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Safety of mirogabalin and pregabalin in Japanese patients with neuropathic pain: a retrospective cohort study

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ABSTRACT

Background: Few studies have compared the safety risks between the gabapentinoids, pregabalin, and mirogabalin in post-marketing clinical settings. We assessed reported events associated with gabapentinoid use in patients with neuropathic pain.

Research design and methods: We conducted a retrospective cohort study between September 2020 and December 2020 using the community pharmacies records in Japan. The pharmacists identified new vs. prevalent users of mirogabalin and pregabalin in September 2020 and reported data regarding baseline and adverse events to the Japan Pharmaceutical Association using web-based questionnaires. The incidence of events and hazard ratio (HR) were consequently compared.

Results: New users of mirogabalin and pregabalin were identified (n = 1,650 and 2,244; mean age (SD): 69 (15) and 68 (16) years; women: 59% and 56%, respectively). Although serious events were not reported, a marked difference in HRs of common adverse events, including somnolence (1.6), dizziness (1.3), nausea (2.8), edema (3.1), and acetaminophen (2.0)/antidepressant (2.4) addition, was observed.

Conclusion: No new serious safety concerns were found for mirogabalin and pregabalin use in patients with neuropathic pain, although the HR of some events indicated increased risk among mirogabalin users. However, further studies are needed as estimates for events occurring in small numbers with wide confidence intervals.

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drug event monitoring; mirogabalin; pregabalin; primary data collection; retrospective cohort study

1. Introduction

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory system [1]. The most common pattern is distal sensory polyneuropathy (DSP), which typically reduces the quality of life (QOL) due to pain, gait instability, and associated depression [2]. Neuropathic pain is relatively common among older individuals aged > 60 years and women [3]. Its prevalence is 2.4%–10.9% in the Netherlands, 6.9% in France, and 14.6% in the United States [4–8]. In Japan, the prevalence of neuropathic pain in the general population with a mean age of 53 years is 3.2% [9], while that in the community-dwelling population with a mean age of 64 years is 5.2%, which is slightly higher [10]. In addition, the incidence of neuropathic pain is higher in individuals aged 70–74 years than in those aged 20–39 years [11]. The estimated proportion of the population aged > 65 years in Europe and the United States (18.3% in 2020 to a projected 22.2% in 2030) and Japan (28.4% in 2020 to a projected 30.9% in 2030) is increasing [12]. Since neuropathic pain is associated with poor health status [13] and QOL both physically and mentally regardless of pain intensity [14], therapeutic management and monitoring of neuropathic pain may become essential in the older population.

According to guidelines [15,16] and reviews [17,18], the gabapentinoid pregabalin is recommended as a first-line pharmacological treatment for neuropathic pain. Its analgesic effect may be due to the reduction in excitatory neurotransmitter release and inhibition of synaptic transmission by binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels [19]. Pregabalin is widely used in some countries, including Japan [20], Australia [21], and the United Kingdom [22]. Serious adverse events may be rare; however, dizziness, peripheral edema, somnolence, and weight gain are the most common adverse events [23].

A novel selective ligand for the $\alpha_2\delta$ calcium channel subunit, mirogabalin [24,25], was first approved for peripheral neuropathic pain in Japan in 2019. In a study using rat models of neuropathic pain [26], the analgesic effects of mirogabalin were more potent and longer lasting than and its safety indices were superior to those of pregabalin. However, in randomized controlled studies comparing mirogabalin and pregabalin, the incidence proportion of somnolence [27,28], dizziness [27,28], headache [27,28], nausea [27], vomiting [28], weight gain [27,28], peripheral edema [28], and constipation [27] were more frequent in the

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mirogabalin and pregabalin groups than in the placebo group. Moreover, somnolence, dizziness, and weight gain are described as important risk factors in the risk management plan (RMP) for mirogabalin in Japan [29]. However, these events were more common with the use of pregabalin than with that of a placebo in a previous study [30]. As randomized controlled studies have strict inclusion and exclusion criteria, the generalizability of these findings may be limited. Further, previous studies [27,28] mainly included male patients with a mean age of approximately 60 years. In addition, the follow-up period of these previous studies was short (≤9 weeks) [27,28].

In real-world settings, the incidence of common adverse events due to mirogabalin and pregabalin use may be inconsistent. Therefore, this retrospective cohort study involving community pharmacists aimed to assess the safety of the newly approved mirogabalin and pregabalin as active comparators in a real-world setting.

2. Patients and methods

2.1. Study design

A retrospective cohort study with concurrent active control using new-user design [31] to prevent bias, such as healthy user bias and healthy adherer bias, in the schema of drug event monitoring (DEM) by the Japan Pharmaceutical Association (JPA) was conducted in February 2021. In the fiscal year 2020, of the 60,951 community pharmacies in Japan [32], 48,395 were affiliated with the JPA (as of February 2021), accounting for 79% of all pharmacies in Japan. The JPA sent paper-based questionnaires to all community pharmacies. The questionnaires were completed by pharmacists working in 6,486 pharmacies affiliated with the JPA. The questionnaires were used to identify all patients using the study drugs (mirogabalin or pregabalin), distinguish new users from prevalent users, and collect baseline and event data [33,34]. When data from the paper-based questionnaires were entered into the web-based online form by pharmacists, the personal information of patients was anonymized using study identification data for each pharmacy, similar to that in previous studies [33,34].

Among the 6,486 participating community pharmacies, 938 and 1,128 community pharmacies identified new users of mirogabalin and pregabalin in September 2020, respectively, based on pharmacy records. Patients who did not receive any prescribed drugs from a given pharmacy before February 2020 were excluded from the total prevalent users. This is because unless the patient is a regular user of the same pharmacy, the 6-month prescribing record for judging whether the patient is a new user of the study drug is not available. Additionally, as part of the overall study cohort, patients who started taking the study drugs in September 2020 after a period (March–August 2020) of using neither mirogabalin nor pregabalin were deemed new users by pharmacists; new users [31] of any study drug did not include patients who were prescribed either study drug within 6-months period prior to September 2020. To maintain comparability between groups of study drug users, we asked pharmacists not to include patients who switched between the study drugs during the study period in the questionnaire. The study lasted for 4 months (1 September 2020, to 31 December 2020). Follow-up was conducted for at least 3 months after study drug initiation. Patients who had never visited the pharmacy after the date of study drug initiation were excluded because they could not be followed up.

Using pharmacy records, including data on health insurance, prescriptions (drug name, dispensing date, daily dose, and days' supply), follow-up regarding effectiveness and adverse drug reactions during treatment by pharmacists, and demographic data of patients, including information on current smoking status, alcohol consumption, over-the-counter (OTC) drug use, co-medications, and comorbidities, the pharmacists collected the baseline data for 6 months before study drug initiation (baseline period).

2.2. Definition of events

Using a methodology similar to that used in previous studies [33,34], we defined an event, including adverse events, during the follow-up period as any suspected drug reaction, unexpected deterioration in concurrent illness, or reasons for discontinuing the study drug (if discontinued) or addition of a new drug (if added). Information on add-on drugs or drug discontinuation was considered to be complimentary to event data. To encode events reported by pharmacists, we used the Medical Dictionary for Regulatory Activities (MedDRA) version 23. We selected the lowest-level terms in MedDRA, which were converted to the preferred term level and counted as an event [35]. In addition, pharmacists reported data on events and their incidence dates using pharmacy records.

2.3. Statistical analysis

Summary statistics for the overall cohort were used to describe demographic characteristics (age, sex, alcohol consumption, current smoking status, OTC drug use, and history of hospitalization), comorbidities (hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, cancer, and rheumatoid arthritis), and co-medications (antihypertensives, antidiabetics, lipid-lowering drugs, antidepressants, hypnotic drugs, antipsychotic drugs, antiulcerative drugs, steroid drugs except those for external use, and antirheumatic drugs) during the baseline period. To assess the difference in baseline characteristics between the groups, we calculated the standardized difference [36]. When the absolute standardized difference was > 0.1, the difference was considered important.

We calculated the incidence of events reported at least once. The crude risk ratio (RR) of mirogabalin for the reported total events was estimated and compared with that of pregabalin as a reference. We then calculated the incidence of five or more events reported for either drug. However, serious events were considered even if the number of reported events was fewer than five. In addition, if the same event was reported more than once by the same patient, only the first event was counted. As somnolence and dizziness were

preidentified risks in the RMP of mirogabalin, the time to onset of these events was depicted using the Kaplan–Meier curve and compared using the log-rank test.

In the primary analysis of the overall cohort using a Cox proportional hazards model, unadjusted, age–sex-adjusted, and multivariate-adjusted hazard ratios (HRs) for common events in both groups and their 95% confidence intervals (CIs) were estimated. The proportional hazards assumption regarding the most frequently reported events was then confirmed. To adjust the HR, we used covariates, including age, sex, comorbidities, and co-medications, as shown in Supplementary Table S1. In addition, to estimate the multivariate-adjusted HR, logistic regression was used to calculate the propensity score (PS) using baseline characteristics, such as comorbidities and co-medications, and incorporate it as a covariate in our model; PS is a convenient and effective tool for adjusting many covariates [37]. The observation period for assessing an event was defined as the period from the date of study drug initiation to the incidence date of the event, date of switching or discontinuation of the study drug, date of addition of the other study drug, last visit date, or 31 December 2020, whichever occurred first. For sensitivity analyses, we created a PS-matched cohort (matched cohort) using 1:1 matching and the estimated HR. For matching, we used sex and PS as matching factors between the 2.5th and 97.5th percentiles of the PS for mirogabalin.

No statistical sample size calculations were conducted, as new users (study population) were selected from all patients prescribed study drugs during the time period to identify study patients from September 2020 for prevention of selection bias. However, the total sample size was estimated to be 3,550 assuming that the incidence proportion of event at control group was 1.3% when $\alpha = 0.05$, power = 0.8, and relative risk = 2.0. Statistical significance was set at $p < 0.05$. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

2.4. Ethical consideration

This retrospective cohort study was performed in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics review committee of the JPA (no. 2020–001), which waived the need for individual informed consent because the study data were fully anonymized.

3. Results

In total, 9,182 and 26,504 prevalent users of mirogabalin and pregabalin, respectively, were identified in September 2020. Among them, 1,650 (18%) and 2,244 (9%) patients were selected as new users of mirogabalin and pregabalin, respectively.

3.1. Patient characteristics

Table 1 shows baseline characteristics of new users of the study drugs. In the overall cohort, the mean age (SD) and proportion of women were 68.7 (14.7) years and 58.6%, respectively, for mirogabalin users and 68.1 (15.5) years and 56.1%, respectively, for pregabalin users. The mean follow-up

Table 1. Baseline characteristics of new users of mirogabalin or pregabalin.

	Overall cohort			Matched cohort[a]		
	Mirogabalin (n = 1,650)	Pregabalin (n = 2,244)	Standardized difference	Mirogabalin (n = 1,532)	Pregabalin (n = 1,532)	Standardized difference
Mean age, years (SD)	68.7 (14.7)	68.1 (15.5)	0.039	68.4 (4.6)	67.7 (15.6)	0.049
Women (%)	967 (58.6)	1,260 (56.1)	0.050	891 (58.2)	891 (58.2)	-
Mean follow-up period (days)	88.4	88.8	-	87.8	87.7	-
Mean daily dose	8.0	76.2		8.0	75.5	-
Current smoking (%)						
Yes	181 (11.0)	269 (12.0)	−0.032	169 (11.0)	154 (10.1)	0.032
Missing	282 (17.1)	388 (17.3)	−0.005	264 (17.2)	256 (16.7)	0.014
Alcohol consumption (%)						
Yes	415 (25.2)	561 (25.0)	0.004	394 (25.7)	385 (25.1)	0.014
Missing	290 (17.6)	403 (18.0)	−0.010	273 (17.8)	262 (17.1)	0.019
Over-the-counter drug	30 (1.8)	41 (1.8)	−0.001	28 (1.8)	16 (1.0)	0.066
History of hospitalization	20 (1.2)	45 (2.0)	−0.063	9 (0.6)	11 (0.7)	−0.016
Comorbidity (%)						
Hypertension	784 (47.5)	1,100 (49.0)	−0.030	736 (48.0)	734 (47.9)	0.003
Diabetes mellitus	238 (14.4)	367 (16.4)	−0.054	219 (14.3)	233 (15.2)	−0.026
Dyslipidemia	481 (29.2)	667 (29.7)	−0.013	456 (29.8)	470 (30.7)	−0.020
Myocardial infarction	31 (1.9)	55 (2.5)	−0.039	24 (1.6)	19 (1.2)	0.028
Cancer	109 (6.6)	113 (5.0)	0.067	51 (3.3)	47 (3.1)	0.015
Rheumatoid arthritis	41 (2.5)	56 (2.5)	−0.001	17 (1.1)	11 (0.7)	0.041
Co-medication (%)						
Antihypertensives	789 (47.8)	1,111 (49.5)	−0.034	741 (48.4)	737 (48.1)	0.005
Antidiabetics	235 (14.2)	364 (16.2)	−0.055	217 (14.2)	238 (15.5)	−0.039
Lipid-lowering drugs	490 (29.7)	695 (31.0)	−0.028	459 (30.0)	481 (31.4)	−0.031
Antidepressants/hypnotic drugs/antipsychotic drugs	273 (16.5)	397 (17.7)	−0.030	255 (16.6)	244 (15.9)	0.019
Antiulceratives	356 (21.6)	569 (25.4)	−0.089	313 (20.4)	309 (20.2)	0.007
Steroids except those for external use	490 (29.7)	619 (27.6)	0.047	457 (29.8)	447 (29.2)	0.014
Antirheumatic drugs except methotrexate	45 (2.7)	86 (3.8)	−0.062	23 (1.5)	19 (1.2)	0.023
Methotrexate	15 (0.9)	33 (1.5)	−0.052	7 (0.5)	3 (0.2)	0.046

[a]1:1 matching by propensity score and sex was conducted.

period was approximately 90 days for both drugs. Among women in both groups, history of hospitalization; diabetes mellitus; cancer; and use of antidiabetic, antiulcerative, antirheumatic drugs other than methotrexate, and methotrexate showed absolute standardized differences of approximately 0.1 (i.e. dissimilarities between groups were evident).

3.2. Proportion and reason for discontinuation

The proportions of drug discontinuation were 36.4% (n = 600) and 35.2% (n = 790) in the mirogabalin and pregabalin groups, respectively. The crude RR for discontinuation of mirogabalin was 1.03 (95% CI: 0.95–1.12). The crude RRs for improvement, any suspected adverse drug reaction, and lack of effectiveness as reasons of drug discontinuation were 0.99 (95% CI: 0.84–1.17), 1.09 (95% CI: 0.84–1.41), and 1.22 (95% CI: 0.88–1.68), respectively.

3.3. Incidence of events

The incidence of adverse drug reactions reported at least once was 30.2% for mirogabalin and 26.5% for pregabalin. The crude RR for any adverse reaction to mirogabalin was 1.10 (95% CI: 1.03–1.18) and was compared with that of pregabalin as reference. For mirogabalin and pregabalin, the incidences of reported events, HR, and its 95% CI are shown in Table 2. In mirogabalin users, preexisting conditions improved (14.7%), and somnolence (7.1%) and dizziness (6.8%) were most frequently reported, while in pregabalin users, preexisting conditions improved (15.7%), and nonresponse to therapy (5.8%) and dizziness (5.3%) were most frequently reported. No serious events were reported in either group of patients.

3.4. Preidentified important risks in RMP

The Kaplan–Meier curves for time to onset of somnolence ($p < 0.001$ for log-rank test) and dizziness ($p = 0.03$ for log-rank test) for each study drug are shown in Figure 1. The hazard function for the time to these events showed a considerable difference throughout the follow-up period.

3.5. Comparison of common events between study drugs

Table 2 shows the unadjusted, age–sex-adjusted, and multivariate (PS)-adjusted HRs for events with mirogabalin compared with those with pregabalin as reference. The incidence of somnolence (HR = 1.60; 95% CI: 1.23–2.09), dizziness (HR = 1.31; 95% CI: 1.01–1.70), nausea (HR = 2.81; 95% CI: 1.48–5.33), edema (HR = 3.06; 95% CI: 1.25–7.54), and hypoesthesia (HR = 3.32; 95% CI: 1.04–10.63) was considerably higher among mirogabalin users than among pregabalin users. HR for common events adjusted by PS only and that adjusted by multiple confounders were similar (Supplementary Table S1).

3.6. Comparison of common events for any add-on drugs

Table 3 shows the unadjusted, age–sex-adjusted, and multivariate (PS)-adjusted HRs for the incidence of add-on drug

Table 2. Incidence and HR of common events reported among mirogabalin and pregabalin users.

	Overall cohort					Matched cohort
Event (%)	Mirogabalin (n = 1,650)	Pregabalin (n = 2,244)	Unadjusted HR[a] (95% CI)	Age–sex-adjusted HR[a] (95% CI)	Multivariate[b]-adjusted HR[a] (95% CI)	Unadjusted HR[a] (95% CI)
Preexisting condition improved	243 (14.7)	353 (15.7)	0.96 (0.82–1.13)	0.96 (0.81–1.13)	0.95 (0.80–1.11)	0.99 (0.83–1.18)
Somnolence	117 (7.1)	102 (4.5)	1.61 (1.23–2.10)	1.61 (1.23–2.10)	1.60 (1.23–2.09)	1.58 (1.18–2.13)
Dizziness	112 (6.8)	119 (5.3)	1.31 (1.01–1.69)	1.29 (1.00–1.67)	1.31 (1.01–1.70)	1.27 (0.94–1.72)
Therapy nonresponder	99 (6.0)	130 (5.8)	1.06 (0.82–1.38)	1.07 (0.83–1.39)	1.09 (0.84–1.41)	1.12 (0.83–1.51)
Nausea	29 (1.8)	14 (0.6)	2.85 (1.51–5.40)	2.79 (1.48–5.28)	2.81 (1.48–5.33)	2.72 (1.31–5.63)
Pain	21 (1.3)	30 (1.3)	0.98 (0.56–1.71)	0.99 (0.56–1.72)	0.94 (0.54–1.65)	0.93 (0.51–1.69)
Edema	15 (0.9)	7 (0.3)	3.02 (1.23–7.41)	3.02 (1.23–7.40)	3.06 (1.25–7.54)	4.48 (1.27–15.78)
Constipation	9 (0.5)	11 (0.5)	1.14 (0.47–2.75)	1.13 (0.47–2.73)	1.11 (0.46–2.70)	1.15 (0.44–3.01)
Malaise	8 (0.5)	9 (0.4)	1.24 (0.48–3.20)	1.20 (0.46–3.12)	1.28 (0.49–3.32)	0.88 (0.29–2.63)
Therapeutic response decreased	7 (0.4)	8 (0.4)	1.23 (0.44–3.38)	1.28 (0.47–3.55)	1.29 (0.47–3.59)	1.03 (0.36–2.95)
Therapy cessation	7 (0.4)	15 (0.7)	0.65 (0.26–1.59)	0.65 (0.26–1.59)	0.70 (0.28–1.71)	0.46 (0.16–1.33)
Abdominal discomfort	6 (0.4)	9 (0.4)	0.93 (0.33–2.61)	0.92 (0.33–2.60)	0.93 (0.33–2.63)	0.58 (0.17–1.99)
Fall	6 (0.4)	3 (0.1)	2.76 (0.69–11.02)	2.58 (0.64–10.38)	2.96 (0.73–11.91)	Not presented
Blood pressure increased	7 (0.4)	13 (0.6)	0.75 (0.30–1.88)	0.79 (0.31–1.98)	0.80 (0.32–2.01)	1.19 (0.40–3.57)
Feeling abnormal	6 (0.4)	7 (0.3)	1.18 (0.40–3.52)	1.16 (0.39–3.44)	1.21 (0.40–3.62)	1.21 (0.37–3.96)
Hypoesthesia	10 (0.6)	4 (0.2)	3.53 (1.11–11.27)	3.66 (1.15–11.67)	3.32 (1.04–10.53)	1.81 (0.53–6.18)
Back pain	6 (0.4)	5 (0.2)	1.70 (0.52–5.55)	1.80 (0.55–5.92)	1.59 (0.48–5.25)	2.06 (0.52–8.23)
Diarrhea	6 (0.4)	6 (0.3)	1.38 (0.45–4.27)	1.39 (0.45–4.32)	1.38 (0.44–4.30)	1.27 (0.34–4.71)
Peripheral edema	4 (0.2)	3 (0.1)	1.87 (0.42–8.37)	1.90 (0.43–8.49)	2.07 (0.46–9.33)	4.09 (0.46–36.44)
Weight gain	4 (0.2)	6 (0.3)	0.93 (0.26–3.31)	0.92 (0.26–3.28)	0.87 (0.24–3.09)	0.82 (0.22–3.09)
Headache	4 (0.2)	3 (0.1)	1.85 (0.41–8.28)	1.80 (0.40–8.05)	1.71 (0.38–7.69)	0.68 (0.11–4.09)
Dry mouth	3 (0.2)	2 (0.1)	2.09 (0.35–12.53)	2.04 (0.34–12.19)	2.24 (0.37–13.53)	1.53 (0.26–9.17)
Vomiting	1 (0.1)	3 (0.1)	0.45 (0.05–4.35)	0.44 (0.45–4.24)	0.49 (0.05–4.78)	1.00 (0.06–16.00)

CI: confidence interval, HR: hazard ratio, [a] with pregabalin users as reference. [b] Adjusted by propensity score.

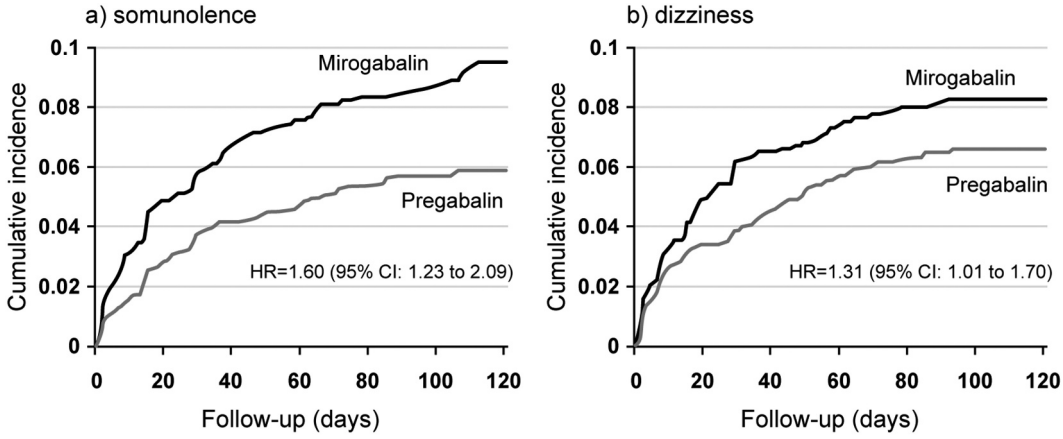

Figure 1. Cumulative incidence of (a) somnolence and (b) dizziness among mirogabalin and pregabalin users HR: hazard ratio; CI: confidence interval.

administration with mirogabalin compared with those with pregabalin as reference. Nonsteroidal anti-inflammatory drugs (2.4%), antacids (1.6%), acetaminophen (1.3%), and antidepressants (1.3%) were most frequently administered as add-on drugs in the mirogabalin group, whereas nonsteroidal anti-inflammatory drugs (2.5%), antacids (1.4%), and opioids (1.4%) were most frequently administered as add-on drugs in the pregabalin group. The events of addition of acetaminophen (HR = 1.95, 95% CI: 1.01–3.77) and antidepressants (HR = 2.42, 95% CI: 1.19–4.93) were significantly ($p < 0.05$) higher for mirogabalin users than for pregabalin users. HR of common events for any add-on drugs adjusted by PS only and that adjusted by multiple confounders were similar (Supplementary Table S2).

3.7. Sensitivity analysis using the matched cohort

To assess the consistency of our results, we conducted a similar analysis to the main analysis using the PS-matched cohort. Among the baseline characteristics of the matched cohort, only the absolute standardized difference of OTC drug use was approximately 0.1 (Table 1). Compared with those associated with pregabalin use as reference, the events of somnolence (HR = 1.58, 95% CI: 1.18–2.13), nausea (HR = 2.72, 95% CI: 1.31–5.63), edema (HR = 4.48, 95% CI: 1.27–15.78), addition of acetaminophen (HR = 2.49, 95% CI: 1.03–6.03), and addition of antidepressants (HR = 2.14, 95% CI: 1.03–4.44) were more associated with mirogabalin use.

4. Discussion

We conducted a retrospective cohort study on the safety of mirogabalin and pregabalin using the DEM project conducted in 2020 by the JPA. In clinical settings, the crude RR for any adverse drug reaction was higher (RR = 1.10, 95% CI: 1.03–1.18) for mirogabalin users than for pregabalin users, although the crude RR for drug discontinuation was similar between both groups. In particular, the events of somnolence, dizziness, nausea, edema, addition of acetaminophen, and addition of antidepressants were more associated with mirogabalin use in the overall cohort. If mirogabalin is initiated for neuropathic pain, patients should be counseled and actively monitored by medical staff and family members.

In Japan, somnolence and dizziness have been identified as important risks in RMP for mirogabalin. In randomized trials between mirogabalin and placebo, the crude RR of mirogabalin for somnolence and dizziness was 2.2–2.8 and 2.1–2.3, respectively [38,39]. These events were most commonly reported in a review of clinical trials for pregabalin [40] and in mirogabalin studies [38,39]. In randomized trials carried out in the United States as well as in Asian countries, including Japan, the crude RR for somnolence and dizziness

Table 3. Incidence and HR for any add-on drug reported for mirogabalin and pregabalin users.

	Overall cohort					Matched cohort
Add-on drug (%)	Mirogabalin (n = 1,650)	Pregabalin (n = 2,244)	Unadjusted HR[a] (95% CI)	Age–sex-adjusted H [a] (95% CI)	Multivariate[b]-adjusted HR[a] (95% CI)	Unadjusted HR[a] (95% CI)
Nonsteroidal anti-inflammatory drug	39 (2.4)	55 (2.5)	0.99 (0.66–1.49)	1.01 (0.67–1.52)	1.00 (0.66–1.51)	0.97 (0.63–1.50)
Antacid	26 (1.6)	32 (1.4)	1.14 (0.68–1.91)	1.14 (0.68–1.92)	1.16 (0.69–1.95)	0.98 (0.57–1.71)
Acetaminophen	22 (1.3)	15 (0.7)	2.06 (1.07–3.97)	2.09 (1.09–4.03)	1.95 (1.01–3.77)	2.49 (1.03–6.03)
Antidepressants	21 (1.3)	12 (0.5)	2.44 (1.20–4.95)	2.47 (1.21–5.02)	2.42 (1.19–4.93)	2.14 (1.03–4.44)
Opioid	19 (1.2)	32 (1.4)	0.82 (0.47–1.45)	0.84 (0.48–1.48)	0.83 (0.47–1.46)	0.69 (0.37–1.28)
Antiepileptic	13 (0.8)	8 (0.4)	2.28 (0.94–5.49)	2.29 (0.95–5.52)	2.28 (0.94–5.53)	2.22 (0.84–5.84)
Vitamin B12	12 (0.7)	13 (0.6)	1.29 (0.59–2.83)	1.27 (0.58–2.79)	1.22 (0.55–2.68)	0.84 (0.35–2.03)
Laxative	10 (0.6)	12 (0.5)	1.16 (0.50–2.68)	1.17 (0.51–2.71)	1.14 (0.49–2.64)	1.02 (0.40–2.57)
Antiulcerative	9 (0.5)	13 (0.6)	0.96 (0.41–2.25)	0.97 (0.42–2.27)	1.06 (0.45–2.49)	1.02 (0.38–2.72)
Anticoagulant	7 (0.4)	8 (0.4)	1.23 (0.45–3.40)	1.32 (0.48–3.64)	1.21 (0.44–3.34)	2.07 (0.52–8.30)
Diuretic	5 (0.3)	3 (0.1)	2.38 (0.57–9.97)	2.59 (0.62–10.90)	2.45 (0.58–10.30)	1.75 (0.42–7.36)

CI: confidence interval, HR: hazard ratio, [a] with pregabalin users as reference. [b] Adjusted by propensity score.

was directly compared between mirogabalin and pregabalin users and was found to be similar between both groups [27,28]. However, in our retrospective cohort study, using pregabalin users as a reference, the risk of somnolence in mirogabalin users was high in the overall (HR = 1.60, 95%CI: 1.23–2.09) and matched (HR = 1.58, 95% CI: 1.18–2.13) cohorts. Additionally, the risk of dizziness in mirogabalin users tended to increase in the overall (HR = 1.31, 95% CI: 1.01–1.70) and matched (HR = 1.27, 95% CI: 0.94–1.72) cohorts. Although further studies are needed to evaluate the risk between these groups, the study population in randomized trials [27,28] was slightly younger, included fewer women, and had a shorter follow-up period than that in our study, which may have contributed to these findings.

No significant difference in the risk of headache, vomiting, constipation, peripheral edema, and weight gain (a preidentified risk) was found between groups; however, the risk of nausea was higher in mirogabalin users than in pregabalin users (HR = 2.81, 95% CI: 1.48–5.33 in the overall cohort). In a real-world setting, medical staff might need to monitor nausea development in mirogabalin users, although these findings differed between the present study and previous randomized trials [27,28].

The additional risk of requiring acetaminophen (HR = 1.95, 95% CI: 1.01–3.77) and antidepressants (HR = 2.42, 95% CI: 1.19–4.93) was higher among mirogabalin users than among pregabalin users. However, the reason why acetaminophen requirement for mirogabalin users was high is unclear. According to a study by Acker et al., patients with neuropathic pain administered acetaminophen for painful neuropathic symptoms [14]. Acetaminophen may enhance the analgesic activity of anti-neuropathic drugs [41], although no high-quality reports represent the association of acetaminophen with neuropathic pain [16]. On the other hand, antidepressants are commonly used as first-line drugs in patients with neuropathic pain [15,17,18]. Since antidepressants are highly effective in reducing pain [42], they may be prescribed as pain relievers [14]. Therefore, antidepressants might have been added in situations where monotherapy was insufficient [43], although the concomitant use of the drug at baseline was similar in both groups.

This study has several strengths. First, this was a post-marketing cohort study with a mean follow-up period of 3 months that used primary data from community pharmacies to compare the incidence of any adverse drug reaction between mirogabalin and pregabalin users. Previous phase 2 randomized trials comparing mirogabalin and pregabalin users in the United States had a follow-up period of 5–7 weeks [27,28]. Second, to prevent channeling bias, we excluded patients with a history of mirogabalin or pregabalin use within 6 months before the date of study drug initiation. In a previous cohort study [44], patients who were switched from pregabalin to mirogabalin had a high incidence of somnolence and dizziness, although the incidence of peripheral edema was low. However, in a retrospective cohort study of patients who switched from pregabalin to mirogabalin, patients who discontinued mirogabalin had a higher incidence of dizziness (p = 0.01) and edema (p = 0.02) than those who continued to use mirogabalin [45]. In addition, incidence of somnolence (p = 0.84) was not significant regardless of mirogabalin continuation/discontinuation [45]. Had patients for whom the drugs were switched been not excluded from our study population, appropriate comparison of the incidence of events between the groups might have been difficult.

This study, however, has some limitations. First, the dose relationship for individual events could not be considered in this study. As our study population involved new users of the study drugs, the mean doses of both study drugs were low. Further studies with larger sample sizes and longer follow-up periods are needed to assess the association between doses and events. Second, baseline characteristics may have differed between the groups as the absolute standardized difference in some variables was approximately 0.1. Therefore, we estimated adjusted HR using many confounders (Supplementary Tables S1 and S2). In addition, we created a matched cohort using PS and sex matching for sensitivity analysis and obtained almost the same findings as those of the main analysis in the overall cohort. However, there might be residual confounding. Third, the proportions of older patients and women were higher in our study population compared with those of study populations of previously reported randomized trials [27,28]. Therefore, the generalizability of our findings to young patients and men may be limited. However, the population is likely to be representative of the target population in the real world as neuropathic pain is relatively common in older individuals (aged >60 years) and women [3]. Fourth, in patients taking co-medications, it is up to the pharmacist at each pharmacy to decide whether this is an event; thus, events from concomitant medications may be misinterpreted as events due to the study drug. However, if there is a similar degree of misinterpretation between new users of study drug, the effects may be offset.

5. Conclusions

No new serious safety concerns were found regarding the use of mirogabalin or pregabalin. However, the crude RR for any adverse drug reaction was higher among mirogabalin users than among pregabalin users. In addition, the risk of common events, such as somnolence, dizziness, nausea, edema, addition of acetaminophen, and addition of antidepressants, was higher with mirogabalin use than with pregabalin use. In patients with neuropathic pain who are newly administered mirogabalin, monitoring of such events by medical staff will contribute to the enhancement of clinical care in real-world clinical settings.

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Abbreviations

DEM, drug event monitoring; CI, confidence interval; HR, hazard ratio; JPA, Japan Pharmaceutical Association; MedDRA, Medical Dictionary for Regulatory Activities; OTC, over-the-counter; PS, propensity score; RMP, risk management plan; RR, risk ratio

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, and royalties.

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Author contributions

All authors were involved in the conception and design of this study. Nakajima and Ooba analyzed and interpreted the data. All authors critically reviewed the manuscript, revised the paper for intellectual content, provided detailed feedback, read and approved the final manuscript, and agreed to be accountable for all aspects of this work.

Data availability

The data used to support the findings of this study have not been made publicly available due to patient privacy or ethical restrictions by the Japan Pharmaceutical Association Ethics Committee.

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