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Title: Risk of pregabalin-induced hypoglycemia: Analysis of the Japanese Adverse Event Report database

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The authors declare that they have no conflicts of interest.

Data Availability Statement

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Tomoyuki Yamada and Junko Makino were responsible for the organization and coordination of the study. Tomoyuki Yamada and Satoru Mitsuboshi designed the study and were responsible for data analysis. Kaoru Suzuki and Masami Nishihara managed this project, and Masashi Neo supervised the study. All authors contributed to the writing of the final manuscript and to the management and administration of the study.

Abstract

Pregabalin is a first-line treatment option for neuropathic pain. Recently, some cases of pregabalin-induced hypoglycemia have been reported, which can complicate the treatment of neuropathic pain and worsen patient outcomes. Therefore, a better understanding of the clinical condition of patients with pregabalin-induced hypoglycemia is desirable. In this study, we evaluated the risk of hypoglycemia in patients administered pregabalin, using the Japanese Adverse Drug Event Report database. All patients on pregabalin not taking any antidiabetic agents were screened from April 2004 to July 2020, and data on adverse events related to hypoglycemia, sex, age, weight, and the presence of chronic kidney disease were collected. Gabapentin and duloxetine, which are usually indicated for neuropathic pain, were used for comparison. Among 242,275 patients, 4,287 were administered pregabalin, which included 37 patients who reported hypoglycemic incidents. Disproportionality of hypoglycemia was observed in patients administered pregabalin (reporting odds ratio, 2.25; 95% confidence intervals [CI], 1.16–3.13; $P < 0.01$), whereas this was not the case in patients taking gabapentin and duloxetine. Multivariate logistic regression showed that hypoglycemia in patients on pregabalin was associated with age ≥ 70 years (odds ratio, 2.76; 95% CI, 1.29–5.91; $P < 0.01$) and weight < 40 kg (odds ratio, 2.97; 95% CI, 1.32–6.71; $P < 0.01$). These findings suggest that pregabalin may be associated with a higher risk of hypoglycemia, especially in elderly individuals with low body weight. Healthcare providers may need to be aware of pregabalin-induced hypoglycemia in patients with these risk factors during therapy.

Keywords: adverse event, hypoglycemia, pregabalin, gabapentinoid, neuropathic pain

Introduction

Pregabalin, a gabapentinoid derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA),[1] is one of the first-line drugs for the treatment of neuropathic pain.[2, 3] The use of pregabalin has been increasing as a potential alternative to opioids for pain management because of the recent increase in opioid abuse.[4] In the US, non-discounted spending on pregabalin was the sixth highest, at $5.2 billion in 2018.[4] Although the adverse effects of pregabalin are generally mild, including somnolence, dizziness, and edema, pregabalin can sometimes cause serious adverse events such as respiratory depression.[4] Moreover, the increased use of pregabalin may increase the number of patients who develop rare but serious adverse events.

Recently, several cases of pregabalin-induced hypoglycemia have been reported[5, 6]; their occurrence has also been mentioned in the package insert provided with pregabalin.[7, 8] Hypoglycemia can lead to not only confusion, loss of consciousness, and seizures, but also cardiovascular events and even death.[9, 10] Moreover, pregabalin-induced hypoglycemia may complicate the treatment of neuropathic pain and worsen patient outcomes. There is concern that incidents of pregabalin-induced hypoglycemia may increase with increased use of pregabalin, but the risk factors causing pregabalin-induced hypoglycemia have not been

clarified. Therefore, a better understanding of the clinical presentation of patients with pregabalin-induced hypoglycemia is desirable for optimal treatment, and it can enable healthcare providers to intervene early, leading to the prevention of severe hypoglycemia. In this study, we evaluated the risk of developing hypoglycemia in patients administered pregabalin using the Japanese Adverse Drug Event Report (JADER) database.

Methods

As the present study was observational in nature and anonymized patient data from the open-access JADER database were used, institutional review board approval and patient consent were not required.

The JADER database contains aggregated adverse events spontaneously reported by pharmaceutical companies or medical institutions. The database consists of four categories: patient demographic information, “DEMO;” drug information, “DRUG;” adverse events information, “REAC;” and primary disease information, “HIST.” Information about patient demographics, concomitant drug use, adverse events, and comorbidities can be obtained from

the DEMO, DRUG, REAC, and HIST categories, respectively. The DRUG category has three types of adverse events: "suspected drug," "concomitant drug," and "interacting drug."

Data collection

Data from April 2004 to July 2020 were downloaded from the Pharmaceuticals and Medical Devices Agency website (http://www.pmda.go.jp/) on December 9, 2020.

All patients on pregabalin were screened regardless of whether the data reporter suspected a possible adverse event from the "DRUG" table. Data on adverse events related to hypoglycemia, sex, age, weight, and the presence of chronic kidney disease (CKD) were collected. In the JADER database, age is categorized in 10-year increments in the "DEMO" table (<10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90–99, and ≥100 years). Other age categories including neonate, baby, infant, child, young adult, adult, elderly, first trimester, second trimester, and third trimester were excluded due to the inherent difficulties in classifying them into age categories. Weight is also categorized in 10-kg increments in the "DEMO" table (< 10, 10– <20, 20– <30, 30– <40, 40– <50, 50– <60, 60–

<70, 70– <80, 80– <90, 90– <100, 100– <110, 110– <120, 120– <130, 130– <140, 140– <150, 150– <160, 160– <170, 170– <180, 180– <190, 190– <200, ≥200 kg).

Gabapentin and duloxetine, which are first-line drugs for neuropathic pain,[2, 3] were used as standards for comparison. The exclusion criteria were duplicate reports for the same patient; absence of data on sex, age, and weight; and concomitant administration of two or more of the following drugs: pregabalin, gabapentin, and duloxetine. Patients on antidiabetic drugs were also excluded because these agents are more likely to cause hypoglycemia.

Definitions

The outcome was the occurrence of hypoglycemia, which was defined according to the standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) index with a "narrow" scope from MedDRA/J (https://www.jmo.pmrj.jp/) version 24.0. "Narrow" scope includes the "Preferred Terms" that are highly likely to represent the condition of the adverse events.[11] We used 15 preferred terms for hypoglycemia detection based on the SMQ "Hypoglycaemia" (SMQ code: 20000226) and collected data from the "REAC" table (Table S1). CKD was defined based on the preferred terms for "CKD," "kidney failure," and/or "dialysis" as a comorbidity in the JADER database and collected

from the "HIST" table. Antidiabetic drugs included insulin, biguanides, thiazolidine, dipeptidyl peptidase-4 inhibitors, sulfonylureas, glinides, alpha-glucosidase inhibitors, sodium glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists (Table S2).

Statistical analysis

A disproportionality analysis was performed by calculating the reporting odds ratios (RORs) and the corresponding 95% confidence intervals (CIs) to compare the frequency of hypoglycemia between patients on pregabalin, gabapentin, or duloxetine and patients not on the drugs. ROR and CI were calculated using a two-by-two contingency table for the presence of specific drugs and adverse events in case reports (Figure 1).[12] Two-tailed P-values were also calculated using Fisher's exact test, and statistical significance was set at $P < 0.05$. Multivariate logistic regression was performed to identify risk factors for pregabalin-induced hypoglycemia in patients taking pregabalin. Sex, elderly status (≥ 70 years), and CKD were included in the multivariate logistic regression model. Since the body surface area is not recorded in the JADER database, we also included low body weight (< 40 kg) in the analysis as an alternative indicator for the effect of body size. Odds ratios (ORs) and 95% CIs

for multivariate logistic regression analysis were calculated, with two-tailed P-values at a statistical significance of $P < 0.05$. Lack of data was handled using listwise deletion, and a complete case analysis was used for study modeling. Two reviewers (Tomoyuki Yamada and Satoru Mitsuboshi) separately performed the analyses, and the reproducibility of the results was confirmed. JMP ® Pro 14 (SAS Institute Inc., Cary, NC, USA) was used in all analyses.

Results

Figure 2 shows the flowchart outlining the patient selection process. A total of 654,795 individuals were initially screened from the JADER database during the stated period. Of these, 378,993 individuals were excluded due to lack of data on age, sex, and weight. A total of 432 individuals who used pregabalin and gabapentin, pregabalin and duloxetine, or gabapentin and duloxetine concomitantly were also excluded. Moreover, 33,095 patients using antidiabetic agents along with the aforementioned drugs were excluded. Of the remaining 242,275 individuals, 955 hypoglycemic reports were extracted. Among these 242,275 patients, 4,287 were administered pregabalin, and of these, 37 had reported hypoglycemic incidents, 613 were on gabapentin with 5 having a hypoglycemic event, and 945 were taking duloxetine and no hypoglycemic reports were associated with this group.

Disproportionality of hypoglycemia was observed in patients on pregabalin (ROR, 2.25; 95% CI, 1.16–3.13; P < 0.01), while this was not the case in patients taking gabapentin and duloxetine (Table 1). Multivariate logistic regression showed that pregabalin-induced hypoglycemia was associated with age ≥ 70 years (OR, 2.76; 95% CI, 1.29–5.91; P < 0.01) and body weight < 40 kg (OR, 2.97; 95% CI, 1.32–6.71; P < 0.01) (Table 2).

Discussion

Our results suggest that the use of pregabalin may increase the risk of hypoglycemia using real-world data from an adverse event database, with patients on pregabalin who are ≥ 70 years of age and weighing < 40 kg possibly being at a higher risk of developing hypoglycemia. The recommended pregabalin dosages are 150–600 mg per day for neuropathic pain, which must be adjusted according to kidney function; however, the dosage adjustment for the elderly or patients with low body weight is not specified in the package insert distributed in Japan.[7] Furthermore, the blood glucose levels of patients administered pregabalin and not taking antidiabetic drugs may not frequently be measured in a clinical setting. Therefore, healthcare providers may need to be aware of the risk of hypoglycemia in

these patients and may consider careful monitoring of hypoglycemic symptoms or perform measurements of blood glucose levels as needed.

Our results also suggest that increased exposure to pregabalin may contribute to pregabalin-induced hypoglycemia. Since pregabalin clearance tends to decrease with increasing age,[8] drug exposure is generally higher in elderly patients. In addition, the occurrence of hypoglycemia has been reported to be related to aging because of defective glucose counter regulation and unawareness of hypoglycemia.[13] Furthermore, pregabalin is prescribed in fixed doses and not adjusted per unit body weight[7]; thus, lower body weight may result in higher drug exposure than normal body weight. Although pregabalin is primarily eliminated via the kidneys,[8] the presence of CKD was not associated with hypoglycemia in the current study ($P = 0.39$). This may be because the dosage of pregabalin for patients with reduced kidney function is defined in the package insert according to kidney function.[7, 8]

The mechanism of pregabalin-induced hypoglycemia remains unclear. Gabapentin, another gabapentinoid, has also been reported to cause hypoglycemia.[14] The mechanism of gabapentin-induced hypoglycemia may be related to the secretion of insulin through the action of gabapentin on the $GABA_A$ receptor or the action of the α2δ subunit of voltage-

sensitive Ca^{2+} channels in the β-cells of the pancreas; however, this postulation is still not clearly understood.[14] A similar mechanism to gabapentin-induced hypoglycemia can be considered for pregabalin. Nonetheless, in this study, disproportionality of hypoglycemia was not observed in patients taking gabapentin. One reason for this may be the small number of reported cases. In addition, differences in the background disease between patients on pregabalin and those on gabapentin may have influenced the risk of hypoglycemia.

The current study has several limitations. First, this was an observational study and the JADER database may have been affected by reporting bias. Second, there may be differences in patient backgrounds regarding the use of pregabalin, gabapentin, and duloxetine. Third, hypoglycemia is usually categorized as "Documented symptomatic," "Severe," "Asymptomatic," "Probable symptomatic," or "Pseudohypoglycemia" according to its symptoms and blood glucose level[15]; however, categorization of hypoglycemia or categorization in terms of blood glucose level was not recorded in the JADER database. However, of the 15 preferred terms for hypoglycemia (SMQ code: 20000226) defined in this study, most reports were of "Hypoglycaemia" (Table S1), and the blood glucose level could have been 70 mg/dL or less in many cases. In addition, pseudohypoglycemia was neither included in the definition of hypoglycemia used in this study nor in the analysis. Finally,

accurate kidney function and pregabalin dosage could not be considered because these data were not recorded or were missing in the JADER database. Despite these limitations, as drug-induced hypoglycemia is a generally uncommon adverse event for drugs other than antidiabetic drugs, a clinical trial with an appropriate sample size may be needed to assess this risk factor.

Conclusions

The current study suggests that pregabalin may be associated with a risk of developing hypoglycemia and that elderly individuals with low body weight may be at a higher risk. Therefore, healthcare providers may need to be aware of pregabalin-induced hypoglycemia during therapy in patients with these risk factors.

Conflict of interest statement: The authors declare that they have no conflicts of interest.

Data availability statement: Data supporting the findings of this study are available from the author upon reasonable request.

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Figure 1. Two by two contingency table for calculating the reporting odds ratio and 95% confidence interval

Figure 2. Flow chart depicting the patient selection process

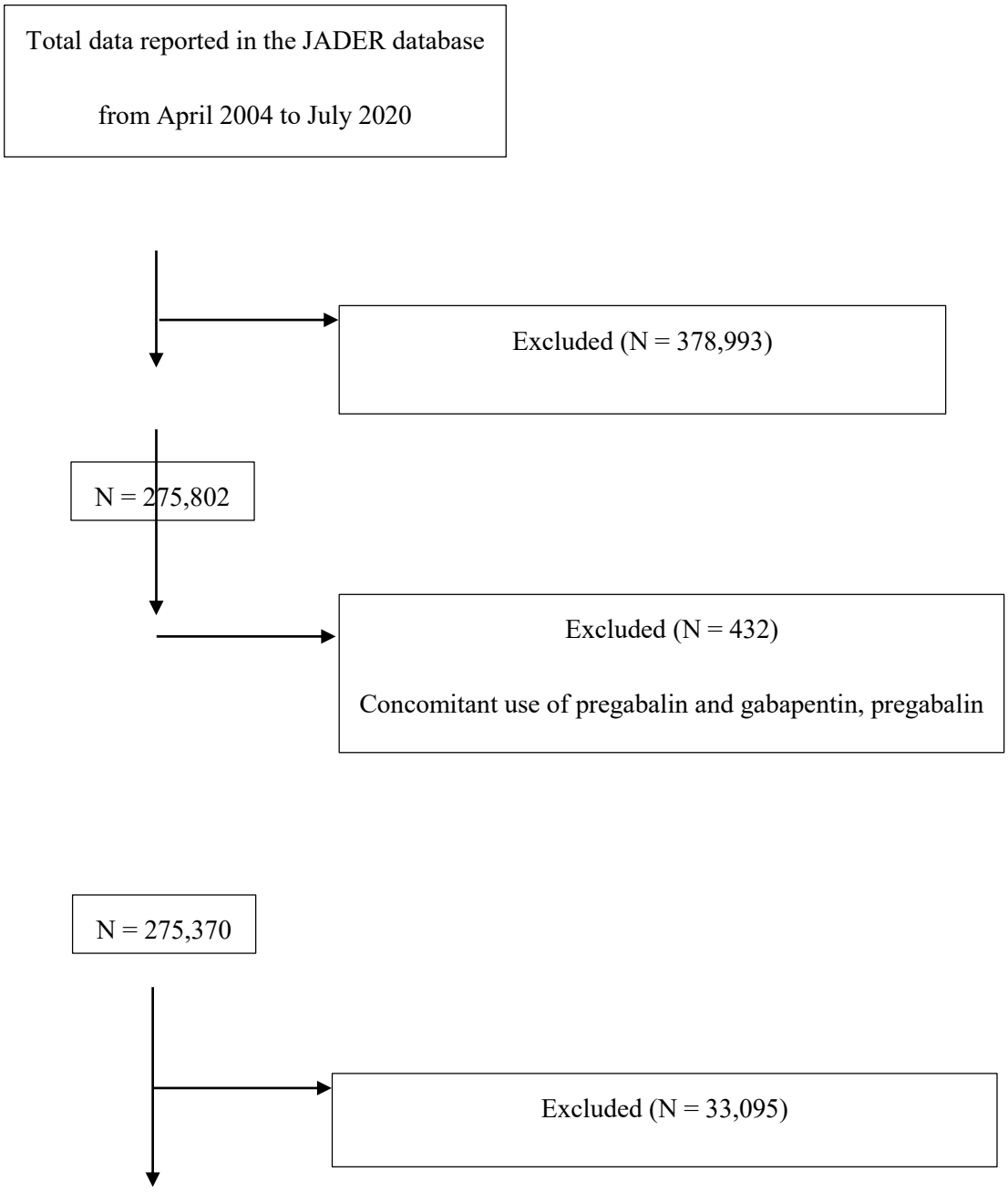
JADER, Japanese Adverse Drug Event Report; ROR, reporting odds ratio

Figure 1

	Adverse event of interest	Not adverse event of interest	Total
Administered drug X	a	b	a+b
Not administered drug X	c	d	c+d
Total	a+c	b+d	a+b+c+d

Reporting odds ratio (ROR) $= \frac{a/c}{b/d}$; 95% confidence interval $= e^{\ln(ROR) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$

Figure 2



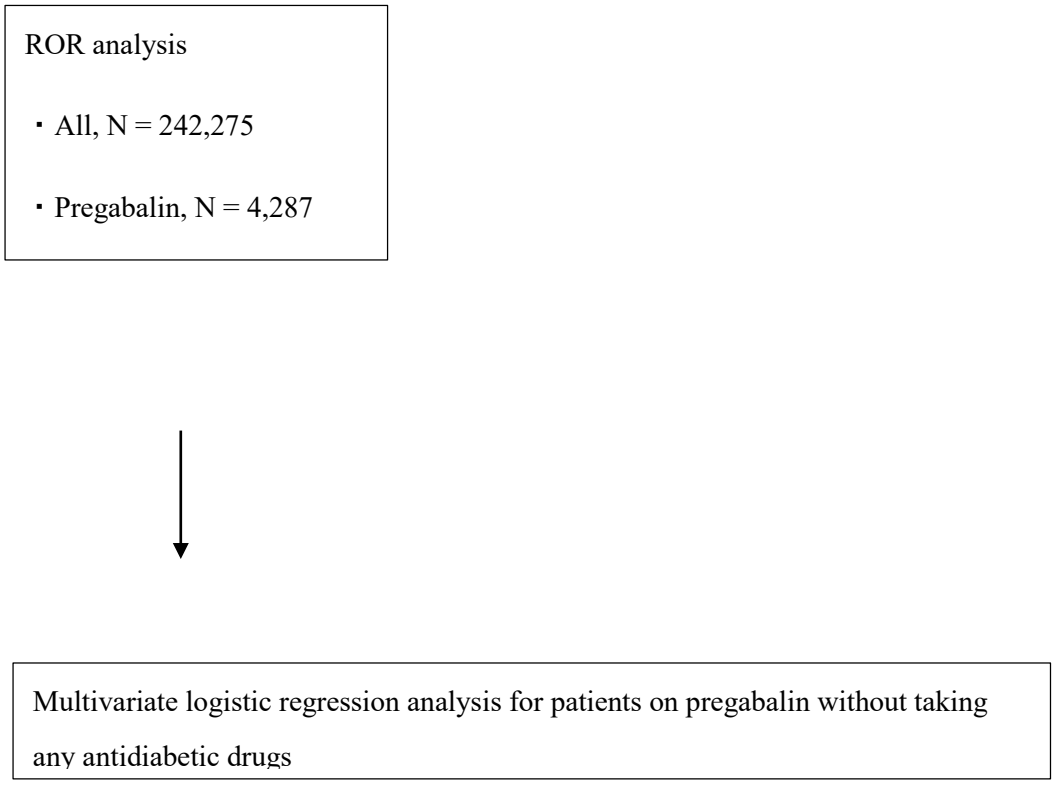


Table 1. Proportion of hypoglycemia in patients taking pregabalin, gabapentin, and duloxetine

Drug A	Without Drug A	With Drug A	ROR (95% CI)	p value
	Hypoglycemia /total, N (%)	Hypoglycemia /total, N (%)		
Pregabalin	918/237,988 (0.39)	37/4,287 (0.86)	2.25 (1.16–3.13)	<0.01

Gabapentin	950/241,662 (0.39)	5/613 (0.82)	2.08 (0.86–5.04)	0.10
Duloxetine	955/241,330 (0.40)	0/945 (0)	NA	NA

Fisher's exact test was performed for the analysis.

Threshold for significance was set at $p<0.05$.

CI, confidence interval; NA, not applicable; ROR, reporting odds ratio

Table 2. Multivariable logistic regression analysis of the factors associated with hypoglycemia in patients taking pregabalin without antidiabetic drugs (N=4287)

	Hypoglycemia /total, N (%)	Odds ratio (95% CI)		
		Crude	Adjust	p value [a]
Female	23/2,148 (1.07)	1 [reference]	1 [reference]	
Male	14/2,139 (0.65)	0.61 (0.31–1.19)	0.78 (0.38–1.59)	0.50
Age <70 years	9/2,124 (0.42)	1 [reference]	1 [reference]	
Age ≥70 years	28/2,163 (1.29)	3.08 (1.45–6.55)	2.76 (1.29–5.91)	<0.01
Weight ≥40 kg	28/3,950 (0.71)	1 [reference]	1 [reference]	
Weight <40 kg	9/337 (2.67)	3.84 (1.80–8.21)	2.97 (1.32–6.71)	<0.01
Without CKD	32/3,950 (0.81)	1 [reference]	1 [reference]	
With CKD	5/337 (1.48)	1.84 (0.71–4.76)	1.52 (0.58–3.97)	0.39

Threshold for significance was set at $p<0.05$

CKD, chronic kidney disease; CI, confidence interval

[a] Multivariable logistic regression analysis