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Original Research

Daily Doses of Gabapentinoids for Pain Management Among Opioid Users Aged Below and Above 65 years

Che Suraya Zin, PhD; Nor Elina Alias, PhD; Nabil Husaini Abrar, BPharm (Hons); Naeem Mubarak, PhD; and Mazlila Meor Ahmad Shah, MMed (Anaesthesia)

Objective: Gabapentinoids (gabapentin and pregabalin) are increasingly prescribed for neuropathic pain, often as adjuncts to opioid therapy. However, limited evidence exists regarding their dosing patterns and duration of use across different age groups, particularly in older adults. To examine trends in daily doses and duration of gabapentinoid use among opioid users aged below and above 65 years.

Methods: We conducted a retrospective cross-sectional study using prescription data from a tertiary hospital in Malaysia between 2010 and 2020. The analysis included all gabapentin and pregabalin prescriptions for patients aged ≥18 years with concurrent opioid use for pain management. Daily dose and days of supply were analyzed at the individual prescription level and stratified by age group (<65 and ≥65 years). Descriptive statistics and linear trend analyses were performed using Stata version 15.

Results: The study included 6,734 prescriptions from 2,338 patients (mean age: 56.6 years; 54.3% female). Gabapentin comprised 91.3% of prescriptions. Among patients aged ≥65-years, mean daily gabapentin dose increased by 237.96% (P<0.001), compared to a 110.96% increase in younger patients (P<0.001). Pregabalin showed smaller, non-significant increases in dose across both groups. The duration of supply for gabapentin increased by 54.1% (P<0.001) in older adults and 76.8% (P<0.001) in younger adults. Pregabalin supply days increased by 171.7% (P=0.003) and 116.4% (P=0.002), respectively.

Conclusion: Gabapentinoid use has risen in both dose and duration over time, particularly among older adults. These findings underscore the importance of age-informed prescribing and monitoring practices in opioid-treated populations.

Keywords: Daily doses; Duration; Gabapentin; Pregabalin; Opioid users

Corresponding Author: Che Suraya Zin, Big Data Research Group, Kulliyyah of Pharmacy, International Islamic University Malaysia, Kuantan, Pahang, Malaysia, Tel: +6 09 570 4909
Email: chesuraya@iium.edu.myF

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Disclosures: Ethics approval. This study obtained ethical approval from the Medical Research Ethical Committee, Ministry of Health of Malaysia (NMRR-16-2135-33068). To ensure confidentiality, patient data were anonymized, and only aggregated findings were reported. Since no patients were directly involved, the requirement for informed consent was waived by the committee. *Conflicts of Interest.* The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. *Data availability.* The datasets generated and/or analysed during the current study are not publicly available. Request to access the datasets should be directed to Medical Research Ethics Committee Malaysia. The de-identified data could be shared with interested researchers after obtaining the approval from the above ethical committee (https://www.nmrr.gov.my). The reason for the restriction on public data deposition is due to the privacy and confidentiality of patients' health data.

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Gabapentin and pregabalin, collectively known as gabapentinoids, rank among the most frequently prescribed medications worldwide,[1] primarily used for managing neuropathic pain conditions such as spinal cord injury, postherpetic neuralgia, diabetic peripheral neuropathy, and fibromyalgia.[2–5] Gabapentin is typically initiated at 300 mg daily and can be titrated up to a maximum of 3600 mg per day,[6] whereas pregabalin is generally started at 150 mg per day in divided doses, with a maximum allowable dose of 600 mg per day.[7,8] The optimal dosing of these medications is highly individualized based on patient response and tolerability.[5,9] Despite their therapeutic benefits, gabapentinoids are frequently associated with adverse effects including dizziness, somnolence, and cognitive impairment.[10,11]

While gabapentinoids are effective in pain management, emerging evidence highlights potential harms associated with their use[12] including increased rates of emergency department visits, hospitalizations, and fatal overdoses in multiple countries.[13] Although these risks are relatively low when gabapentinoids are used as monotherapy, the danger significantly escalates when combined with central nervous system (CNS) depressants, such as benzodiazepines or opioids.[14] The US Food and Drug Administration (2019) issued warnings about the heightened risk of severe respiratory depression when gabapentinoids are taken alongside these substances.[15] Additionally, gabapentinoids exhibit potential for misuse and abuse, particularly among individuals with a history of substance use disorders, especially opioid users. Some patients may misuse these medications to experience euphoria, enhance the effects of other substances, or self-medicate, especially when exceeding therapeutic dosing limits.[13,16]

Gabapentin misuse has been observed across a broad range of doses, including within the recommended therapeutic range of 900–3600 mg per day.[17] Tomko et al.[18] (2018) suggested patients requesting gabapentin doses of ≥1800 mg per day should be evaluated for potential substance use disorders. At this dosage, the risk of adverse effects is doubled.[19] Furthermore, supratherapeutic doses (i.e., gabapentin >3600 mg/day and pregabalin >600 mg/day) have demonstrated no additional clinical benefit but are associated with increased risks of misuse and abuse.[18,20–22] These higher doses have also been linked to severe complications, including respiratory depression, falls, and altered mental status.[23]

Regarding treatment duration, gabapentinoids are typically prescribed for a finite period, ranging from several weeks to months, depending on the indication.[5,24,25] However, it is important to note that clinical trials have not assessed the long-term safety of gabapentinoid use beyond 12 weeks.[5] Once pain is stabilized, a gradual tapering process, lasting at least one week, is recommended to mitigate withdrawal symptoms and minimize adverse effects.[25] Prolonged use may lead to tolerance, necessitating escalating doses over time and increasing the risk of side effects.[17,19]

In elderly populations, gabapentinoids are often considered safer alternatives to opioids for pain management. However, their use requires careful monitoring due to heightened risks associated with polypharmacy, comorbidities, and age-related physiological changes.[26] Older adults, particularly those with impaired renal function, experience reduced drug clearance, resulting in prolonged half-life and increased drug accumulation, which elevates the risk of toxicity.[27] A study in patients with chronic kidney disease (CKD) found gabapentinoids with higher doses (gabapentin >300 mg/day or pregabalin >75 mg/day) were associated with increased risks of hospital visits due to falls, encephalopathy, respiratory depression, and fractures, compared to lower doses (gabapentin <300 mg/day or pregabalin <75 mg/day).[28] Consequently, in older or frail patients, treatment should begin with the lowest effective dose, such as pregabalin at 25-50 mg/day or gabapentin at 100 mg/day, with gradual titration based on tolerability and response.[3,25]

Despite their widespread use and the safety concerns, real-world data on gabapentinoid prescribing patterns, particularly daily doses and treatment durations, remain limited, especially in older adults. A better understanding of prescribing trends is necessary to evaluate how gabapentinoids are used in clinical practice and whether notable differences exist between younger and older patients. Such insights could enhance prescribing practices, optimize patient outcomes, and minimize potential adverse effects. Therefore, this study aimed to investigate the daily dosing and duration of gabapentin and pregabalin use for pain management in opioid users, stratifying the patterns between patients aged below and above 65 years.

Methods

Study design and data source

This study employed a retrospective cross-sectional design utilizing prescription databases from a public tertiary hospital in Malaysia between 2010 and 2020. Approval was obtained from the Medical Research Ethics Committee, Ministry of Health Malaysia (NMRR-16-2135-33068). All patient data were de-identified, and findings were presented in aggregate. Given the absence of direct patient involvement, the ethics committee exempted the requirement for informed consent.

This study included all gabapentinoid (gabapentin and pregabalin) prescriptions. All adults aged ≥18 years who were receiving opioids for pain management and had at least one gabapentinoid (gabapentin or pregabalin) prescription between 2010 and 2020 were eligible for inclusion in the study. The exclusion criteria were prescriptions with incomplete information such as missing dose, strength, quantity, or frequency, or prescriptions not associated with pain management.

Data extracted from the prescriptions encompassed the drug name, prescription date, dose, strength, frequency, quantity, issuing department, and patient demographic details such as age and gender. These data represent prescriptions written at the point of care. Because the dataset was extracted at the prescription level, all inclusion and exclusion criteria were applied to prescriptions first (Figure 1). After data cleaning, prescriptions were linked to unique patient identifiers to form the analytic cohort for patient-level analyses.

Patient age was calculated using the date of the earliest recorded prescription in the database and were stratified according to age <65 years and ≥65 years. The overall study design, data flow, and analytical process are summarized in Supplementary Figure S1 (Study schematic diagram, available online), which provides an overview of data extraction, inclusion criteria, stratification, and outcome assessment. Patients were categorized into gabapentin or pregabalin groups, with individuals counted multiple times if they were prescribed both medications. In this study, "patients" refers to those who were issued a gabapentinoid prescription during the study period.

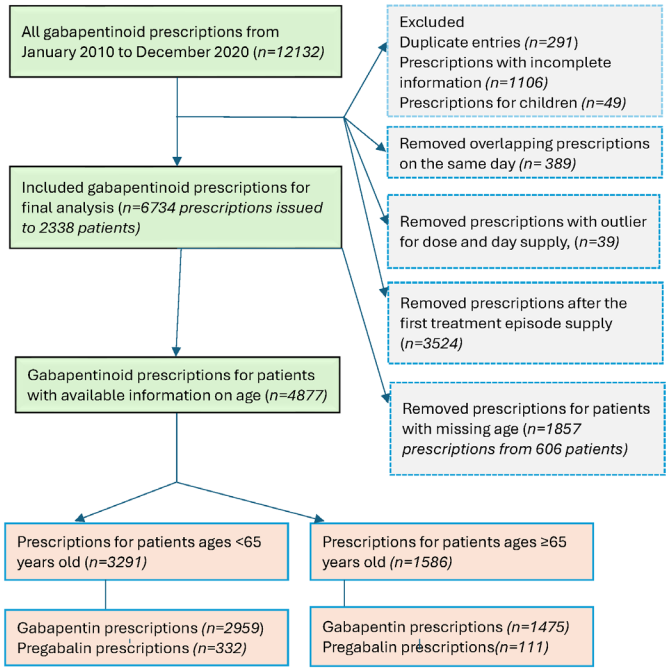

Figure 1. Flow diagram of gabapentinoid prescription selection and patient identification.

Notes: *The flowchart illustrates the stepwise selection of prescriptions included in the analysis. Data cleaning and exclusions were performed at the prescription level, reflecting the dataset's extraction structure. After exclusions for duplicates, incomplete data, overlapping prescriptions, outliers, and pediatric cases, a total of 6,734 prescriptions were retained for analysis. These prescriptions corresponded to 2,338 unique patients, who were subsequently included in the patient-level analyses. Patients with missing age information (n = 606; 1,857 prescriptions) were excluded from age-stratified analyses.*

Measurement of gabapentinoid dose and day supply

The index date for the study was defined as the first day a gabapentinoid prescription was issued to a patient. A 60-day gap was defined as an absence of a subsequent gabapentinoid prescription for 60 consecutive days. For patients who experienced multiple gaps of more than 60 days between successive prescriptions, only the first episode was included in the analysis. Given that only a small number of patients continued using gabapentinoids toward the end of the study period (132 months), follow-up months with at least 10 prescriptions were considered to ensure more reliable results. Consequently, the duration of the follow-up period was limited to 44 months for gabapentin and 19 months for pregabalin. Each patient was tracked until the end of this follow-up period, discontinuation of gabapentinoid treatment, the first 60-day gap, or death from any cause, whichever occurred first.

Exposure to gabapentinoids was assessed separately for gabapentin and pregabalin, starting from the index date and continuing until the last prescription date plus the days supplied for that prescription. The duration covered by each prescription was calculated by dividing the total quantity dispensed by the prescribed daily frequency. For each patient, the day supply of all prescriptions issued within a given month were summed to determine the total monthly coverage period. The monthly mean day supply was then calculated by averaging these values across all patients. Any overlapping coverage days during the follow-up period were adjusted by subtracting redundant days to prevent overestimation.

For the first treatment episode following the index date, the total dose of each prescription was determined by multiplying the prescribed quantity by the strength (in milligrams) of gabapentin or pregabalin. To calculate the monthly total dose for each patient, the doses from all prescriptions issued during this period were summed. The average daily dose of gabapentin or pregabalin was then derived by dividing the total dose by the number of days covered with the medication during each follow-up month for each patient.

Outcome measures

The primary outcome measures included the monthly mean daily doses of gabapentin and pregabalin over the follow-up period. Additionally, the duration of use for each gabapentin and pregabalin prescription was also calculated. The number of patients that were titrated with dose of ≥ 1800 mg/day for gabapentin and ≥600 mg/day for pregabalin was also recorded. The above outcome measures were stratified by age groups (<65 years and ≥65 years), allowing for a deeper understanding

of how prescribing patterns and treatment durations varied across different demographic populations.

Data analysis

Descriptive statistics were used to summarize patient characteristics and outcome measures, with categorical variables presented as percentages and numbers, and continuous variables expressed as mean ± SD. Analyses of this study were conducted descriptively and stratified by age group (<65 years and ≥65 years) to illustrate temporal trends within each group rather than to test for statistical differences between them. For all ages group, the analysis included all patients regardless of age information availability to represent the entire analytic cohort. Because age-stratified analyses excluded records with missing age, the overall mean values were not expected to be equal to the sum or direct combination of the subgroup means. These measures included daily doses and the duration of supply. The percentage change in monthly dose and duration of supply between first and the final follow-up period was calculated. This provided a cumulative measure of change over the study period, complemented by a continuous assessment of trends across all months.

Linear trend analysis was conducted over the follow-up period to evaluate changes in these variables, with daily dose and duration of supply as the dependent variables and the follow-up period as the independent variable. The regression coefficient (β) from ordinary least squares regression represented the monthly rate of change for each age group, enabling descriptive comparison of the magnitude and direction of trends between groups. The results were reported as regression coefficients with 95% confidence intervals (CIs). A *P* value of <0.05 was considered statistically significant. All analyses were performed using Stata version 15.[29]

Results

Patient demographics

A total of 2,338 patients were included, of whom 54.3% (n=1,058/1949) were female and 45.7% (n=891/1949) were male. There were 389 patients with missing gender information. These 2338 patients were issued 6,734 gabapentinoid prescriptions, with 91.3% (n=6,148/6734) prescriptions being for gabapentin and 8.7% prescriptions (n=586/6734) for pregabalin (Figure 1). Among non-repeated patients (based on first prescription), 94% (n=2200/2338) were prescribed gabapentin, while 5.9% (n=138/2338) received pregabalin. When considering repeated patients (counting multiple patients if both gabapentin and pregabalin were used), 91.45% (n=2215/2422) used gabapentin, and 8.55% (n=207/2422) were prescribed pregabalin.

The patients' ages ranged from 18 to 91 years, with a mean age of 56.62 years (SD = 14.88) and a mode of 55 years. The majority of patients (67.1%; n=1167/1739) were younger than 65 years, while 32.9% (n=572/1739) were aged 65 years or older. Regarding ethnicity, the largest group was Malay patients (45.5%), followed by Chinese patients (27.4%), and Indian patients (25.7%). A small percentage of patients were classified as "Others" (1.4%) (Table 1).

The mean follow-up duration was 9.54 months (SD 7.41) for patients on gabapentin and 7.39 months (SD 5.52) for those on pregabalin. The follow-up duration was similar for both gabapentin and pregabalin when stratified by age groups (<65 and ≥65 years). The number of patients contributing to the monthly means declined steadily over time (from ~2,200 for gabapentin and ~155 for pregabalin at baseline to <20 and <10, respectively, by the end of follow-up), consistent with the observed widening of standard error bars shown in Figures 2-5. Monthly patient counts are presented in Supplementary Table S1 (available online). The prescriptions were issued by several departments, with the majority coming from the Anesthesia department (39.9%), followed by Orthopedic (19.9%), Medical (6.5%), Palliative Care (6.8%),

Table 1. Patient demographics

Descriptions	n	%
Total patients (n)	2338	
Gender		
Female	1058	54.30
Male	891	45.70
Age (years old)		
Ages <65 y	1160	
Ages ≥65 y	572	
Mean (SD)	56.62 (14.88)	
Age range	18-91	
Mode	55	
Ethnicity	1062	45.42
Malay	642	27.46
Chinese	600	25.66
Indian	34	1.45
Others	1062	45.42
Number of prescriptions		
Gabapentin	6148	91.3
Pregabalin	586	8.7
Issuing departments		
Anesthesia	2,683	39.84
Medical	437	6.49
Nephrology	371	5.51
Orthopedic	1,337	19.85
Palliative Care	459	6.79
Rheumatology	338	5.02
Surgical	357	5.30
Others	754	11.20

Notes: Missing gender, n=389, missing age, n=606

Surgical (5.3%), Nephrology (5.5%), Rheumatology (5.0%), and Others (11.2%), (Table 1).

Monthly daily dose

Gabapentin

In all patient ages, over the follow-up period, the use of gabapentin and pregabalin showed notable changes. Gabapentin usage increased significantly, rising from a mean daily dose of 547.43 mg/day at the beginning of follow up month to 1680 mg/day at end of follow up (month 44). This represents a 206.89% increase (Coefficient: 20.50 [95% CI: 18.50, 22.49]; *P*<0.001) throughout the follow up months (Supplementary Table 2 (available online) and Figure 2). At the start of the follow-up month, the mean gabapentin daily dose for individuals under 65 years was 568.84 mg/day. By the end of the follow-up at month 44, this value had more than doubled to 1200 mg/day, representing an impressive 110.96% increase (15.53 [95% CI: 12.47, 18.60]; *P*<0.001). For the older age group (those above 65 years), the mean gabapentin daily dose started at 443.84 mg/day in month 1 (Figure 2). Remarkably, by month 44, the mean dose surged to 1500 mg/day, reflecting a dramatic 237.96% increase (14.15 [95% CI: 11.03, 17.28]; *P*<0.001). This substantial growth underscores an intensified reliance on gabapentin within the elderly population during the follow-up period.

For the gabapentin dose of ≥1800 mg/day, 3.74% (n=83/2215) of patients aged <65 years and 1.08% (n=24/2215) of those aged ≥65 years were titrated to this high dose. The mean follow-up duration to reach this dose was 5.03 months for patients aged <65 years and 4.77 months for those aged ≥65 years.

Pregabalin

Pregabalin usage in the all ages group exhibited a more modest increase. The mean dose rose from 169.69 mg/day at month 1 to 250 mg/day at the end of follow-up period (month 19). This corresponds to a 47.32% increase (0.88 [95% CI: -1.32, 3.07]; *P*=0.433) over the follow-up period (Supplementary Table 2, available online). In the case of pregabalin use among individuals younger than 65, the mean daily dose was recorded at 180.24 mg/day at the beginning of the study (Figure 3). By month 19, this had risen to 250 mg/day, marking a 38.70% increase (1.08 [95% CI: -2.16, 4.32]; *P*=0.512). Although less dramatic compared to gabapentin, this increase still highlights a growing trend in pregabalin usage over time. Among those aged 65 years and older, the mean pregabalin daily dose began at 150.65 mg/day in month 1, climbing to 225 mg/day by month 19. This represents a 49.35% increase (1.27 [95% CI: -3.04, 5.58]; *P*=0.561), indicating a steady rise in pregabalin use among the older population throughout the study period. However, the results are not statistically significant.

For the pregabalin dose of ≥600 mg/day, 2.41% (n=5/207) of patients aged <65 years and 0.48% (n=1/207) of those aged ≥65 years were titrated to this high dose. The mean follow-up duration to reach this dose was 2.4 months for patients <65 years and 1 month for those ≥65 years. Across the observation window, mean daily doses increased steadily for both gabapentin and pregabalin in each age group, as shown by the positive fitted linear trends in Figures 2 and 3.

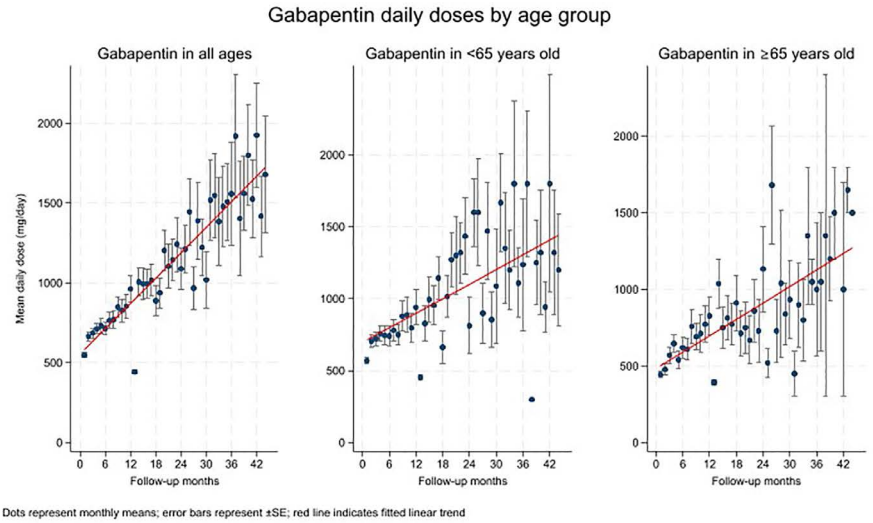

Figure 2. Mean daily doses of gabapentin across follow-up months by age group.

***Notes:** The 'All ages' group includes all patients, including those with missing age data; therefore, its mean values are not a direct average of the <65 and ≥65 year groups.*

Monthly day supply

Gabapentin

For gabapentin, the mean day supply increased steadily across all age groups between month 1 and month 44 (Figure 4). In this group, the mean supply rose from 68.97 days in month 1 to 105.1 days in month 44, reflecting a 52.4% increase (0.856 [95% CI: 0.696, 1.015] *P*<0.001) (Supplementary Table 2, available online). For individuals aged <65 years, the mean supply increased from 67.60 days to 119.6 days over the same follow up period, a 76.8% increase, (0.886 [95% CI: 0.650, 1.123]; *P* <0.001) which is the largest change observed among the age groups. Meanwhile, for individuals aged ≥65 years, the mean supply rose from 77.80 days in month 1 to 120 days in month 44, marking a 54.1% increase (1.229 [95% CI: 0.848, 1.611]; *P*<0.001)

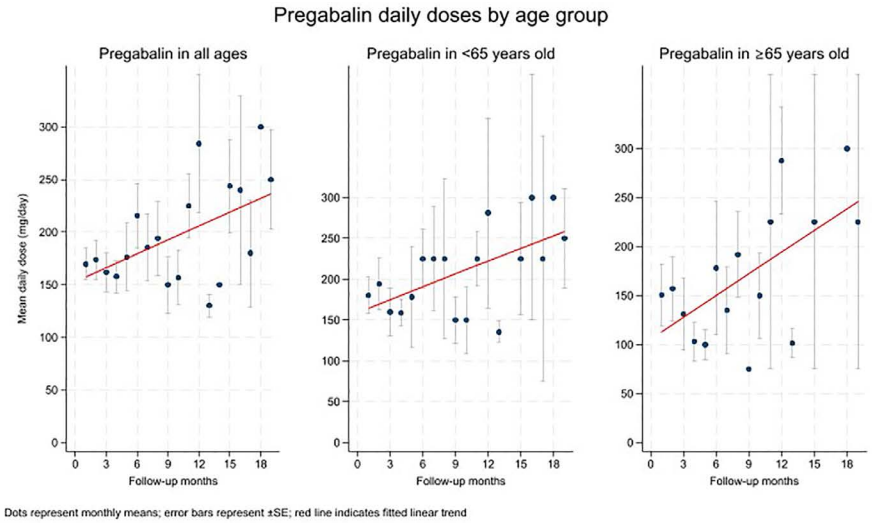

Figure 3. Mean daily doses of pregabalin across follow-up months by age group.

(See note in Figure 2 caption regarding inclusion of all ages.)

These findings suggest that the younger age group experienced a sharper increase in supply over time, although the elderly started with slightly higher initial prescriptions.

Pregabalin

For pregabalin, there was a sharper increase in the mean day supply compared to gabapentin over a shorter time frame, from month 1 to month 19 (Figure 5). Across all ages, the mean supply rose dramatically from 47.82 days in month 1 to 110 days in month 19, a 130.7% increase (2.191 [95% CI: 1.422, 2.959]; *P*<0.001) (Supplementary Table 2, available online). Among those aged <65 years, the mean supply increased from 46.23 days to 100 days, showing a 116.4% rise (1.545 [95% CI: 0.568, 2.522]; *P*=0.002). For the ≥65 years group, the increase was even more pronounced, from 55.21 days in month 1 to 150 days in month 19, representing a 171.7% increase (2.719 [95% CI: 0.977, 4.463]; *P*=0.003). These results highlight a distinct prescribing trend for pregabalin, where older adults not only started with higher supplies at an initial follow up but also experienced the largest relative increase over time.

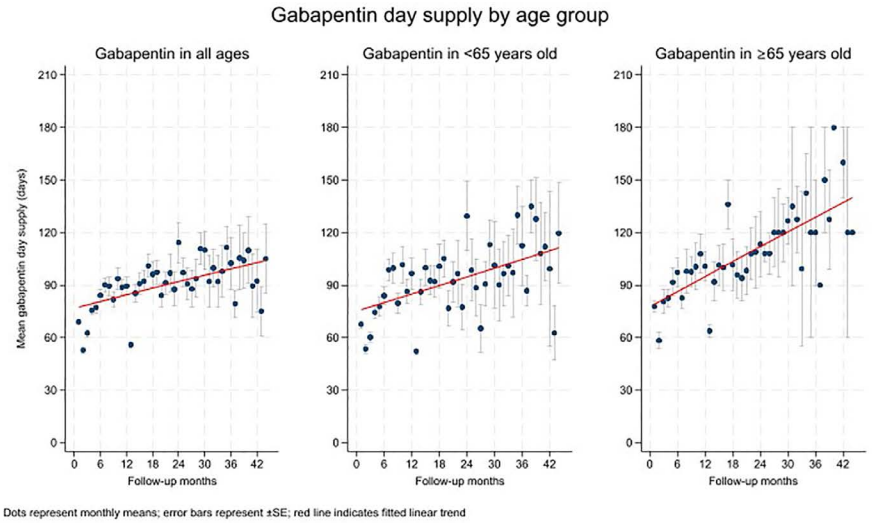

Figure 4. Mean days supply of gabapentin across follow-up months by age group.

(See note in Figure 2 caption regarding inclusion of all ages.)

Discussion

This study revealed a notable increase in the mean daily doses and duration of supply for gabapentin and pregabalin over the follow-up period, particularly among older adults (≥65 years). An exception was observed for gabapentin duration, where the increase was greater in younger adults. The mean gabapentin dose increased by 238% in older adults and by 111% in younger adults. Similarly, pregabalin doses rose by 49% in older adults and by 39% in younger adults. A gradual increase in gabapentinoid dosage is generally part of a normal titration process to meet therapeutic needs.[25]

However, prolonged use may lead to tolerance, in which a diminished drug response requires progressively higher doses to achieve the same effect.[12 30,31] Tolerance to gabapentin has been reported in individuals using it for both therapeutic and supratherapeutic doses, particularly among those with a history of substance use.[17] While the present study cannot confirm tolerance directly because of its prescription-based design, the sustained upward trends observed over the 44-month and 19-month follow-up periods are consistent with progressive long-term dose adjustments that could, in part, reflect tolerance or evolving clinical requirements. Future analyses examining early (e.g., first 60–90 days) versus later dosing phases may help differentiate titration effects from tolerance-related increases.

The shorter duration of pregabalin use observed in this study may reflect differences in clinical practice, pharmacological

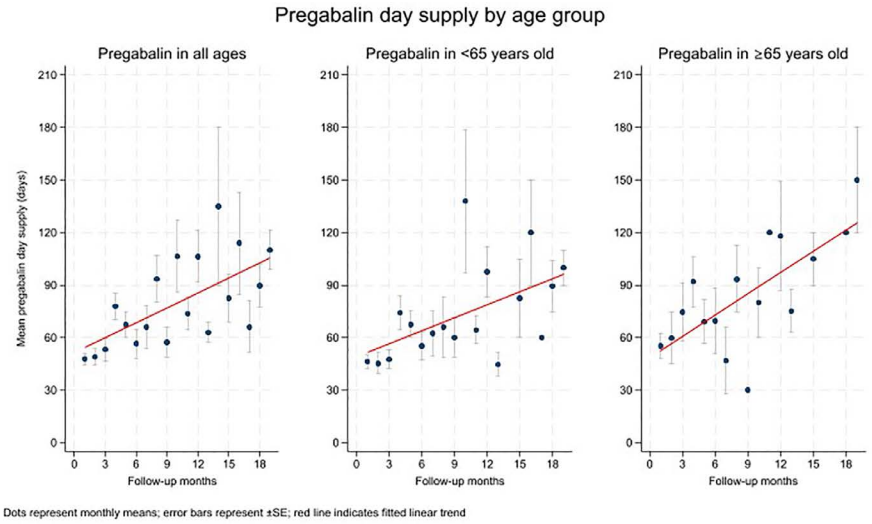

Figure 5. Mean days supply of pregabalin across follow-up months by age group.

(See note in Figure 2 caption regarding inclusion of all ages.)

profiles, and cost considerations. Pregabalin, being more potent and associated with a higher risk of sedation, dizziness, and dependency, is often prescribed for shorter periods or as an adjunct for refractory pain. In contrast, gabapentin is more commonly continued long-term, partly due to its lower cost and wide availability in generic formulations. At the time of data extraction, pregabalin was predominantly available as a branded product, whereas multiple generic versions of gabapentin were accessible, which may have encouraged switching or preferential continuation of gabapentin. Although direct evidence on switching from pregabalin to gabapentin is limited, clinical guidance supports rotation between gabapentinoids when one agent is less effective or poorly tolerated.[32,33]

For the gabapentin high dose of ≥1800 mg/day, the current study showed 3.74% of young adults and 1.08% of older adults were titrated to this high dose. At this dose, gabapentin was reported to be associated with a twofold increase in adverse effects.[19] A study by Tomko et.al.[18] recommended patients who request gabapentin of ≥1,800 mg/day to undergo further investigation of substance use disorder status. For the pregabalin dose of ≥600 mg/day (supratherapeutic dose), the present study demonstrated 2.41% of younger adults and 0.48% of older adults were titrated to this high dose. At this dose, pregabalin has been observed to have no additional clinical benefit and was correlated with the potential for abuse and misuse.[18,20–22] as well as increased risk of severe adverse effects such as respiratory depression, falls, and altered mental status.[23]

The duration of the day supply for both gabapentin and pregabalin in this study demonstrated a significant increase over time. While patients are advised to continue taking gabapentin or pregabalin if they experience benefits, provided the advantages outweigh potential adverse effects and risks.[34] It is recommended that the need for dose reduction or discontinuation be reassessed every 6 months for individuals on long-term gabapentinoid therapy.[25] The pronounced increase in the day supply of pregabalin depicted in the current study (116.4% in younger adults and 171.7% in older adults) suggests a trend toward more prolonged treatment with pregabalin regimens for managing chronic pain conditions. However, this pattern may also reflect emerging non-therapeutic use, particularly given the increasing recognition of pregabalin potential for misuse and abuse due to its psychoactive properties, faster onset of action, and higher bioavailability.[14]

Misuse of pregabalin is particularly common among individuals with a history of substance use disorders, where it is often used recreationally or in combination with other substances.[35] Among younger adults, gabapentinoids may similarly be used to enhance the euphoric effects of other substances, such as opioids and benzodiazepines.[36] Younger age has been identified as one of the risk factors for gabapentinoid misuse apart from poly-drug use history, opioid use disorder, and psychiatric comorbidities.[12,13] Consistently, a French population-based cohort study found the same, such that new and younger users were more likely to misuse pregabalin.[37] This growing concern surrounding gabapentinoid misuse naturally parallels broader discussions about opioid misuse and dependence.[24] The ease of access to gabapentinoids appears to be a key factor driving their misuse, particularly when contrasted with the stricter regulations imposed on opioids. The perception of gabapentinoids as an alternative to opioids raises concerns about their misuse potential and reinforces the notion that tighter opioid regulations may unintentionally contribute to the increasing use and misuse of gabapentinoids.[24]

Following a rise in deaths linked to gabapentinoid misuse and addiction,[40] the UK government reclassified pregabalin and gabapentin as Schedule Class C drugs in 2019. This reclassification imposed restrictions on multiple dispensations and limited prescription validity to one month.[41,42] In the US, pregabalin is federally classified as a controlled substance, while gabapentin is scheduled in certain states,[14,43] with legislative efforts underway in several others to regulate or monitor its use.[43--45] In Malaysia, both gabapentin and pregabalin are regulated under the Poisons Act 1952, requiring a prescription from a medical professional.

Beyond misuse concerns, gabapentinoids are primarily eliminated via the kidneys, making renal function an important consideration in older adults. Impaired renal clearance can lead to drug accumulation and prolonged half-life, warranting lower initial doses and slower titration.[23,46] In frail or older adults, gabapentin should be started at 100 mg once daily with gradual titration, while pregabalin should begin at 25-75 mg once daily and be increased slowly to minimize adverse effects.[3,25] Despite these recommendations, the current study observed relatively high doses among older adults (gabapentin: 443.84-1500 mg/day; pregabalin: 150.65-225 mg/day), which may increase the risk of adverse effects due to reduced renal function and the presence of polypharmacy and comorbidities in older adults.[24,26] Previous research has shown that gabapentin doses above 600 mg/day in older adults were associated with a higher risk of hospitalization for altered mental status.[47]

Given the established risks of gabapentinoid misuse, dose escalation, and dependence, the findings from the current study highlight the importance of careful monitoring of patients on prolonged gabapentin or pregabalin therapy.[38,39] Beyond regulatory controls, addressing this issue should also involve patient and healthcare provider education, along with a broader reform of healthcare and substance use management systems.[48] Such strategies are essential to balance the therapeutic benefits of gabapentinoids with the prevention of misuse and associated harms.

Strengths and Limitations

This study has several notable strengths. First, it provides a comprehensive longitudinal analysis of gabapentinoid use over 44 months for gabapentin and 19 months for pregabalin, offering valuable insights into long-term prescribing trends and patterns in a real-world clinical setting. Second, the evaluation of gabapentinoid use among different age groups (<65 years and ≥65 years), contributes to a better understanding of how gabapentinoids are utilized in practice, highlighting the heightened risks, particularly among older populations. Third, the study focuses on detailed trends in both dose escalation and duration of day supply, providing critical data to assess potential issues such as tolerance, misuse, and dependency. Additionally, the use of a prescription database ensures reliable and objective data, minimizing recall bias and enabling precise analysis of prescribing practices.

However, the study also has several limitations. Firstly, it does not differentiate between new and existing users of gabapentinoids, which restricts insights into initial prescribing patterns and trajectories of dose escalation. Additionally, the absence of clinical diagnosis data prevents determination of the specific indications for gabapentinoid use, such as differentiating between neuropathic pain and other conditions. The findings are also confined to a single tertiary hospital in Malaysia, limiting their generalizability to other healthcare settings or countries with differing prescribing practices. Another limitation is the progressive decline in patients contributing to the monthly means due to treatment discontinuation, 60-day gaps, or death. Consequently, later follow-up months were based on smaller sample sizes and should be interpreted with caution, although the overall trends remained consistent across age groups. Furthermore, the analysis is based solely on prescription data, meaning drug dispensation is assumed to equate to consumption, which may not accurately reflect actual patient usage. This assumption could lead to an overestimation or underestimation of actual drug exposure.

Despite its limitations, the study adds value to the ongoing discussion about gabapentinoid use, safety, and regulation, providing a foundation for further investigation and improvement in clinical practices globally. Moreover, the findings underscore the importance of cautious prescribing and monitoring practices, especially for vulnerable populations such as the elderly.

Conclusion

While the observed increases in gabapentinoid doses and treatment duration may reflect appropriate titration, they highlight the need for careful monitoring and individualized prescribing, particularly among opioid users and older adults. Long-term use at higher doses can increase the risk of tolerance, dependence, and adverse outcomes.

Future studies should focus on new-user cohorts with clinical diagnosis data to clarify indications for gabapentinoid use. They should also assess the impact of dose escalation and prolonged therapy on pain relief, tolerance, and dependence, and validate these findings across multi-center or population-based settings.

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Author Affiliations

Che Suraya Zin, PhD;[*] Nor Elina Alias, PhD;[*] Nabil Husaini Abrar, BPharm (Hons);[*] Naeem Mubarak, PhD;[†] and Mazlila Meor Ahmad Shah, MMed (Anaesthesia)[‡]

[*]Kulliyyah of Pharmacy, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

[†]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Lahore University of Biological and Applied Sciences, Lahore, Pakistan

[‡]Department of Anaesthesia and Intensive Care, Hospital Selayang, Batu Caves, Selangor, Malaysia

Author Contributions

Conceptualization: CSZ, MMAS, NM. Research question: CSZ, MMAS, NM. Methodology: CSZ, MMAS, NM. Data extraction: CSZ, NEA, NH Data management: CSZ, NEA, NH. Data synthesis: CSZ, NEA, NH. Data analysis: CSZ, NEA, NH. Writing — original draft: CSZ. Writing — reviewing and editing: CSZ, MMAS, NM, NEA, NH.