow-up visits after initiating gabapentin or pregabalin. The sample size was considered adequate for exploratory descriptive analysis and basic hypothesis testing using chi-square methods.

Inclusion Criteria: Patients were included if they had a confirmed clinical diagnosis of neuropathic pain, were newly initiated on either gabapentin or pregabalin, and had at least two neurology clinic follow-ups over a 6-month period.

Exclusion Criteria: Patients with incomplete records or those who missed follow-up visits within 6 months of treatment initiation were excluded.

Data collected included patient demographics (age, gender), primary neurological diagnosis, duration of pain, treatment details (type and duration of medication), and documentation of any neuropsychiatric adverse effects. Severity of adverse events was classified as mild, moderate, or severe based on patient-reported impact on daily activities. Statistical analysis was performed using IBM SPSS Statistics Version 20. Categorical variables were summarized using frequencies and percentages. Relationships between categorical variables were evaluated using the Chi-square test, with a significance threshold set at $p<0.05$.

Ethical approval for this study was obtained from the Research Ethics Committee of the University of Jeddah.

RESULTS

A total of 110 patients were included in the study, with 54.5% being male and 45.5% female. Additionally, 50.9% of the patients were aged 60 years or older, Table 1 provides further insight into patients' demographics.

Table 1. Patients' Demographics Including Age Groups and Gender

Age Group	Number of patients	Percentage
20-30 years	9	8.20%
31-40 years	18	16.40%
41-50 years	11	10.00%
51-60 years	16	14.50%
Above 60 years	56	50.90%
Gender		
Male	60	54.50%
Female	50	45.50%

Among the participants, the main diagnoses included polyneuropathy in 45% of the patients and radiculopathy in 40%. Specific diagnoses are outlined in Figure 1.

Regarding the duration of neuropathic pain, 30.9% of the patients had been in pain for more than 12 months, and 24.5% reported neuropathic pain for 7-12 months. Figure 2 further illustrates treatment duration in the study.

74 patients received gabapentin at a median dose of 600 mg, and the remaining 36 patients received pregabalin with a median dose of 300 mg.

Most of the patients (94.5%) did not report any psycho-behavioral adverse effects. 6 patients demonstrated minimal to moderate symptoms. Three patients complained of sleep disturbances, two of apathy, and one patient of anxiety (Figure 3). 5 out of those 6 patients were above 50 years of age, and no patient stopped either gabapentin or pregabalin due to these adverse effects. Of these, the symptoms were rated as mild by 2 patients and as moderate by 4 patients. No patients under the age of 30 years reported any adverse effects.

No statistically significant differences between the genders in symptom occurrence were seen. Further details on the severity of adverse effects and the relation with age are given in Table 2, while Table 3 gives a view on the relation between the severity of adverse effects and treatment duration.

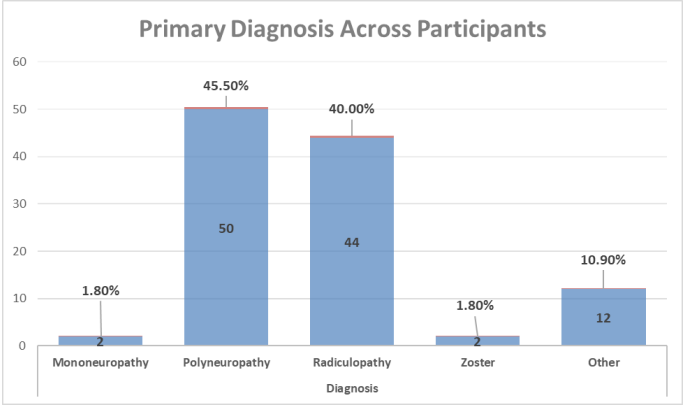

Figure 1. The Primary Diagnosis of the Participants

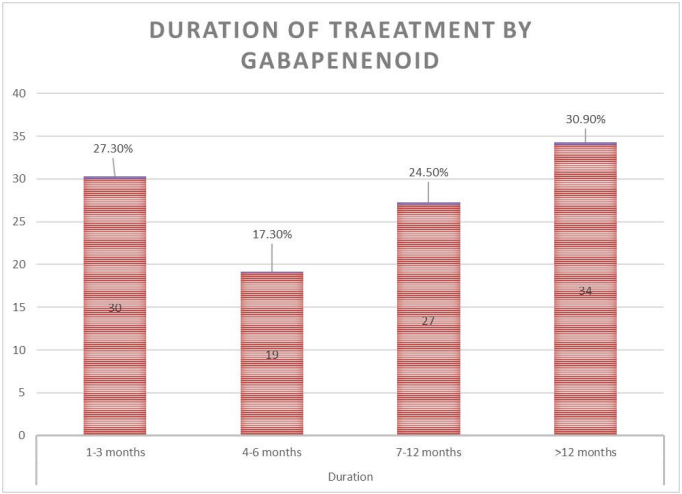

Figure 2. Duration of Treatment by Gabapentin and Pregabalin

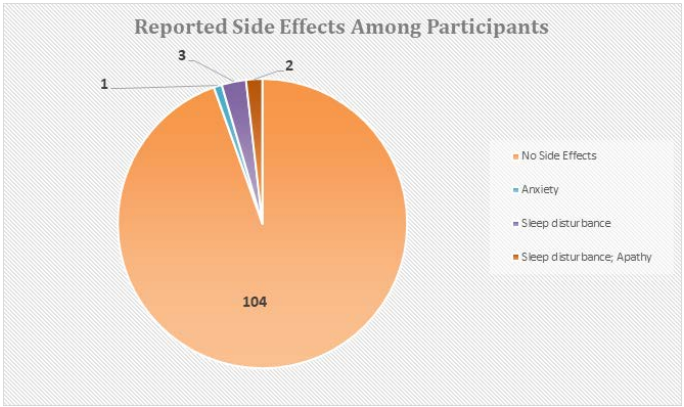

Figure 3. Numbers of Participants Who Reported Neuro-psychiatric Side Effects

Table 2. Relation Between Age and Severity of Adverse Effects of Gabapentinoids

Severity	Age	Medication		Total
		Gabapentin	Pregabalin	
No Adverse Effects Reported	20-30 years	7	2	9
		77.8%	22.2%	100.0%
	31-40 years	13	4	17
		76.5%	23.5%	100.0%
	41-50 years	9	2	11
		81.8%	18.2%	100.0%
	51-60 years	9	6	15
		60.0%	40.0%	100.0%
	above 60 years	34	18	52
		65.4%	34.6%	100.0%
Mild	51-60 years		1	1
			100.0%	100.0%
	above 60 years		1	1
			100.0%	100.0%
Moderate	31-40 years	1	0	1
		100.0%	0.0%	100.0%
	above 60 years	1	2	3
		33.3%	66.7%	100.0%

Table 3. Relation Between Duration of Treatment and Severity of Adverse Effects of Gabapentinoids

Severity	Duration	Medication		Total
		Gabapentin	Pregabalin	
No Adverse Effects Reported	1-3 months	19	7	26
		73.1%	26.9%	100.0%
	4-6 months	13	5	18
		72.2%	27.8%	100.0%
	7-12 months	18	8	26
		69.2%	30.8%	100.0%
	>12 months	22	12	34
		64.7%	35.3%	100.0%
Mild	1-3 months		1	1
			100.0%	100.0%
	7-12 months		1	1
			100.0%	100.0%
Moderate	1-3 months	2	1	3
		66.7%	33.3%	100.0%
	4-6 months	0	1	1
		0.0%	100.0%	100.0%

DISCUSSION

Role of Gabapentinoids in Neuropathic Pain: Most clinical guidelines recommend gabapentin and pregabalin as first- or second-line treatments for various types of neuropathic pain, either alone or in combination with other analgesics as part of a multimodal pain management approach[17,18]. Both agents share a similar mechanism of action: they bind to the α2δ subunit of voltage-gated calcium channels in the central nervous system. This interaction modulates the release of excitatory neurotransmitters including glutamate, substance P, and norepinephrine, thereby reducing neuronal hyperexcitability, a hallmark of neuropathic pain[19,20]. While their pharmacological profiles overlap in many respects, pregabalin offers notable advantages over gabapentin, including higher potency, faster absorption, more predictable bioavailability, and stronger binding affinity. It also demonstrates a steep dose-response curve without plateauing at recommended doses[16,21]. Consequently, the choice between gabapentin and pregabalin is often guided by individual patient factors, such as comorbidities, previous treatment response, and risk of adverse effects[22,23]. Gabapentinoids are generally preferred as initial treatment options for neuropathic pain due to their efficacy, tolerability, and higher rates of compliance when compared to alternative medications[24,25].

Incidence of Neuropsychiatric Adverse Effects in This Study: In the present study, the incidence of neuropsychiatric adverse effects was low. Only 5.5% of patients reported mild to moderate symptoms. These findings support the favorable safety and tolerability profile of gabapentinoids in the treatment of neuropathic pain and underscore their minimal impact on treatment adherence.

Comparison with Use in Epilepsy and Other Agents: Gabapentinoids are also used as add-on therapy in epilepsy, where they are associated with a higher incidence of adverse effects, likely due to the higher doses typically required in that context[26,27,28]. As such, while these agents are widely used in neuropathic pain management due to their safety profile,

other antiseizure medications are often preferred as first-line treatments for epilepsy[28,29]. In this study, the incidence of neuropsychiatric adverse effects was significantly lower than in studies involving gabapentinoids for epilepsy, where neurotoxic side effects like dizziness (22.2%), drowsiness (14.8%), amnesia (11.1%), and tingling (11.1%) were common[30]. Similarly, a meta-analysis of pregabalin in treatment-resistant focal epilepsy reported a higher relative risk of ataxia (RR 3.90), dizziness (RR 3.15), and somnolence (RR 2.05) compared to placebo[27]. Other studies evaluating the safety of pregabalin in epilepsy have reported discontinuation rates of up to 15% due to neuropsychiatric adverse events. In contrast, no patients in our study discontinued treatment due to such effects[31,32]. Gabapentinoids also appear to compare favorably to other neuropathic pain medications. For example, somnolence was reported in 36% of patients on amitriptyline and 31% on duloxetine, while dizziness and lethargy were also more frequent[33]. The much lower incidence observed in our study highlights the superior neuropsychiatric tolerability of gabapentin and pregabalin in this population.

Association with Patient Age and Duration of Treatment: Most adverse effects in our study emerged within the first three months of treatment, suggesting that the early treatment period carries the highest risk for side effect development. Conversely, longer treatment durations may be associated with fewer side effects, improved symptom control, and greater compliance. To our knowledge, no previous studies on gabapentinoid safety have examined the role of treatment duration in the emergence of neuropsychiatric symptoms. In line with previous literature, most patients who experienced side effects were aged over 50. A pooled analysis of 11 clinical studies found that older adults are more likely to discontinue pregabalin due to side effects[34]. These findings underscore the need for cautious dosing in older populations to maintain adherence and optimize long-term outcomes.

CONCLUSION

The safety profile of gabapentin and pregabalin for neuropathic pain has remained stable in recent years, supporting high patient compliance and enhancing quality of life. Compared to the adverse effects associated with their use for other indications, such as epilepsy, gabapentinoids tend to present a lower risk of psychiatric side effects when used for treating neuropathic pain. This lower risk makes them a preferred first-line option for achieving improved outcomes and symptom control in neuropathic pain management.

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Potential Conflicts of Interest: None

Competing Interest: None

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