Original Article

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Disproportionality and time-to-onset analyses of drug-induced weight gain using the Japanese Adverse Drug Event Report database

Naohito Ide[1,*], Rika Shibata[1], Ken-ichi Sako[2], Tomoji Maeda[2]

[1] Department of Practical Pharmacy, Nihon Pharmaceutical University, Saitama, Japan;
[2] Department of Clinical Pharmacology, Nihon Pharmaceutical University, Saitama, Japan.

SUMMARY: Drug-induced weight gain is a clinically important adverse event that can lead to obesity, metabolic syndrome, cardiovascular disease, and reduced treatment adherence. Although several drug classes are known to cause weight gain, the onset timing and underlying mechanisms remain incompletely understood. This study aimed to investigate signals and evaluate time to onset of drug-induced weight gain using the Japanese Adverse Drug Event Report (JADER) database. We analyzed JADER data from April 2004 to June 2025, and in the disproportionality analysis reporting odds ratios with 95% confidence intervals were calculated. Time to onset was also assessed, and Weibull distribution analysis was applied to evaluate onset patterns. Among 975,869 reports, 814 cases of drug-induced weight gain were identified. Signals were detected for known drugs such as antipsychotics, pregabalin, and pioglitazone, as well as for drugs without weight gain listed in their package inserts, including benzodiazepines. Pregabalin showed the earliest median onset at 19 days (early failure), followed by olanzapine and risperidone at 1–2 months, pioglitazone at 2 months, and clozapine at 6 months, all classified as random failure types. This study demonstrated that drug-induced weight gain varies by drug class in both onset timing and mechanisms. These findings underscore the need for careful weight monitoring during treatment, particularly early with pregabalin and long-term with clozapine and pioglitazone. Prospective studies are warranted to clarify causal relationships and clinical implications.

Keywords: weight gain, Japanese Adverse Drug Event Report database, disproportionality analysis, time to onset, Weibull distribution

1. Introduction

Drug-induced weight gain is a clinically important adverse event, as it can lead to obesity, metabolic syndrome, and cardiovascular disease, as well as reduced quality of life and treatment adherence (*1*). Several drug classes are known to cause weight gain, including second-generation antipsychotics, antiepileptic drugs, antidepressants, and antidiabetic agents such as thiazolidinediones (*2*). Although these associations are well recognized, the risk profiles differ across drug classes, and the onset timing and underlying mechanisms remain incompletely understood.

Previous pharmacovigilance studies using spontaneous reporting systems (SRS), such as the US Food and Drug Administration Adverse Event Reporting System (FAERS) and the Japanese Adverse Drug Event Report (JADER) database, have provided valuable insights (*3-6*). For example, Ahmed *et al.* investigated drug-induced weight gain using FAERS (*7*), but their study was limited to a descriptive analysis of the number of reported cases and did not evaluate onset patterns in detail. Comprehensive analyses of drug-induced weight gain using SRS databases remain scarce.

Therefore, the aim of this study was to investigate drug-induced weight gain using JADER. Specifically, we sought to identify signals through disproportionality analysis and to evaluate the time to onset of weight gain. By clarifying these aspects, our findings may contribute to improved monitoring and management of drug-induced weight gain in clinical practice.

2. Materials and Methods

2.1. Data source

We obtained data from the JADER database, which is managed by the Pharmaceuticals and Medical Devices

Agency (PMDA). The JADER database contains fully anonymized data submitted by healthcare professionals and pharmaceutical companies. The database is structured into 4 tables: "Demo", "Drug", "Reac", and "Hist". The "Demo" table includes basic patient information, such as age, sex, and reporting year. The "Drug" table contains details on drug administration, including the drug name, route of administration, start and end dates, dosage, and classification of involvement in adverse reactions (*e.g.*, suspected, concomitant, or interaction). The "Reac" table contains adverse events, outcomes, and onset dates, and the "Hist" table contains information on patient medical history. We downloaded the JADER database for April 2004 to June 2025 from the PMDA website (*https://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp*) on August 4, 2025. We analyzed patient age and sex, reporting year, drug name, administration start date, adverse event onset date, and clinical outcome.

2.2. Definition of adverse reactions

Adverse events in the JADER database are categorized using the preferred terms (PTs) from the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA/J). In this study, we extracted adverse events by using the PTs in MedDRA/J ver. 28.0. In this study, we defined the PT names (PT codes) for weight gain as "weight gain" (10047899) and "abnormal weight gain" (10000188).

2.3. Target drugs

Only cases of weight gain for which drug involvement was classified as "suspected" were included in the analysis. We analyzed the drugs for which there were 10 or more reports of weight gain.

2.4. Signal detection

The reporting odds ratio (ROR) is used by the PMDA and the Netherlands Pharmacovigilance Center to detect signals of adverse events in SRS (*8*). The ROR, along with its 95% confidence interval (95% CI), is a quantification of the disproportionality in adverse event reporting between groups (*9*). Therefore, the ROR is conceptually analogous to the odds ratio in case–control studies, representing the odds of exposure in reported cases compared with non-cases.

We calculated the ROR and 95% CI for weight gain adverse reactions (Figure 1); the signal of adverse reactions was considered to be positive when the lower limit of the 95% CI was greater than 1.

2.5. Analysis of time to onset

When a positive signal for weight gain was detected in the disproportionality analysis, we analyzed the time to onset. Cases were excluded if either the start date of drug administration or the onset date of the adverse event was unavailable. Cases were also excluded if the time to onset of the adverse event exceeded 1,095 days (*i.e.*, 3 years). Time to onset was analyzed for cases with 5 or more reports after exclusion. The time to onset was defined as the difference between the start date of drug administration and the onset date of weight gain, plus 1. To evaluate the pattern of onset, we used the Weibull distribution model and examined the Weibull shape parameters (*10,11*). Weibull shape parameters characterize the distribution of failure rates over time, where failure rates correspond to the onset of adverse events. The scale parameter α indicates the distribution breadth, with larger values representing a wider spread. The shape parameter β describes whether the hazard rate is increasing, decreasing, or constant over time. If the scale parameter β is equal to 1 or the 95% CI includes 1, the frequency of adverse events is considered to remain constant overtime; if β exceeds 1 and its 95% CI does not include 1, the frequency is assumed to increase over time; and if β is less than 1 and its 95% CI does not include 1, the frequency is assumed to decrease over time.

2.6. Ethical considerations

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The database used in this

	Target adverse events	Other adverse events	Total
Target drugs	a	b	a+b
Other drugs	c	d	c+d
Total	a+c	b+d	a+b+c+d

Reporting odds ratio (ROR) = (a/c)/(b/d) = ad/bc

95% Confidence interval = $\exp(\ln(ROR) \pm 1.96 \sqrt{1/a + 1/b + 1/c + 1/d})$

Figure 1. Two-by-two contingency table for disproportionality analysis.

study is completely anonymized. Therefore, the study was reviewed by the Ethics Committee of Nihon Pharmaceutical University, but it has been confirmed that ethical approval is not required.

2.7. Statistical analysis

All statistical analyses were performed with JMP Student Edition (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Descriptive analysis of adverse reactions with weight gain

The JADER database contains a total of 975,869 cases, of which 814 cases were drug-induced weight gain. The characteristics and clinical outcomes of the patients with drug-induced weight gain and the specialties of the reporters are shown in Table 1. The number of male and female patients was similar. Patient age ranged from young to elderly, and the distribution across age groups did not differ significantly. Approximately 80% of reporters were medical professionals such as physicians and pharmacists, while a minority were consumers. The clinical outcomes were mostly good, but 16.8% of patients did not recover. The number of reports was relatively low before 2010, followed by a sharp increase in 2011 and a peak in 2014 (70 cases) (Figure 2). Since 2011, the number of reports generally remained above 30 cases per year. Although some fluctuations were observed, the overall reporting frequency after 2011 was consistently higher compared with the earlier period.

3.2. Signal detection of weight gain

The number of reports of weight gain as an adverse event for each drug, the RORs, and whether weight gain is described in the package insert are shown in Figure 3. Among the drugs without weight gain listed in the package insert, signals were detected for bromazepam, limaprost alfadex, sennoside, prednisolone, flunitrazepam, etizolam, zolpidem, furosemide, diclofenac, and ciclosporine.

Table 1. Characteristics of patients with drug-induced weight gain in the Japanese Adverse Drug Event Report database

Items	n	%
Sex		
Male	358	44.0
Female	430	52.8
Unknown	26	3.2
Age group, years		
< 10	16	2.0
10-19	20	2.5
20-29	52	6.4
30-39	87	10.7
40-49	109	13.4
50-59	103	12.7
60-69	98	12.0
70-79	110	13.5
80-89	62	7.6
90-99	14	1.7
Unknown	143	17.6
Specialty of the reporters		
Healthcare professional	641	78.7
Consumer	167	20.5
Unknown	6	0.7
Clinical outcome		
Good outcome		
Recovery	132	16.2
Improvement	163	20.0
Poor outcome		
Sequelae	0	0.0
Unrecovered	137	16.8
Death	3	0.4
Unknown	379	46.6

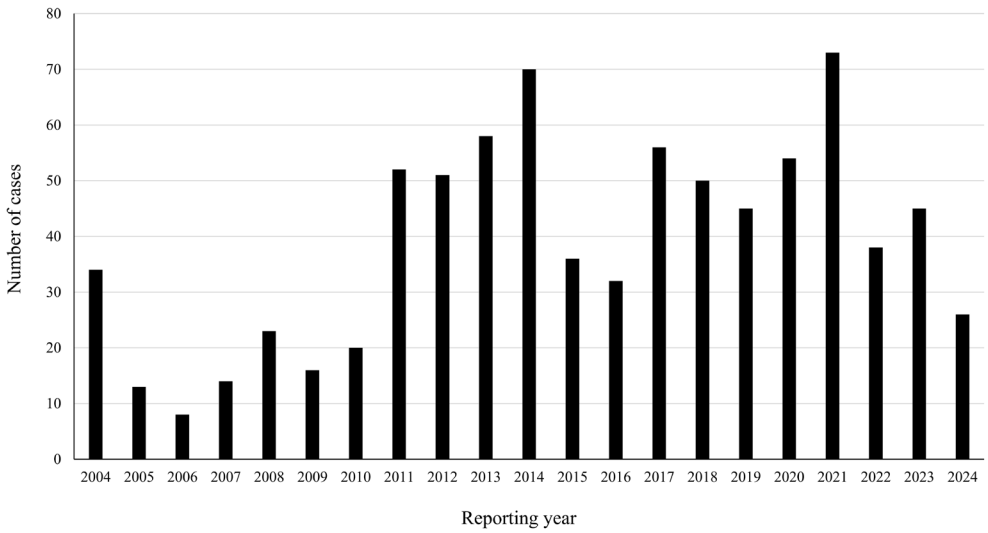

Figure 2. Yearly number of cases of drug-induced weight gain.

3.3. Time to onset of weight gain

The median time to onset for pregabalin was the earliest at 19 days, showing an early failure pattern (Table 2). For antipsychotic drugs, the median time to onset was approximately 1 to 2 months for olanzapine and risperidone but about 6 months for clozapine. The onset pattern of all antipsychotic drugs was classified as random failure. The median time to onset of pioglitazone was approximately 2 months, and the pattern was also random failure.

4. Discussion

Ahmed *et al.* investigated drug-induced weight gain using FAERS (*7*); however, their study only described the number of adverse event reports. In contrast, in the present study we conducted a disproportionality analysis of drug-induced weight gain using Japanese pharmacovigilance data and additionally examined the time to onset.

Many of the drugs for which signals were detected already listed weight gain in their package inserts and are widely recognized to be associated with weight gain. These include antipsychotics such as olanzapine and clozapine, antiepileptic drugs such as pregabalin and valproic acid, antidepressants such as mirtazapine and paroxetine, and tyrosine kinase inhibitors such as lorlatinib and imatinib.

However, signals were also detected for drugs that did not list weight gain in their package inserts, with benzodiazepines accounting for the majority of these signals. Sleep medications such as benzodiazepines are often used concomitantly with antipsychotics (*12*), suggesting that the signals detected for these drugs may be attributable to confounding. As a supplementary analysis, we investigated concomitant medications in 45 reports of weight gain associated with bromazepam, etizolam, zolpidem, and flunitrazepam. Notably, in 41 of these reports (91.1%), antipsychotics or other drugs known to induce weight gain were listed as "suspected drugs." This finding strongly suggests that the signals observed for benzodiazepines and zolpidem are likely attributable to confounding by concomitant antipsychotic medications rather than a direct effect of benzodiazepines and zolpidem themselves.

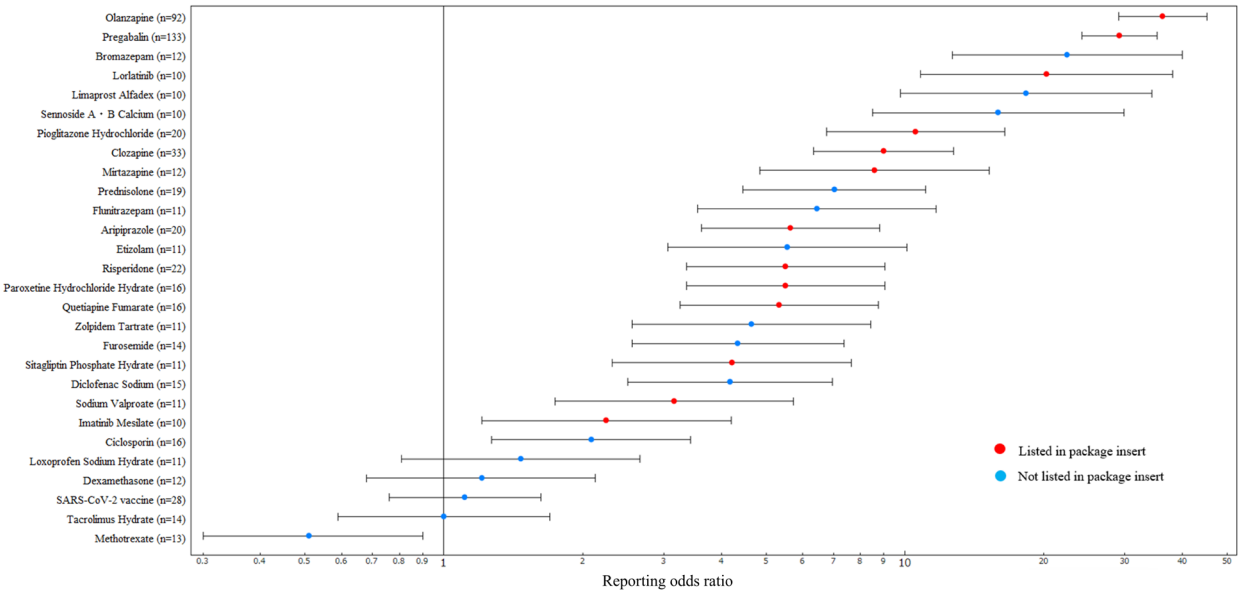

Figure 3. Reporting odds ratio and 95% confidence interval of weight gain, and whether or not included in the package insert.

Table 2. Time to onset and Weibull parameters of drug-induced weight gain

Drug	Cases, n	Median time to onset, days	IQR	Weibull scale parameter		Weibull shape parameter		
				α	95% CI	β	95% CI	Pattern
Pregabalin	35	19	9-91	47.14	28.57-75.84	0.74	0.56-0.94	Early failure
Olanzapine	22	52	16-121	84.12	47.97-143.04	0.85	0.60-1.13	Random failure
Clozapine	21	184	89-309	231.57	150.02-350.62	1.11	0.76-1.53	Random failure
Risperidone	5	39	16-296	96.33	18.07-473.65	0.69	0.32-1.19	Random failure
Pioglitazone Hydrochloride	9	64	45-499	199.68	80.41-465.61	0.88	0.50-1.39	Random failure

CI: confidence interval; IQR: interquartile range.

In previous reports, approximately 60% of patients were female (*7*), whereas in this study the ratio of males to females was nearly equal. In addition, while about 60% of reports in the previous study were submitted by consumers (*7*), approximately 80% of reports in our study originated from healthcare professionals. It has been reported that women are more conscious of weight loss behaviors and treatment than men (*13*). For adverse events that are readily recognized by patients themselves, such as weight gain, there may be substantial differences in reporting patterns between FAERS and JADER, as observed in the present study, and further investigation is warranted in this respect.

In the time-to-onset analysis, pregabalin showed a short onset time of approximately 3 weeks and was classified as an early failure type. Pregabalin is known to cause adverse events such as somnolence and dizziness, and several studies have investigated these adverse events using JADER and FAERS (*4,14*). However, there are few reports focusing on weight gain as an adverse event associated with pregabalin.

Previous reports on pregabalin have indicated that weight gain of 7% or more from baseline is generally observed within 1 to 2 months (*15*), whereas in the present study the time to onset appeared to be earlier. However, because this study used an SRS database, the specific amount of weight gain was not available, and therefore a direct comparison is not possible. Nevertheless, our findings suggest that weight gain associated with pregabalin may occur at an early stage of treatment.

The mechanisms underlying pregabalin-induced weight gain are not fully understood. One proposed explanation is that pregabalin increases food intake by inhibiting dopamine function in the lateral hypothalamic area (*16*). In addition, pregabalin has been reported to inhibit the α2δ1 subunit of calcium channels, thereby promoting appetite (*17*), and to suppress glutamate release, resulting in decreased corticotropin-releasing hormone levels and increased food intake (*18*). Further studies are needed to clarify these mechanisms.

Second-generation antipsychotic drugs such as olanzapine, clozapine, and risperidone have been reported to cause weight gain within 2 weeks to approximately 3 months (*2*), with olanzapine and clozapine being most strongly associated. In the present study, signals of weight gain were detected for the antipsychotics olanzapine, clozapine, risperidone, aripiprazole, and quetiapine. The median time to onset of weight gain was 1 to 2 months for risperidone and olanzapine, consistent with previous reports, but was longest for clozapine at 184 days. Results of the Weibull distribution analysis indicated that all were classified as random failure types, suggesting that weight gain may occur over an extended period, particularly with clozapine.

The mechanism by which second-generation antipsychotics cause weight gain is thought to involve their actions on multiple receptors, including dopamine receptors D1, D2, and D4; 5-hydroxytryptamine (serotonin) receptors 1A, 2A, 2C, 6, and 7; histamine receptor H1; and muscarinic acetylcholine receptor M3, leading to increased appetite and subsequent weight gain (*19*). Olanzapine and clozapine have higher affinity for serotonin, histamine, and muscarinic receptors than for dopamine receptors, which may explain their stronger appetite-stimulating effects and greater impact on weight gain (*19*). Therefore, careful monitoring of body weight is warranted during long-term treatment with second-generation antipsychotics, particularly clozapine, given the potential for progressive weight gain over time.

Pioglitazone-induced weight gain has been reported to increase significantly within 2 months (*20*). The median onset time in this study was approximately 2 months, which was similar to the previously reported results. Weight gain induced by pregabalin and second-generation antipsychotics is attributed to increased appetite. However, thiazolidinediones, including pioglitazone, are associated with fluid retention and increased fat mass. Thiazolidine increases insulin sensitivity and binds to peroxisome proliferator-activated receptor gamma receptors, which increases fat mass and leads to weight gain (*21*). It also causes fluid retention by reducing sodium excretion in the distal tubules (*22*), which leads to weight gain.

This study has several limitations. First, it was conducted using the JADER database, an SRS. As with other studies employing similar databases, it was not possible to calculate the incidence of adverse events, and inaccuracies or underreporting in the registered data may have been present (*4*). Second, in the time-to-onset analysis, many reports lacked information on the start date of drug administration or the onset date of adverse events, resulting in a limited number of analyzable cases. Because the Weibull distribution is sensitive to outliers in small samples, its accuracy may decrease under such conditions (*23*); therefore, caution may be warranted when interpreting onset patterns. Third, the potential influence of concomitant medications was not assessed. As noted previously, although weight gain signals were detected for benzodiazepines and zolpidem, they are likely attributable to concomitant use of antipsychotics. To overcome these limitations, prospective clinical trials or well-designed case–control studies are required.

In conclusion, this study identified signals and evaluated the time to onset of drug-induced weight gain using the JADER database. Signals were detected not only for well-known drugs such as antipsychotics and pregabalin but also for drugs without weight gain listed in their package inserts. Pregabalin showed early onset at approximately 3 weeks, whereas clozapine exhibited a later onset at around 6 months. These findings underscore the importance of careful weight monitoring during treatment and highlight the need for prospective studies to clarify causal relationships.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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**Address correspondence to:*
Naohito Ide, Department of Pharmaceutical Sciences, Nihon Pharmaceutical University, 10281 Komuro, Ina-Machi, Kitaadachi-Gun, Saitama, 362-0806, Japan.
E-mail: n-ide@nichiyaku.ac.jp

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