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ORIGINAL ARTICLE

Adverse events, including fractures, among older patients receiving mirogabalin versus pregabalin: A retrospective cohort study using a large claims database in Japan

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ABSTRACT

BACKGROUND

Mirogabalin has a mechanism similar to that of pregabalin in the treatment of neuropathic pain. However, it remains unclear whether these drugs differ in terms of serious side effects, such as fall-related fractures, in older patients. This study aimed to investigate whether mirogabalin is associated with a decrease in adverse events, including fall-related fractures, compared with pregabalin.

METHODS

We performed a retrospective cohort study using the DeSC database, a large administrative claims database in Japan. This study included 130,244 patients ≥65 years taking mirogabalin or pregabalin between April 2019 and May 2021. The primary outcome was defined as the occurrence of fractures or switching to other medications and was compared between those receiving mirogabalin and pregabalin using Kaplan-Meier curves and multivariable Cox proportional hazards models. A sensitivity analysis was performed regarding patients who received mirogabalin or pregabalin without other analgesic medications at the initial dose.

RESULTS

During a median follow-up of 2.8 months, 29,686 (22.8%) and 100,558 (77.2%) received mirogabalin and pregabalin, respectively. The rates of the outcome in the mirogabalin and pregabalin groups were 50.1 and 42.8 per 100 person-years. Cox regression analysis showed that mirogabalin was associated with a lower risk of the outcome (hazard ratio, 0.93; 95% confidence interval, 0.87–1.00). However, sensitivity analysis did not demonstrate a difference in the outcome between the mirogabalin and pregabalin groups without other analgesic medications (hazard ratio, 0.93; 95% confidence interval, 0.86–1.01).

CONCLUSIONS

Our analyses suggest that the outcome may be less likely in the mirogabalin group; however, the difference appears to be clinically insignificant. Further studies are warranted to confirm these findings.

KEY WORDS

neuropathic pain, pregabalin, mirogabalin, older patients, fractures

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BACKGROUND

Mirogabalin (MGB) is a selective ligand for the α2δ subunits of voltage-gated calcium channels, and it was first approved for treating peripheral neuropathic pain in Japan in 2019. MGB is currently used for both peripheral and central neuropathic pain but can produce adverse events such as dizziness and somnolence. A randomized, double-blind, placebo-controlled phase III study in Asian patients showed dizziness and somnolence in 9.7% and 7.9% of patients, respectively, taking 20 mg/day MGB for diabetic neuropathic pain[1]. Another randomized controlled study showed that dizziness and somnolence occurred in 9.8% and 17.0% of patients, respectively, who received 20 mg/day MGB for postherpetic neuralgia[2].

Pregabalin (PGB) has a mechanism similar to that of MGB and is widely used to manage chronic pain conditions. However, some patients must discontinue PGB before it becomes efficient because of adverse events. A Cochrane review of 19 randomized controlled trials involving 7,003 patients showed that the major adverse effects were somnolence (15–25%) and dizziness (27–46%) when patients received a PGB dose of 600 mg/day. Treatment discontinuation was observed in 18–28% of these patients[3]. MGB is expected to be an alternative for PGB when patients taking PGB have to cease treatment due to adverse events, however, information about the difference in adverse events between PGB and MGB is limited[4].

Somnolence and dizziness may cause falls, resulting in fractures. In the present study, we compared the incidence of side effect-related outcomes, including fractures, between MGB and PGB users aged 65 years or older using a large Japanese administrative claims database. We hypothesized that MGB would be associated with a lower incidence of side effect-related events than PGB.

METHODS

DATA SOURCE

We used the DeSC database, which contains health insurance claims and health checkup data from 2014. The cumulative dataset contains approximately 4.4 million patients as of May 2021. The database contains three health insurance systems: employment-based health insurance for salaried employees (Kempo and Kyokai Kempo); national health insurance for non-employees such as individual proprietors, pensioners, and irregular employers (Kokuho); and a medical care system for those aged 75 or older[5]. The patient data was collected from each insurer. Therefore, tracking them longitudinally when their insurance status changed was impossible.

The database includes the following detailed patient data: age; sex; diagnoses and comorbidities recorded as text data in the Japanese language and encoded with International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes with the starting date and the month of the insurance claim. It also includes daily medical procedures encoded with Japanese original codes; daily dispensed medications encoded with World Health Organization Anatomical Therapeutic Chemical codes and Japanese original codes at physician visits; and medical checkup examination data.

As this study was based on a secondary analysis of anonymous administrative data, the requirement for informed consent was waived. This study was approved by the Institutional Review Board in Japan (IRB number: 2021010NI). This work was supported by a grant from the Ministry of Health, Labour and Welfare, Japan (23AA2003).

STUDY COHORT

We identified patients who received MGB or PGB for the first time and continued for 30 days with a gap between successive prescriptions set to be within 7 days between April 2019 and May 2021. We defined the first prescription as the absence of an MGB or PGB prescription in the six months preceding it. We excluded patients aged 64 years or younger on the date of the first prescription and those prescribed both MGB and PGB within the first 30 days.

From the DeSC database, we extracted information on baseline patient characteristics, including age; sex at the time of the first MGB or PGB prescription; underlying disease related to pain; comorbidities; and use of medication. We also collected data on past medical history within a year before the initial prescription of MGB or PGB; nerve block; daily doses of MGB or PGB for the first 30 days; fracture dates; dates of medical procedures for fractures; and dates of switching to other medications after the initial prescription of MGB or PGB.

Eligible patients were categorized into three age groups (65–74, 75–84, and ≥85 years). We defined underlying diseases related to pain conditions as follows: cancer (ICD-10 codes: C00-97, D00-D48, M90.7); headache (R51, G43-44); herpes zoster infection (B02, G53.0); trigeminal neuralgia (G50.0-1); nerve root disorders, dorsopathies, sciatica, and disorders of the musculoskeletal

system (G54.2-54.4, M40-54.1, M54.3-54.4, M95.4-96.1, M99.6-99.7); peripheral nerve disorders (G50.9, G54.0-54.1, G54.5-54.9, G56.0-56.3, G57.0, G57.2-57.6, M79.2); peripheral neuropathy (G57.8-63.2, G99.0); articular disorders (M00-02, M07-11, M12.4-21.6, M21.8-24.2, M24.5-25.5, M25.8-25.9, M86-88.9, M89.3-90.2, M91.3-M94.8, Q65.2-66.8, Q74.0-74.2, Q78); rheumatoid arthritis (M05-06, M79.0, M12.3); myositis, synovitis, and tenosynovitis (M60-65.2, M65.4-65.9, M67.8-M77.9, M12.2); fibromyalgia (M79.7); complex regional pain syndrome (G56.4, M89.0); and abscess and ulcer (I83.0, L02-3, L97, L98.4). The mean daily doses of MGB or PGB were calculated by dividing the total doses for the 30 days from the initial prescription by 30 days. We transformed the comorbidities encoded with ICD-10 codes to Charlson Comorbidity Index scores, which are widely used as validated measures to predict morbidity and mortality for each patient[6].

Nerve block therapies were identified as having been performed within one month before the first prescription of MGB or PGB using original Japanese procedure codes. (See **Table S1** in the Electronic Supplementary Material for details).

EXPOSURE AND OUTCOMES

The exposure was defined as a continuous prescription of MGB or PGB for the first 30 days during the study period, with a gap between successive prescriptions set to within 7 days. The patients were divided into two groups: (i) individuals who received MGB (World Health Organization Anatomical Therapeutic Chemical code: N02BG11) and (ii) those who received PGB (N03AX16).

The outcome was a composite measure, including the occurrence of a first closed fracture and switching to other medications within 90 days after the last prescription (prescription date plus prescribed days). If MGB or PGB was discontinued within 90 days following the last prescription (prescription date plus prescribed days), the final day of treatment was considered as censoring. For example, if the last prescription of PGB within the first 30 days was on April 2, 2020, with a prescription period of 14 days, and MGB was prescribed within 90 days after April 16, 2020 (14 days after April 2), it was considered a switching event. In this scenario, if neither MGB nor PGB was prescribed within 90 days following April 16, 2020, April 16 was considered the discontinuation date. If PGB was subsequently prescribed without a 90-day gap after April 16, 2020, the discontinuation date was considered the final day (prescription date plus prescribed period) in the continuous series of PGB prescriptions. A fracture event was identified using ICD-10 codes (See **Tables S2A** and **S2B** in the Electronic Supplementary Material for details) or both ICD-10 codes and the original Japanese procedure codes (See **Table S3** in the Electronic Supplementary Material for details). We also separately identified fractures more likely to result from falls, including vertebral, forearm, hip, and proximal humerus fractures. (See **Table S2B** in the Electronic Supplementary Material for details)[7,8]. The observation period was from the date of the initial prescription to the date of the outcome, death, discontinuation, the last date with valid medical insurance data, 31 May 2021, or whichever occurred earlier.

STATISTICAL ANALYSIS

Patient characteristics in the MGB and PGB groups were described using numbers and proportions for categorical variables, and means and standard deviations for continuous variables. The differences between the two groups were estimated using the absolute standardized difference. An absolute standardized difference of >10% was considered to indicate a meaningful imbalance in the covariates between the groups.

We calculated the incidence rates using person-years as the denominator. The incidence rates were compared between the groups using the Kaplan-Meier method. Potential confounding factors for outcomes were defined as follows: the mean daily dose of MGB or PGB for the first 30 days; articular disorder; history of stroke[9,10] (ICD-10 code: I69); and history of fractures (See **Table S2B** in the Electronic Supplementary Material for details); use of analgesics, including serotonin noradrenaline reuptake inhibitors (World Health Organization Anatomical Therapeutic Chemical code: N06AX17, N06AX21, N06AX1), tricyclic antidepressants (N06AA9, N06AA02, N06AA10, N06AA04), or opioids (N01AH, N02AA, N02AB, N02AD, N02AE, N02AJ, N02AX); antihypertensives (C02, C03, C07, C08, C09); antidiabetics (A10); antiepileptics (N03); anti-Parkinson medications (N04); antipsychotics (N05A); anxiolytics (N05B); antidepressants (N06A); hypnotics and sedatives (N05C); corticosteroids (H02A, A07EA, A07EB) and bisphosphonates (H05B) within a year before the initial prescription. To adjust for confounders, including age, sex, the abovementioned diseases, medications and Charlson Comorbidity Index, we fitted a multivariable Cox proportional hazards model to compare the outcomes between MGB and PGB users. We verified the proportional hazards assumption using the Schoenfeld residual test and complementary log plots.

We performed a sensitivity analysis including patients who received MGB or PGB without other analgesics (serotonin noradrenaline reuptake inhibitors, tricyclic antidepressants, or opioids) at the initial dose because PGB and MGB are generally used as the first step in neuropathic pain management. Median doses of PGB and MGB during the first prescription were calculated.

Two additional sensitivity analyses were also conducted. First, we fit the fine-gray sub-distribution hazard models with death as a competing risk for the outcome[11,12]. Second, we redefined fractures as those requiring surgical procedures in the same month or one month after the fracture event or fractures that could be likely caused by a fall. We also conducted a multivariable Cox proportional hazards regression analysis. All analyses were performed using Stata/MP 18.0 (StataCorp, College Station, TX, USA).

RESULTS

We identified 164,489 patients from the DeSC database who received PGB or MGB for the first time and have been continuously prescribed for 30 days between April 2019 and May 2021. **Fig. 1** shows a flowchart of the patient selection process. After excluding 34,245 patients, 130,244 patients were included in the study cohort (**Fig. 1**).

Table 1 summarizes the baseline patient characteristics. The mean patient age was 77.3 years (standard deviation, 6.8). The proportion of male patients was 58.1%. The most frequent pain conditions were nerve root disorders, dorsopathies, sciatica, and disorders of the musculoskeletal system (81.6%), whereas the proportions of complex regional pain syndrome and fibromyalgia were 0.1% and 0.6%, respectively. The proportion of patients receiving nerve blocks was 13.6%; patients tend to undergo spinal canal blocks and trigger point blocks frequently. Approximately a quarter (25.4%) of patients used opioids with MGB or PGB. Absolute standardized differences were less than 10% for all variables without nerve blocks.

Table 2 presents the results of the main and sensitivity analyses. The rates of the outcome in the MGB and PGB groups were 50.1 and 42.8 per 100 person-years, respectively. The MGB group was statistically significantly associated with a lower risk of the outcome than the PGB group. (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.87–1.00; P = 0.04). Similar results were obtained in the Fine-Gray competing-risk model (HR, 0.93; 95% CI, 0.87–1.00; P = 0.04). Although MGB showed a significant association with the outcome defined as switching or fractures potentially caused by a fall (HR, 0.88; 95% CI, 0.81–0.96; P = 0.005) compared to PGB, it did not show a significant association when the outcome was defined as switching or features requiring surgical procedures (HR, 1.00; 95% CI, 0.88–1.13; P = 0.95) (**Table 2**). The median follow-up period was 2.8 months. The cumulative probability of the outcome, defined as switching or fractures using only ICD-10 codes, rose sharply in the initial months and gradually increased thereafter (**Fig. 2**).

Another sensitivity analysis did not demonstrate a significant difference in the outcome between MGB and PGB among patients who did not use any analgesic (HR, 0.93; 95% CI, 0.86–1.01; P = 0.10) (**Table 2**). The initial

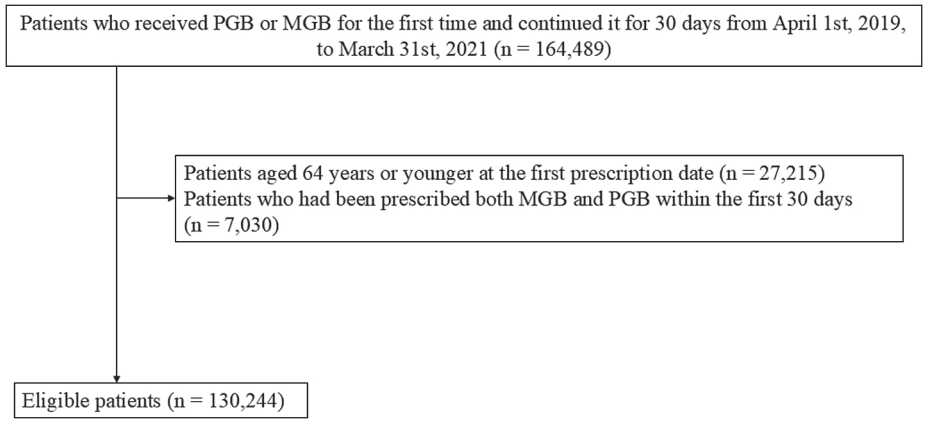

Fig. 1 **Flow diagram of patient selection**
MGB, mirogabalin; PGB, pregabalin

Table 1 Baseline characteristics of the patients

	Total n, (%)	Pregabalin n, (%)	Milogabalin n, (%)	ASD, (%)
Total	130,244	100,558 (77.2)	29,686 (22.8)	
Age, years (standard deviation)	77.3(6.8)	77.3(6.8)	77.4(6.7)	0.4
Age, years				
65–74	38,665 (29.7)	29,776 (29.6)	8,889 (29.9)	0.7
75–84	71,921 (55.2)	55,507 (55.2)	16,414 (55.3)	0.2
≥85	19,658 (15.1)	15,275 (15.2)	4,383 (14.8)	1.2
Sex, male	75,726 (58.1)	57,815 (57.5)	17,911 (60.3)	5.8
Chronic pain condition				
Cancer	37,330 (28.7)	29,100 (28.9)	8,230 (27.7)	2.7
Headache	15,546 (11.9)	11,981 (11.9)	3,565 (12.0)	0.3
Herpes zoster infection	18,489 (14.2)	14,162 (14.1)	4,327 (14.6)	1.4
Trigeminal neuralgia	1,901 (1.5)	1,444 (1.4)	457 (1.5)	0.9
Nerve root disorders, dorsopathies sciatica and disorders of the musculskeletal system	106,241 (81.6)	81,717 (81.3)	24,524 (82.6)	3.5
Peripheral nerve disorder	14,423 (11.1)	11,011 (10.9)	3,412 (11.5)	1.7
Neuropathy of peripheral nerve	42,094 (32.3)	32,479 (32.3)	9,615 (32.4)	0.2
Articular disorders	74,785 (57.4)	57,327 (57.0)	17,458 (58.8)	3.7
Rheumatoid arthritis	7,659 (5.9)	5,937 (5.9)	1,722 (5.8)	0.4
Myositis, synovitis and tenosynovitis	44,053 (33.8)	33,656 (33.5)	10,397 (35.0)	3.3
Fibromyalgia	775 (0.6)	635 (0.6)	140 (0.5)	2.2
Complex regional pain syndrome	152 (0.1)	113 (0.1)	39 (0.1)	0.5
Cutaneous abscess and ulcer	11,739 (9.0)	9,143 (9.1)	2,596 (8.7)	1.2
Others	137 (0.1)	113 (0.1)	24 (0.1)	1.0
Chalson comorbidity index				
0	41,094 (31.6)	31,437 (31.3)	9,657 (32.5)	2.7
1	17,483 (13.4)	13,451 (13.4)	4,032 (13.6)	0.6
2	25,610 (19.7)	19,728 (19.6)	5,882 (19.8)	0.5
3	16,457 (12.6)	12,704 (12.6)	3,753 (12.6)	0.0
≥4	29,600 (22.7)	23,238 (23.1)	6,362 (21.4)	4.0
Use of medications				
Antihypertensives	88,454 (67.9)	68,463 (68.1)	19,991 (67.3)	1.6
Antidiabetes	25,322 (19.4)	19,717 (19.6)	5,605 (18.9)	1.8
Antiepileptics	4,956 (3.8)	3,892 (3.9)	1,064 (3.6)	1.5
Anti-Parkinson drugs	428 (0.3)	333 (0.3)	95 (0.3)	0.2
Antipsychotics	9,798 (7.5)	7,696 (7.7)	2,102 (7.1)	2.2
Anxiolytics	42,147 (32.4)	32,766 (32.6)	9,381 (31.6)	2.1
Antidepressants	25,096 (19.3)	19,293 (19.2)	5,803 (19.5)	0.9
Hypnotics and Sedatives	4,911 (3.8)	3,789 (3.8)	1,122 (3.8)	0.1
Corticosteroids	45,106 (34.6)	34,544 (34.4)	10,562 (35.6)	2.6
Bisphosphonate	3,391 (2.6)	2,638 (2.6)	753 (2.5)	0.5
Use of other analgesic medications				
SNRI	8,685 (6.7)	6,220 (6.2)	2,465 (8.3)	8.2
TCA	1,496 (1.1)	1,051 (1.0)	445 (1.5)	4.1
Opioid	33,086 (25.4)	25,822 (25.7)	7,264 (24.5)	2.8
Nerve block	17,741 (13.6)	12,794 (12.7)	4,947 (16.7)	11.2
Head and neck block	458 (0.4)	289 (0.3)	169 (0.6)	4.3
Upper extremity nerve block	501 (0.4)	342 (0.3)	159 (0.5)	3.0
Celiac or lumbar plexus block	54 (0.0)	32 (0.0)	22 (0.1)	1.8
Spinal canal block	6,812 (5.2)	4,844 (4.8)	1,968 (6.6)	7.8
Lower extremity nerve block	813 (0.6)	617 (0.6)	196 (0.7)	0.6
Trigger point block	10,618 (8.2)	7,719 (7.7)	2,899 (9.8)	7.4

Values are presented as n (%).
ASD = Absolute standardized difference; n = number; SNRI = serotonin noradrenaline reuptake inhibitors; TCA = tricyclic antidepressants.

Table 2 Association between the use of mirogabalin and outcomes

The outcomes	Hazard ratio	95% confidence interval
Switching or fractures (Multivariable Cox regression analysis)	0.93	0.87–1.00†
Switching or fractures (Fine-Gray competing-risk model)	0.93	0.87–1.00†
Switching or fractures requiring surgical procedures (Multivariable Cox regression analysis)	1.00	0.88–1.13
Switching or fractures related to a fall (Multivariable Cox regression analysis)	0.88	0.81–0.96†
Switching or fractures in patients not receiving other analgesics (Multivariable Cox regression analysis)	0.93	0.86–1.01

†: P < 0.05, indicating a statistically significant association between mirogabalin use and the specified outcome.

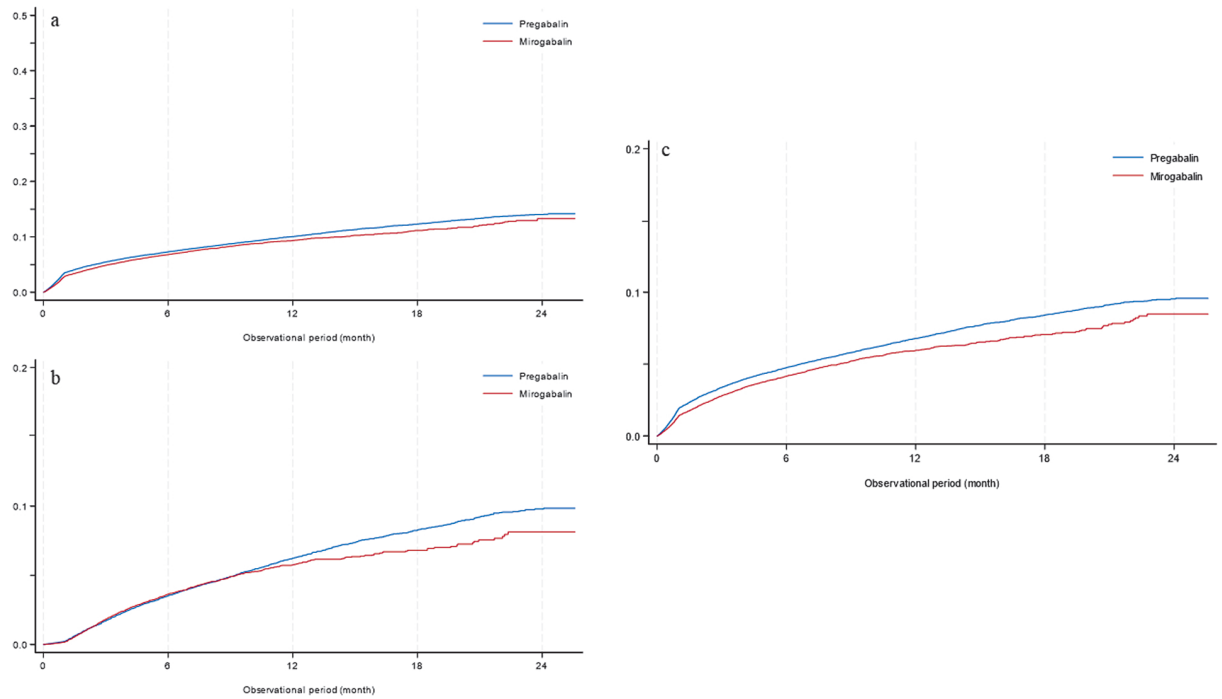

Fig. 2 The cumulative probabilities of outcomes, including switching or fractures (defined using ICD-10 codes), switching or fractures requiring surgical procedures (defined using ICD-10 codes and original Japanese procedure codes), and switching or fractures that could be likely caused by a fall (defined using ICD-10 codes) in the MGB and PGB groups

a: The cumulative probabilities of the outcome in the primary analysis
b: The cumulative probabilities of the outcome, including switching or fractures requiring surgical procedures
c: The cumulative probabilities of the outcome, including switching or fractures that could have been likely caused by a fall
MGB, mirogabalin; PGB, pregabalin

and median doses of PGB and MGB were 50 mg/day and 5 mg/day, respectively.

DISCUSSION

The present study indicated that patients aged 65 and older taking MGB may have a potentially lower risk of side effect-related outcomes compared to those taking PGB. However, the difference in outcomes between the MGB and PGB groups was slight and may not be clinically significant.

The reported proportion of central nervous system (CNS)-related adverse events varies widely according to the prescribed doses of MGB or PGB. A randomized

controlled study on lumbar spinal stenosis demonstrated that the most common adverse events in patients taking MGB (5–15 mg/day) were somnolence (30.0%) and dizziness (25.5%)[13]. Another clinical trial on diabetic peripheral neuropathic pain showed that adverse events related to the CNS were observed for 5 weeks in 2.8%, 14.1%, and 12.0% of the placebo group, the MGB 5–30 mg/day group, and the PGB 300 mg/day group, respectively, and somnolence increased with increasing doses of MGB[14].

Drug-dependent dizziness and somnolence can cause secondary adverse events, including fall-related injuries and fractures[15]. A previous study showed the proportion of at least one fall or a fall-related injury among adults aged ≥65 years was 27.5% or 10.2%, respectively, according to the 2018 Behavioral Risk Factor Surveillance System[16]. Our findings could not be directly compared with those of previous studies because of differences in patient characteristics, defined outcomes, and the fact that the previous surveillance presented the proportion of patients who experienced at least one fall or fall-related injury in the past year. However, falls and fall-related injuries are common, especially among older adults taking analgesics that can cause dose-dependent dizziness and sedation.

A preclinical animal study showed that MGB potentially contributes to a wide CNS safety margin. Both PGB and MGB are ligands for the α2δ subunits of voltage-gated calcium channels, and the α2δ-1 subunit is important for analgesic effects, whereas the α2δ-2 subunit is involved in CNS side effects. MGB had a longer dissociation half-life from the α2δ-1 subunit than from the α2δ-2 subunit compared with PGB. and therefore, the safety margin of MGB was superior to that of PGB[17].

A previous study showed that PGB-induced adverse effects (such as dizziness) often occur at the initiation of therapy[18]. Our results showed no difference in CNS side effect-related outcomes between patients taking MGB (median dose: 5 mg/day) and those taking PGB (median dose: 50 mg/day) when patients did not use other analgesics (serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, or opioids) Although these doses were lower than the recommended starting doses for MGB and PGB, MGB may offer no benefit in terms of adverse events, including fractures over PGB, even at the initial low dose of each therapy[18–20].

PGB is recommended for the treatment of neuropathic pain according to the guidelines and widely used worldwide[21,22]. However, if side effects occurred, there were no alternative medications available for neuropathic pain until 2019 in Japan. In a previous study including patients who switched to MGB due to side effects or lack of efficacy from PGB, the continuation rate of MGB treatment was 78.3%, incidence of adverse events was 28.3%, and response rate of MGB was 66%. However, this study did not examine patients who switched to PGB from MGB treatment[23]. A review, which included three randomized controlled trials for diabetic peripheral neuropathic pain, found that the use of MGB was associated with a significantly decreased average daily pain score compared with the placebo and PGB[24]. The current study did not clarify the efficacy; however, our findings suggested that MGB may not be inferior to PGB regarding the incidence of side effect-related events in patients who could continue the treatment of MGB for at least 1 month.

Our study had several limitations. First, we could not determine whether the observed fractures or medication switching resulted from side effects of these medications. Second, we could not adjust for unmeasured confounders because the DeSC database did not include information on other potential confounders such as smoking and alcohol abuse. Third, we could not determine which exposure or outcome occurred earlier when they occurred in the same month because we used the insurance claim date of diagnosed diseases with the ICD-10 in the DeSC database. Fourth, adverse events such as dizziness and somnolence were more likely to occur during the initial administration and when the dosage was increased. However, because we did not adjust for changes in dosage during the study period, the estimates in our findings may have been biased.

CONCLUSIONS

Since MGB was approved for the treatment of peripheral neuropathic pain in Japan, it has been increasingly prescribed. Although our analysis suggests that CNS side effect-related outcomes may be less likely to occur in the MGB group than in the PGB group, the difference may be clinically insignificant. Therefore, prospective studies are warranted to further investigate differences in side effects between PGB and MGB.

CONFLICTS OF INTEREST STATEMENT

All authors have no conflicts of interest to declare

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AUTHORS' CONTRIBUTIONS

Kanako Makito conducted the study concept and design, analysis, data interpretation, and the first draft manuscript. Prof. Hideo Yasunaga supervised and revised the manuscript for important intellectual content, and Dr. Akira Okada also contributed to revising the manuscript with valuable advice. They approved the final version to be published.

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