Journal of Pain Research Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Prescribing Patterns and Off-Label Use of Gabapentinoid Agents at Dhulikhel Hospital, Nepal: A Cross-Sectional Study

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Purpose: Gabapentinoids are mainly prescribed for neuropathic pain and certain seizure disorders, but their off-label use has increased significantly. This rise raises concerns about the insufficient evidence supporting some applications, as well as potential risks of misuse, dependence, and adverse effects. The study aims to examine the prescribing patterns and off-label use of gabapentinoids at Dhulikhel Hospital (DH), Nepal, focusing on understanding the extent of off-label practices and patient knowledge regarding their medications.

Patients and Methods: A cross-sectional survey of 385 adult patients prescribed gabapentinoids was conducted at the outpatient pharmacy of DH. Data were collected via patient interviews and prescriptions. Off-label use was assessed according to the licensed indications of the US Food and Drug Administration (FDA) and the UK British National Formulary (BNF). Statistical analysis was performed using Statistical Package for the Social Sciences version 26.

Results: Among patients prescribed gabapentinoids, 73.0% received gabapentin while 27.0% were prescribed pregabalin. Most patients were middle-aged females with comorbid conditions, primarily orthopedic outpatients. Off-label use was prevalent, with 96.1% of prescriptions being off-label by FDA indications and 28.1% by BNF indications. Pregabalin was prescribed at a sub-therapeutic dose (75 mg/day) for neuropathic pain. Patient knowledge about gabapentinoids was found to be poor, particularly regarding side effects and drug interactions.

Conclusion: This study highlights the extensive off-label and sub-therapeutic use of gabapentinoids at Dhulikhel Hospital and reveals significant gaps in patient knowledge. This emphasizes the need for stricter prescribing guidelines, improved healthcare provider education, and better patient information to optimize the use and minimize risks. The frequent prescription of low-dose pregabalin for neuropathic pain raises the possibility that it may be used for night-time sedation rather than for pain management, indicating the need for further investigation.

Keywords: off-label use, gabapentin, pregabalin, Nepal, prescribing patterns, patient education

Introduction

The urgent need for alternative pain management strategies during the opioid crisis led to increased prescribing of gabapentinoids for pain relief.[1] Gabapentinoids are antiepileptic medications initially approved for the treatment of seizures because of their anticonvulsant properties. Their ability to reduce neuronal hyperexcitability has expanded their use and made them integral components of multimodal analgesia protocols.[2] Gabapentinoids are now widely recognized and recommended as first-line therapy for neuropathic pain in many international guidelines.[3] Their role as non-narcotic medications for managing both neuropathic and certain non-neuropathic pain conditions has garnered significant attention, offering prescribers valuable tools for addressing persistent challenges in this field.[4]

Currently, both gabapentin and pregabalin have United States Food and Drug Administration (FDA) indications for the treatment of post herpetic neuralgia in adults and as adjunctive therapies for the management of partial-onset seizures, however pregabalin is licensed for neuropathic pain associated with diabetic peripheral neuropathy, fibromyalgia and

Received: 2 September 2024
Accepted: 5 December 2024
Published: 18 December 2024

neuropathic pain associated with spinal cord injury.[5,6] The British National Formulary (BNF) and the Nepalese National Formulary (NNF) both specify a notably broader range of uses for these agents. Gabapentin is indicated for the treatment of peripheral neuropathic pain, whereas pregabalin is approved for both central and peripheral neuropathic pain.[7] However, gabapentinoids are not indicated for sedation or for treating non-neuropathic pain.

The off-label use of gabapentinoids is believed to constitute a significant portion of all prescriptions, although determining accurate prevalence rates at both the national and global levels can be difficult.[8] Gabapentinoids are frequently prescribed for different therapeutic indications, including chronic back pain, perioperative pain, pruritus, anxiety, attention deficit disorder, bipolar disorder, migraines, sleep disorders, alcohol withdrawal seizures and more.[9–11] In the United States, gabapentin is extensively used off-label, often alongside opioid analgesics, with 83% to 95% of its prescriptions being for off-label indications, primarily due to its perceived safety and efficacy in managing pain and other conditions.[12,13] Although off-label drug use is legal and common, the increased use of gabapentinoids has sparked debate owing to insufficient or low-quality evidence supporting their effectiveness in these cases.[14,15] There are growing concerns about the potential misuse of gabapentinoids because of their risk of adverse effects, dependency, and abuse. This risk is heightened when these drugs are prescribed alongside other central nervous system depressants such as opioids.[16]

The off-label use of gabapentinoids is a significant yet understudied issue, particularly in Nepal. This study aimed to address the research gaps by analyzing the prescribing patterns of gabapentin and pregabalin at a tertiary care hospital in Nepal. The objective was to understand both the approved and off-label uses of these medications and to evaluate the knowledge of users about their prescriptions.

Materials and Methods

Study Design, Study Site and Sample Size

This study was a cross-sectional survey conducted from April 7 to June 15, 2024, at the outpatient pharmacy department of Dhulikhel Hospital, Kathmandu University Hospital, Nepal. The sample size was calculated to be 385 patients based on 95% confidence interval and a 5% margin of error, assuming a 50% prevalence of off-label use of gabapentinoids. Purposive sampling was used in this study.

Eligibility Criteria

Adult patients (≥18 years) who were prescribed gabapentinoids as outpatients and who visited the outpatient pharmacy for these medications were included in the study. Proxy medication recipients and patients who did not consent to participate in the study were also excluded.

Ethical Approval and Informed Consent

Ethical approval for this study was granted by the Institutional Review Committee of the School of Medical Sciences at Kathmandu University (Approval No: KUSMS-IRC 108/24). Before joining the study, potential participants were given a complete explanation of the procedures. Participation was voluntary, and individuals could withdraw at any time without any repercussions. Informed consent was acquired from all participants prior to the study. The study adhered to the ethical standards outlined in the Helsinki Declaration, ensuring patient data privacy and confidentiality.

Data Collection

Data were collected from copies of prescriptions provided to patients upon receiving their medication. The information gathered included demographic characteristics, indications for gabapentinoid use, specific gabapentinoid prescribed, complete dosage regimen details, department from which the gabapentinoid was prescribed, and other relevant factors. In cases where patients had multiple prescriptions, only prescriptions containing gabapentinoids at the time of the survey were considered. All the participants provided written informed consent. Patients were interviewed face to face via a pretested, structured, and validated investigator-administered questionnaire (Supplementary Figure 1) as they exited the pharmacy. This questionnaire, adapted from a previous study, aimed to evaluate patients' knowledge about their prescribed gabapentinoids.[17]

Categorization of off-Label Use

Gabapentinoid prescriptions were assessed based on the indications specified by the FDA and BNF as listed in Table 1.[18–21] The use of these medications was classified into labeled and off-label categories. Additionally, instances of sub-therapeutic dosing and combination therapy were documented and analyzed.

Categorization of the Knowledge Level of Patients

The questionnaire assessed patients' knowledge of their gabapentinoid medication. Patients were given two points each when they knew the medication's name, dosage, form, and frequency and one point each when they understood its therapeutic use, treatment duration, side effects, interactions, and action taken after missed doses. Scoring was categorized as insufficient knowledge of safe use (≤7 points), average knowledge sufficient for normal use (8–10 points), and good knowledge, ensuring safe use under all circumstances (≥11 points).

Variables

The dependent variables included prescription patterns (frequency of gabapentinoid prescriptions, dosage and duration of prescriptions, and combination with other medications), off-label use (frequency of off-label prescriptions, specific off-label conditions being treated), and knowledge of patients regarding their prescription. Independent variables included

Table 1 List of Indications of Gabapentin and Pregabalin as Listed by Different Authorities

Source	Gabapentin Indications	Pregabalin Indications
FDA	Post herpetic neuralgia	Post herpetic neuralgia
	Adjunctive therapy for partial-onset seizures, with or without secondary generalization, in adults and children aged 3 years and older with epilepsy	Adjunctive therapy for partial-onset seizures in patients aged 4 years and older
		Neuropathic pain associated with diabetic peripheral neuropathy
		Fibromyalgia
		Neuropathic pain associated with spinal cord injury
BNF	Adjunctive therapy for focal seizures with or without secondary generalization	Adjunctive therapy for focal seizures with or without secondary generalization
	Peripheral neuropathic pain	Peripheral and central neuropathic pain
	Monotherapy for focal seizures with or without secondary generalization	Generalized anxiety disorder
	Menopausal symptoms, particularly hot flushes, in women with breast cancer*	
	Oscillopsia in multiple sclerosis*	
	Spasticity in multiple sclerosis*	
	Muscular symptoms in motor neuron disease*	
NNF	Adjunctive treatment of partial seizures, with and without secondary generalization	Adjunctive therapy for focal seizures with or without secondary generalization
	Bipolar affective disorder	Generalized anxiety disorder
	Post herpetic neuralgia	Peripheral and central neuropathic pain
	Neuropathic pain	

Note: (*) denotes indications that are unlicensed in the United Kingdoms.
Abbreviations: BNF, British National Formulary; FDA, Food and Drug Administrations; NNF, Nepalese National Formulary.

patient demographics (age, sex, ethnicity, education status and education level), clinical characteristics (diagnoses, comorbidities), and healthcare system factors (department, insurance coverage).

Statistical Analysis

Data were analyzed using SPSS version 26. Descriptive statistics were used to characterize the dataset and the baseline characteristics were summarized as frequencies and percentages. Non-parametric tests were applied owing to skewed data. Categorical variables were assessed via chi-square tests (or Fisher's exact tests when applicable), whereas continuous variables are reported as medians with interquartile ranges (IQRs) and were compared via the Mann–Whitney *U*-test. Binary logistic regression was performed to identify factors associated with "off-label gabapentinoid use" and "good knowledge of prescribed gabapentinoids." Univariate analysis was followed by multivariate analysis for significant factors, with the results presented as odds ratios (ORs), 95% confidence intervals, and p values. Significance was set at $p < 0.05$.

Results

Baseline Characteristics of the Sample

Table 2 presents the demographic and clinical characteristics of 385 patients, of whom 281 (73.0%) were prescribed gabapentin and 104 (27.0%) were prescribed pregabalin. The cohort was predominantly female (69.1%), with a median age of 49 years (IQR: 39.5–59.5). The majority of prescriptions were for follow-up visits (51.7%), with the orthopedic department accounting for 87.5% of all prescriptions. Additionally, 90.1% of patients had insurance coverage. There is a significant difference in the proportion of patients with diabetes mellitus (p=0.008), orthopedic co-morbidity (p=0.007) and department visited (p<0.001) between those taking gabapentin and pregabalin.

Table 2 Baseline Characteristics of the Patients Prescribed with Gabapentinoids at Dhulikhel Hospital, Nepal

Characters		Total (n=385)	Gabapentin (n=281)	Pregabalin (n=104)	p-value
Gender	Male	119 (30.9)	90 (32.0)	29 (27.9)	0.435[a]
	Female	266 (69.1)	191 (68.0)	75 (72.1)	
Age	*Median (IQR)*	49 (39.5–59.5)	49 (40.0–59.0)	49.5 (37.25–61.5)	0.839[c]
	18–25	11 (2.9)	10 (3.6)	1 (1.0)	0.158[a]
	26–35	57 (14.8)	35 (12.5)	22 (21.2)	
	36–45	85 (22.1)	66 (23.5)	19 (18.3)	
	46–55	106 (27.5)	78 (27.8)	28 (26.9)	
	56–65	67 (17.4)	53 (18.9)	14 (13.5)	
	>65 (Elderly)	59 (15.3)	39 (13.9)	20 (19.2)	
Education Status	Illiterate	154 (40.0)	108 (38.4)	46 (44.2)	0.504[a]
	Literate	231 (60.0)	173 (61.6)	58 (55.8)	
Education Level of Literate Population	Primary Education	105 (27.3)	78 (27.8)	27 (26.0)	0.533[a]
	Secondary Education	111 (28.8)	82 (29.2)	29 (27.9)	
	Higher Education	15 (3.9)	13 (4.6)	2 (1.9)	

(*Continued*)

Table 2 (Continued).

Characters		Total (n=385)	Gabapentin (n=281)	Pregabalin (n=104)	p-value
Comorbidities Present		164 (42.6)	115 (40.9)	49 (47.1)	0.275[a]
Comorbidities	Hypertension	76 (19.7)	50 (17.8)	26 (27.2)	0.115[a]
	Cardiovascular Disorders	7 (1.8)	5 (1.8)	2 (1.9)	0.606[b]
	Dyslipidemia	21 (5.5)	14 (5.0)	7 (6.7)	0.502[a]
	Diabetes mellitus	32 (8.3)	17 (6)	15 (14.4)	0.008[a*]
	Thyroid diseases	29 (7.5)	25 (8.9)	4 (3.8)	0.437[a]
	Orthopedic co-morbidity	31 (8.1)	29 (10.3)	2 (1.9)	0.007[a*]
	Pulmonary co-morbidity	18 (4.7)	13 (4.6)	5 (4.8)	0.563[b]
	Others	25 (6.5)	17 (6.0)	8 (7.7)	0.502[a]
Prescription type	Follow-up	199 (51.7)	151 (53.7)	48 (46.2)	0.071[a]
	New	175 (45.5)	125 (44.5)	50 (48.1)	
	Re-fill	11 (2.9)	5 (1.8)	6 (5.8)	
Department visited	Orthopedics	337 (87.5)	263 (93.6)	74 (71.2)	0.00[b*]
	Medicine	32 (8.3)	11 (3.9)	21 (20.2)	
	Dermatology	9 (2.3)	6 (2.1)	3 (3.3)	
	Others	7 (1.8)	1 (0.4)	6 (5.8)	
Prescription Coverage	Insurance	347 (90.1)	255 (90.7)	92 (88.5)	0.504[a]
	Cash	38 (9.9)	26 (9.3)	12 (11.5)	
Median score of knowledge regarding their Gabapentinoid		8 (7–9)	8 (7–9)	8 (7–9)	0.802[c]
Knowledge Status	Inadequate	168 (43.5)	122 (43.4)	46 (44.2)	0.699[a]
	Average	196 (51.0)	142 (50.5)	54 (51.9)	
	Good	21 (5.5)	17 (6.0)	4 (3.8)	

Notes: (*) Indicates significant differences in the values between the categories after the respective tests at $p<0.05$. [a]Chi-square test of independence, [b]Fischer exact test, [c]Mann–Whitney *U*-test.

Prescribing Patterns of Gabapentinoids

The study revealed that the most common dosage regimen was 300 mg once daily for a month for gabapentin (56.23%) and 75 mg once daily for a month for pregabalin (62.5%). Table 3 shows that among the patients, 60.5% were first-time gabapentinoid users, with neuropathic pain being the primary indication (72.0%). NSAIDs were co-prescribed in 73.2% of the patients and controlled substances were co-prescribed in 9.1% of the patients. The most common supplements included methylcobalamin (62.6%), vitamin D3 (39.5%), and calcium (31.4%). Polypharmacy was observed in 50.6% of patients, with a median of five medications prescribed. Physiotherapy was recommended for 38.0% of patients, and 77.0% had a follow-up scheduled. Off-label prescribing was prevalent, with 96.1% based on FDA indications and 28.1% according to BNF indications.

Table 3 Prescribing Pattern of Gabapentinoids at Dhulikhel Hospital, Nepal

Categories		Total (n=385)	Gabapentin (n=281)	Pregabalin (n=104)
First time users		233 (60.5)	164 (58.4)	69 (66.3)
Off-label use as per FDA indication		370 (96.1)	274 (97.5)	96 (92.3)
Off-label use as per BNF indication		108 (28.1)	81 (28.8)	27 (26.0)
Indication	Neuropathic Pain	277 (71.9)	200 (71.2)	77 (74.0)
	Non-neuropathic Pain	108 (28.1)	81 (28.8)	27 (26.0)
Co-prescribed non-steroidal anti-inflammatory drugs	*Total*	282 (73.2)	220 (78.3)	62 (59.6)
	Etoricoxib	188 (48.8)	146 (52.0)	42 (40.4)
	Aceclofenac	75 (19.5)	60 (21.4)	15 (14.4)
	Naproxen	10 (2.6)	8 (2.8)	2 (1.9)
	Acetaminophen and Ibuprofen combination	6 (1.5)	4 (1.4)	2 (1.9)
	Diclofenac	3 (0.8)	2 (0.7)	1 (1.0)
Co-prescribed controlled substances	*Total*	35 (9.1)	23 (8.2)	12 (11.5)
	Opioids	5 (1.3)	2 (0.7)	3 (2.9)
	Amitriptyline	11 (2.9)	8 (2.8)	3 (2.9)
	Duloxetine	16 (4.2)	12 (4.3)	4 (3.8)
	Olanzapine	3 (0.8)	1 (0.4)	2 (1.9)
Co-prescribed Supplements	Vitamin B12 (Methylcobalamin)	241 (62.6)	188 (66.9)	53 (51)
	Calcium	121 (31.4)	101 (35.9)	20 (19.2)
	Vitamin D3 (Cholecalciferol)	152 (39.5)	132 (47.0)	20 (19.2)
Other co-prescribed medications	Steroids	50 (12.98)	40 (14.23)	10 (9.62)
	Diclofenac gel	47 (12.2)	40 (14.2)	7 (6.7)
	Muscle relaxants	67 (17.4)	57 (20.3)	10 (9.6)
	Proton Pump Inhibitors	140 (36.4)	109 (38.8)	31 (28.8)
	Acyclovir	6 (1.5)	4 (1.4)	2 (1.9)
	Adjuvant orthopedics medications	17 (4.4)	13 (4.6)	4 (3.8)
	Others	86 (22.3)	44 (15.6)	42 (40.4)
Number of medicines prescribed	Gabapentinoid only	3 (0.8)	0	3 (2.9)
	2	39 (10.1)	25 (8.9)	14 (13.5)
	3	62 (16.1)	36 (12.8)	26 (25.0)
	4	86 (22.3)	64 (22.8)	22 (21.2)
	5 or more (Polypharmacy)	195 (50.6)	156 (55.5)	39 (37.5)
	Median number of medicines	5 (3–5)	5 (4–5)	4 (3–5)

(*Continued*)

Table 3 (Continued).

Categories		Total (n=385)	Gabapentin (n=281)	Pregabalin (n=104)
Non-pharmacological measure suggested	Physiotherapy	146 (37.9)	116 (41.3)	30 (28.8)
	Immobilizer/Support	3 (0.8)	2 (0.7)	1 (1.0)
	Physiotherapy and Orthopedics Support	12 (3.1)	10 (3.6)	2 (1.9)
Follow-up scheduled		296 (76.9)	228 (81.1)	68 (65.4)

Off-Label Use of Gabapentinoids

Figure 1 illustrates the dosing of gabapentinoids, highlighting that pregabalin was predominantly prescribed at a sub-therapeutic dose, accounting for 94.0% of the all pregabalin prescriptions. 12 out of 104 pregabalin prescriptions were found to be in fixed dose combinations with methylcobalamin.

Table 4 presents the distribution of gabapentinoid prescriptions across FDA-approved indications, BNF indications for neuropathic pain, and off-label uses without documented neuropathic symptoms. The most common FDA-approved use was post-herpetic neuralgia (13.1%), with pregabalin additionally prescribed for fibromyalgia (3.0%) and diabetic peripheral neuropathy (0.4%). Among the BNF indications, most prescriptions (11.7%) targeted musculoskeletal and neurological conditions. Symptomatic treatment accounted for 19.5% of the cases, predominantly with pregabalin (28.8%). Off-label use was prevalent for musculoskeletal conditions without neuropathic symptoms (14.5%) and for perioperative scenarios (4.7%). Gabapentinoids were also used for psychiatric conditions (1.0%), with pregabalin being more common (3.0%).

Table 5 highlights the factors linked to off-label gabapentinoid use according to FDA guidelines. Patients visiting the orthopedics department were notably more likely to receive off-label prescriptions (OR: 24.750; $p < 0.001$), an association that remained significant after adjustment (AOR: 16.163; $p = 0.001$). Although patient age, type of gabapentinoid prescribed, analgesic co-prescription, and non-pharmacological measures were significant in univariate analysis, these factors were no longer significant after multivariate adjustment.

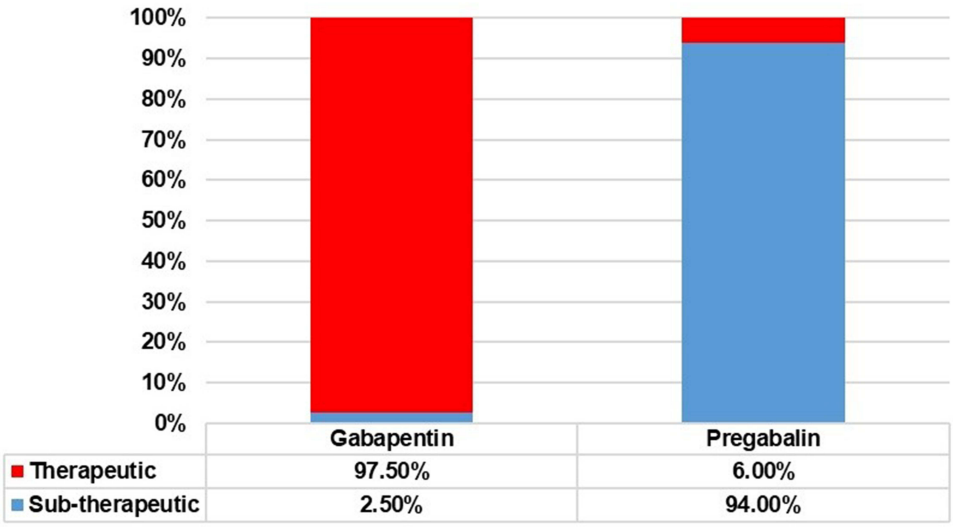

Figure 1 Stacked bar chart illustrating the dosing of gabapentin and pregabalin categorized as therapeutic and sub-therapeutic.

Table 4 Descriptive Statistics of Gabapentinoid Use as per Indication

Indications	Total (n=385)	Gabapentin (n = 281)	Pregabalin (n =104)
FDA-approved indications for both pregabalin and gabapentin			
Post-herpetic neuralgia	12 (3.1)	7 (2.5)	5 (5.4)
FDA-approved indications for pregabalin only			
Fibromyalgia	4 (1)	1 (0.4)	3 (2.9)
Diabetic peripheral neuropathy	1 (0.3)	1 (0.4)	–
BNF Indications (Confirmed or probable neuropathic pain)			
Degenerative orthopedic condition*	27 (7.0)	17 (6.0)	10 (9.6)
Low back pain*	5 (1.3)	4 (1.4)	–
Mechanical back pain*	3 (0.8)	1 (0.4)	2 (1.9)
Musculoskeletal condition*	44 (11.4)	40 (14.2)	4 (3.8)
Musculoskeletal and neurological condition	45 (11.7)	36 (12.8)	9 (8.7)
Nerve compression	19 (4.9)	14 (5.0)	5 (4.8)
Neurological condition	34 (8.8)	27 (9.6)	7 (6.7)
Peripheral neuropathy	10 (2.6)	6 (2.1)	5 (4.8)
Skeletal disorder*	2 (0.5)	2 (0.7)	–
Symptomatic treatment	75 (19.5	45 (16.0)	30 (28.8)
Off-label Use (Diagnosis without labelled indication or documented symptoms of neuropathic pain)			
Degenerative Orthopedic Condition	14 (3.6)	11 (3.9)	3 (2.9)
Low Back Pain	5 (1.3)	5 (1.8)	–
Mechanical Back Pain	7 (1.8)	7 (2.5)	–
Musculoskeletal Condition	56 (14.5)	41 (14.6)	15 (14.4)
Perioperative Use	18 (4.7)	15 (5.3)	3 (2.9)
Psychiatric Condition	4 (1.0)	1 (0.4)	3 (2.9)

Note: (*) denotes indication that included a primary condition with concurrent documentation of neuropathic pain symptoms.

Knowledge of Patients Regarding Their Prescribed Gabapentinoids

Figure 2 illustrates the patient's knowledge status regarding their prescription. The majority (51.0%) of patients had average knowledge, 43.5% had inadequate knowledge and only 5.5% demonstrated good knowledge, suggesting limited in-depth understanding among the study population.

Table 6 shows that 87.8% of patients did not know the name of their gabapentinoid, but most were aware of their dose (91.0%), usage (91.4%), and administration timing (92.5%). Indirect knowledge was limited as only 25.7% knew what to do if they missed a dose, 11.4% were aware of drug/food interactions, and 7.3% understood possible side effects. Table 7 indicates that 233 patients (60.5%) were first-time users of the medication, while 152 patients were repeat users. Among the repeat users of the prescribed gabapentinoid, 23.0% experienced minor side effects. 89.6% of the patients responded with need for more information regarding their prescribed gabapentinoid. According to Table 8, age negatively impacted knowledge (AOR = 0.938, p = 0.003), whereas higher education (AOR = 7.954, p = 0.001) and fewer medications (AOR = 0.684, p = 0.047) were linked to better knowledge. Gender and repeat use had no significant impact.

Table 5 Factors Associated with "Off-Label Use of Gabapentinoids as per FDA Indication"

Variables	OR (95% CI)	p-value	AOR (95% CI)	p-value
Gender				
Male	1.827 (0.506–6.597)	0.358	–	–
Female	Reference			
Patient's Age	0.970 (0.937–1.005)	0.090*	0.983 (0.950–1.019)	0.352
Indication				
Non-neuropathic pain	2.218 (0.615–8.002)	0.223	0.966 (0.228–4.095)	0.962
Neuropathic pain	Reference			
Gabapentinoid prescribed				
Pregabalin	0.307 (0.108–0.868)	0.026*	0.857 (0.249–2.950)	0.807
Gabapentin	Reference			
Department Visited				
Orthopedics	24.750 (7.502–81.658)	0.000*	16.163 (3.061–85.351)	0.001*
Other Departments	Reference			
Polypharmacy				
Yes	0.894 (0.318–2.516)	0.832	–	–
No	Reference			
Analgesics co-prescription				
Yes	6.409 (2.134–19.251)	0.001*	0.890 (0.185–4.257)	0.884
No	Reference			
Non-pharmacological measures				
Yes	10.67 (1.388–81.964)	0.023*	3.06 (0.329–28.456)	0.326
No	Reference			

Note: (*) Indicates odds ratio and adjusted odds ratio with 95% confidence interval is significant at $p<0.05$.
Abbreviations: OR, Odds Ratio; AOR, Adjusted Odds Ratio.

Discussion

There has been a substantial and consistent increase in multinational gabapentinoid consumption over the years where off-label prescriptions accounted for more than half of total prescriptions.[22] Examining gabapentinoid usage patterns is crucial because of their increasing prevalence, particularly concerning off-label and non-medical use, which has been linked to various potential risks.[23] In 2019, the United Kingdom (UK) government reclassified gabapentinoids as scheduled 3 (class C) controlled drugs in the UK because of the high risks and deaths associated with their misuse.[24]

The study revealed that gabapentin was prescribed more often than pregabalin. This preference likely stems from gabapentin's longer history and established reliability in treating neuropathic pain. In contrast, pregabalin, despite being a newer drug, has faced issues with increased dependency and abuse in Nepal, which may have led to its less frequent prescription.[25] Recent studies conducted in the USA have also identified gabapentin as the most commonly used gabapentinoid, possibly because of the classification of pregabalin as a controlled substance nationwide in the

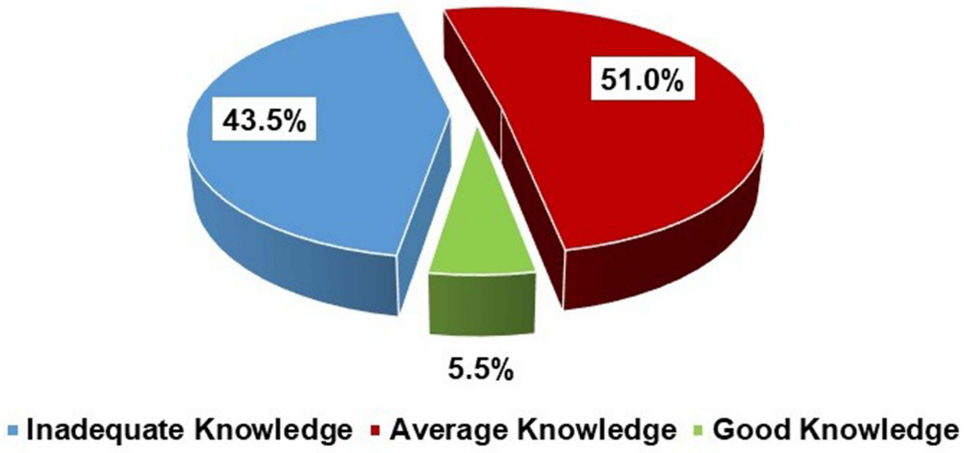

Figure 2 Pie chart depicting the level of knowledge among patients regarding their gabapentinoid prescription.

USA.[26,27] However, studies from Oman and Australia reported greater usage of pregabalin, which was attributed to its more favorable pharmacokinetic and pharmacodynamics profile.[28,29]

Gabapentinoids were predominantly prescribed to middle-aged female patients, many of whom had comorbid conditions and insurance coverage. The majority of prescriptions were made in the orthopedics department for pain-related issues. Similar to previous studies, these prescriptions often addressed both neuropathic and non-neuropathic pain, including musculoskeletal conditions.[30,31] This pattern underscores their broad application within clinical practice despite limited formal approval.

Our study found that gabapentin and pregabalin were frequently used off-label across various departments. This practice may be influenced by factors such as the failure or contraindication of first-line medications, their role as adjuvant therapy, their use alongside surgical interventions, the clinical experience of prescribers, patient feedback, and literature-based guidelines. Gabapentinoids are commonly used off-label for orthopedic, neurological, and psychiatric conditions in pediatric, adult, and geriatric populations, highlighting the need for careful consideration in these settings.[32–35]

Table 6 Survey Responses and Knowledge Scores (Median and IQR) Reflecting Patients' Understanding of Their Prescribed Gabapentinoids

Category	Questions regarding	Did not know	Incorrect response	Correct response	Median score obtained (IQR)
Information Directly related to drug administration[a]	Name of the drug	338 (87.8)	2 (0.5)	45 (11.7)	6 (6–6)
	Dose	31 (8.1)	4 (1.0)	350 (90.9)	
	Form of use	28 (7.3)	5 (1.3)	352 (91.4)	
	Time of administration	26 (6.8)	3 (0.8)	356 (92.5)	
Information Indirectly related to drug administration[b]	Therapeutic indication	129 (33.5)	65 (16.9)	191 (49.6)	2 (1–2)
	Duration of treatment	87 (22.6)	2 (0.5)	296 (76.9)	
	Attitude when one or more dosages are missed	273 (70.9)	13 (3.4)	99 (25.7)	
	Interactions with other drugs and/or foods	319 (82.9)	22 (5.7)	44 (11.4)	
	Adverse effects	336 (87.3)	21 (5.5)	28 (7.3)	

Notes: [a]each question in this category scores 2 points, [b] each question in this category scores 1 point.

Table 7 Additional Information from the Survey

Additional Information	n (%)
Patients who experienced side effect of gabapentinoids on repeat use	35 (23.03)
Patients who needed more drug information	345 (89.6)

Table 8 Factors Associated with "Good Knowledge on Gabapentinoids"

Variables	OR (95% CI)	P-value	AOR (95% CI)	P-value
Gender				
Male	1.732 (0.709–4.229)	0.228	1.785 (0.670–4.751)	0.246
Female	Reference			
Patient's Age	0.926 (0.890–0.964)	0.00*	0.938 (0.899–0.978)	0.003*
Education Level				
Higher Education	15.778 (4.971–50.078)	0.00*	7.954 (2.390–26.472)	0.001*
Below Graduate level	Reference			
Gabapentinoid Use				
Repeat Use	0.94 (0.38–2.325)	0.894	–	–
First time use	Reference			
Total number of medicine	0.6 (0.431–0.835)	0.002*	0.684 (0.471–0.995)	0.047*

Note: (*) Indicates odds ratio and adjusted odds ratio with 95% confidence interval is significant at $p<0.05$.
Abbreviations: OR, Odds Ratio; AOR, Adjusted Odds Ratio.

The evidence on the safety and efficacy of gabapentinoids for off-label uses, such as perioperative care, musculoskeletal pain management, and neurological disorders, ranges from conflicting to significant.[36–38] Gabapentinoids demonstrate only modest effectiveness in managing perioperative pain, and their role in treating spinal stenosis remains unclear.[39,40] However, they are beneficial in multimodal pain management, as they improve pain relief and reduce opioid use in surgical settings.[41] Given the lack of compelling evidence regarding the safety and efficacy of gabapentinoids for both neuropathic and non-neuropathic pain conditions, it is important to exercise caution when prescribing and utilizing these drugs.

The recommended doses for neuropathic pain are 1200–3600 mg/day for gabapentin, starting at 300 mg/day, and 300–600 mg/day for pregabalin, starting at 150 mg/day. These doses are gradually increased based on the patient's response.[42,43] International guidelines indicate that gabapentin and pregabalin are either minimally effective or ineffective at doses below the recommended levels for neuropathic pain.[44] Pregabalin was predominantly found to be prescribed at an initiating dose generally considered to be sub-therapeutic (75 mg once daily) for neuropathic pain. This variability may be attributed to the symptomatic nature of the indications and the lower risk of abuse and potential side effects for the general Nepalese population at sub-standard dosing. The dosage requirements for gabapentinoids have been found to differ across populations and conditions.[45] The frequent prescription of low-dose pregabalin for neuropathic pain raises the possibility that it may be used for night-time sedation rather than for pain management, indicating the need for further investigation.

Pregabalin was often prescribed with methylcobalamin to potentially enhance its analgesic effects for neuropathic pain. Studies in India have shown that pregabalin is frequently initiated at sub-therapeutic doses, which are gradually increased as needed to improve patient tolerance. Additionally, pregabalin is often used in combination with

methylcobalamin to enhance its synergistic effects and improve patient adherence.[46,47] However, this combined use lacks support from national and international guidelines. A study conducted in Germany showed a moderate prevalence of pregabalin dependency.[48] In our study, two patients on a pregabalin regimen were diagnosed with dependency. For those patients, pregabalin discontinuation was planned with a gradual tapering strategy. This approach aimed to prevent withdrawal symptoms, including insomnia, nausea, headache, diarrhea, anxiety, and hyperhidrosis, which can arise from abrupt discontinuation, particularly after long-term use.[49]

The majority of the patients were first-time users and wanted more information about their prescribed gabapentinoids. Some patients reported having experienced minor side effects after drug use, such as somnolence, dizziness, and sedation, which are common with gabapentinoid use.[50] Studies in Scotland and US Medicare beneficiaries revealed that more than half of gabapentinoid prescriptions were co-prescribed with opioids, benzodiazepines, or both, posing potential dangers.[51,52] In contrast to studies in Western countries, our study found that gabapentinoid users were predominantly co-prescribed with non-opioid analgesics and vitamins, and had a very low rate of co-prescription with controlled substances. This suggests more responsible prescribing practices, potentially due to stricter regulations and the associated risks of prescribing or co-prescribing controlled drugs.

Younger patients, those with higher education levels, and those with fewer prescribed medications generally had a better understanding of their treatment. Patients were typically well-informed about drug administration details such as dose, form, and timing. However, there was a significant lack of knowledge about clinical aspects, including therapeutic indications, drug interactions, and adverse effects. This highlights the need for enhanced patient education on these broader aspects of their medication regimens. These findings are consistent with those of a 2020 study in Nepal, which also revealed poor patient knowledge about prescription drugs.[53] Similar findings were reported in Sri Lanka and India, where half of the patients had poor knowledge about their prescribed medications.[54,55] A study in Lebanon found that pharmacists were knowledgeable about the indications, side effects, and addiction risks of gabapentin and pregabalin, but they had misconceptions about drug interactions and off-label use.[56] This underscores the need for further investigation into healthcare prescribers' knowledge, attitudes, and perceptions regarding the use and off-label use of gabapentinoids.

This study has several important limitations while providing insights into gabapentinoid prescribing patterns in Nepal. The single-center data limits the study's generalizability within Nepal, requiring multi-center research for broader applicability. The study also could not establish a direct causal relationship between gabapentinoid use and prescribing behaviors, particularly regarding off-label practices. Reliance on medical records may have led to an underestimation or overestimation of off-label prescriptions and the reasoning behind them. Despite its limitations, this study provides valuable insights into the widespread off-label and sub-therapeutic use of gabapentinoids in Nepal, indicating the need for further research on the specific use of gabapentinoids in the Nepalese population. It identifies the need for enhanced education and training for healthcare providers, stricter guidelines, and improved patient education. Further research is needed to assess long-term outcomes and the effectiveness of gabapentinoids use and off-label use to optimize prescribing practices. Policymakers should also consider reviewing the classification of gabapentinoids in Nepal to mitigate risks of dependency and misuse.

Conclusion

This study offers a comprehensive investigation into gabapentinoid prescribing patterns at Dhulikhel Hospital, revealing a notable prevalence of off-label use and significant gaps in patient knowledge about their prescribed medications. It is important to recognize that prescribing decisions often appear to be guided more by empirical experience than by robust clinical evidence. This reliance on empirical practice may introduce potential concerns regarding the efficacy, safety, and risk of misuse associated with gabapentinoids. Given these issues, there is a clear need for rigorous research to explore optimal dosing regimens and to assess safety and efficacy of gabapentinoid use in the outpatient setting. Continuous monitoring of prescribing practices is essential to ensure they align with established guidelines and to mitigate the risk of misuse. Enhanced patient education and provider training are also crucial in addressing gaps in knowledge and improving adherence to best practices. Policymakers and healthcare providers should consider these findings to refine prescribing practices and develop more precise guidelines, ultimately aiming to enhance the safe and effective use of gabapentinoids and minimize associated risks.

Abbreviations

BNF, British National Formulary; FDA, Food and Drug Administration; IQR, Interquartile Range; KUSMS, Kathmandu University School of Medical Sciences; IRC, Institutional Review Committee; NNF, Nepalese National Formulary; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; OR, Odds Ratio; PPIs, Proton Pump Inhibitors; SPSS, Statistical Package for Social Science; UK, United Kingdom; US, United States.

Data Sharing Statement

The data supporting the findings of this study are presented within the article, and the raw data from the survey have been provided as a supplementary file. (Supplementary table 1)

Acknowledgments

The authors sincerely appreciate the volunteers who took part in this study. We are also grateful to the healthcare professionals and staff of Dhulikhel Hospital for their contribution to the research.

Author Contributions

All authors made substantial contributions across all critical aspects of this work, including conception, study design, execution, data collection, analysis, and interpretation. Additionally, all authors participated in drafting, revising, or critically reviewing the manuscript, approved the final version for publication, agreed on the journal submission, and assumed responsibility for the work throughout.

Disclosure

The authors report no conflicts of interest in this work.

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