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Occurrence of somnolence and respiratory depression induced by pregabalin and mirogabalin use and the influence of opioid treatment using the Japanese adverse drug event report database

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Background: Gabapentinoid anticonvulsants are standard treatment for neuropathic pain and are often combined with opioids for treating cancer. It is assumed that this combination may heighten somnolence and respiratory depression due to the inhibitory effects of opioids on the central nervous system. Although pregabalin, a gabapentinoid, is known to increase somnolence frequency during opioid therapy, whether mirogabalin exerts similar effects on somnolence frequency under opioid therapy remains unknown. This study examined the signals of somnolence and respiratory depression in response to pregabalin and mirogabalin use by utilizing data from the Japanese Adverse Drug Event Report database and assessed their interaction with strong opioid analgesics. *Methods:* Information was obtained from the JADER database from April 2004 to August 2023 via the Pharmaceuticals and Medical Devices Agency website. The study focused on neuropathic pain medications, specifically "pregabalin" and "mirogabalin besilate." Adverse events were defined using preferred terms (PTs) from the Medical Dictionary for Regulatory Activities version 26.1. The PTs considered were "Somnolence (10041349)" and "Respiratory depression (10038678)." To investigate the effect of the combination of strong opioid analgesics with pregabalin and mirogabalin on the occurrence of somnolence, a multivariable logistic regression analysis was conducted. *Results:* Signals for somnolence were detected with the use of both drugs (pregabalin: information component (IC) [95% confidence intervals (CIs)]: 2.89 [2.70 to 3.08]; mirogabalin: IC [95% CIs] 2.50 [1.85 to 3.16]). When evaluating respiratory depression, a typical and serious adverse event of opioid analgesic use, a signal was detected with pregabalin use but not with mirogabalin use (pregabalin: (IC [95% CIs] 1.28 [0.83 to 1.73]; mirogabalin: IC [95% CIs] -0.15 [-2.20 to 1.89]). Multivariable analysis indicated that the use of strong opioid analgesics increased the occurrence of somnolence when combined with pregabalin but not when combined with mirogabalin ($p = 0.004$).
Conclusion:
While the safety of concomitant administation of mirogabalin with opioids remains controversial, caution should be exercised when using pregabalin, especially in combination with opioids for neuropathic pain, compared to that for mirogabalin.

1. Introduction

The "analgesic stepladder" approach recommended by the World Health Organization has proven effective in treating chronic cancer pain (World Health Organization 1996; Caraceni et al. 2012). Patients with moderate-to-severe pain are candidates for initiation of treatment with strong opioid agents. However, neuropathic cancer pain often resists opioid treatment, leading to the use of adjuvant drugs such as antidepressants and anticonvulsants, which have demonstrated efficacy (Guan et al. 2016).

Gabapentinoids, including pregabalin and mirogabalin, are standard neuropathic pain treatments for conditions such as diabetic peripheral neuropathy, postherpetic neuralgia, and spinal cord injury (Goodman and Brett 2017; Kim et al. 2021). While effective, their use is associated with safety concerns such as central nervous system (CNS) depression, leading to somnolence, dizziness, and respiratory depression (Hahn et al. 2022).

The efficacy of pregabalin in treating neuropathic pain is attributed to its modulation of glutamate release from hyperexcited neurons *via* binding to the α2δ subunit of voltage-gated calcium channels, which regulates calcium influx to presynaptic terminals (Taylor et al. 2007). Mirogabalin, which is approved in Japan for peripheral neuropathic pain treatment since January 2019, exhibits prolonged analgesic effects by binding strongly and dissociating slowly from α2δ-1 subunits in the dorsal root ganglion. It also induces fewer central nervous system-specific adverse events (AEs) due to its low affinity and rapid dissociation from α2δ-2 subunits in the cerebellum (Kim et al. 2021).

Recent clinical recommendations advocate the use of adjuvant drugs for neuropathic cancer pain treatment, often in combination opioids (Ripamonti et al. 2012). Consequently, cancer patients receiving gabapentinoids for neuropathic pain are commonly prescribed opioids, which exert CNS inhibitory effects. Combining gabapentinoids with opioids is presumed to enhance somnolence and respiratory depression. Indeed, pregabalin has been reported to be associated with increased somnolence frequency during opioid therapy (Kato et al. 2015; Ohishi et al. 2015). However, whether mirogabalin similarly affects somnolence frequency under opioid therapy remains unknown.

In recent years, pharmacovigilance methods for detecting drug-associated AE signals using databases such as the Japanese Adverse Drug Event Report (JADER) and the US Food and Drug Administration (FDA) adverse event reporting system (FAERS) have advanced. JADER, a nationwide open-access database of spontaneous AE reports provided by Japan's Pharmaceuticals and Medical Devices

Agency (PMDA), contains data on approximately 1,440,000 AEs reported since April 2004. As mirogabalin is approved in Japan and several other Asian countries, JADER serves as a valuable tool for investigating the occurrence of AEs associated with mirogabalin use. In this study, we investigated the signals of somnolence and respiratory depression associated with pregabalin and mirogabalin use using information from the JADER database. Furthermore, we estimated the impact of concomitant use of strong opioid analgesics with pregabalin and mirogabalin on somnolence.

2. Investigations and results

2.1. Data source

Information from the JADER database was sourced from April 2004 to August 2023 from the PMDA website (https://www.pmda.go.jp/english/index.html). This study utilized demographic data from the "demo" table (869,376 patients), drug information "drug" table (4,442,937 cases), and AE information "reac" table (1,442,061 cases) within the JADER database. The "demo" table contained data about patient sex and age. Patients with missing or unknown sex or age data as well as cases with duplicate entries in the "drug" and "reac" tables were excluded. The contribution of drugs to AEs was divided into suspected, concomitant, and interaction categories, all of which were included in the study. The "demo" table was linked to the de-duplicated "drug" and "reac" tables using patient identification numbers. Ultimately, 767,618 patients were included in the analysis dataset for this study (Fig. 1).

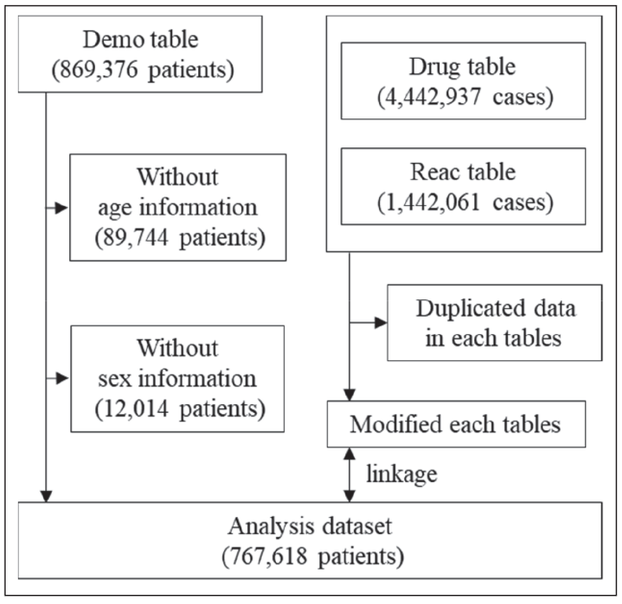

Fig. 1: Flow diagram of the study.

2.2. Target drugs

The study surveyed "pregabalin" and "mirogabalin besilate" as neuropathic pain medications. Additionally, the use of "morphine sulfate hydrate," "morphine hydrochloride hydrate," "oxycodone hydrochloride hydrate," "hydromorphone hydrochloride," "fentanyl citrate," or "methadone hydrochloride" was classified as strong opioid analgesic use.

2.3. Definition of adverse effects

Adverse reactions (AEs) in the "reac" table are defined using preferred terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. For this study, the estimated PT names (PT codes) included "somnolence (10041349)" and "respiratory depression (10038678)."

Table 1: Three-by-three contingency table

	Target AEs	Other AEs	Total
Target drugs	N_{11}	N_{10}	N_{1+}
Other drugs	N_{01}	N_{00}	N_{0+}
Total	N_{+1}	N_{+0}	N_{++}

AEs, Adverse events.

$$E(\mathrm{IC}_{11}) = \log_2 \frac{(N_{11}+\gamma_{11})(N_{++}+\alpha)(N_{++}+\beta)}{(N_{++}+\gamma)(N_{1+}+\alpha_1)(N_{+1}+\beta_1)}$$

$$V(\mathrm{IC}_{11}) = \left(\frac{1}{\ln 2}\right)^2 \left[\frac{N_{++}-N_{11}+\gamma-\gamma_{11}}{(N_{11}+\gamma_{11})(1+N_{++}+\gamma)} + \frac{N_{++}-N_{1+}+\alpha-\alpha_1}{(N_{1+}+\alpha_1)(1+N_{++}+\alpha)} + \frac{N_{++}-N_{+1}+\beta-\beta_1}{(N_{+1}+\beta_1)(1+N_{++}+\beta)}\right]$$

$$\gamma = \gamma_{11}\frac{(N_{++}+\alpha)(N_{++}+\beta)}{(N_{1+}+\alpha_1)(N_{+1}+\beta_1)} \quad \gamma_{11}=1 \quad \alpha_1=\beta_1=1 \quad \alpha=\beta=2$$

$$\mathrm{IC}\ (95\%\mathrm{CI}) = E(\mathrm{IC}_{11}) \pm 2\sqrt{V(\mathrm{IC}_{11})}$$

Fig. 2: IC equations. Abbreviations: IC, information component; CI, confidence intervals.

2.4. Signal detection

To assess signals for targeted AEs, we calculated the information components (ICs) and their 95% confidence intervals (CIs) using three-by-three contingency tables (Table 1) and equations (Fig. 2). ICs and 95% CIs were computed using Microsoft 365 Excel. A positive safety signal was indicated if the lower limit of the 95% CI of the IC exceeded 0 (Noguchi et al. 2021).

2.5. Logistic regression analysis

For investigating the impact of concomitant use of strong opioid analgesics with pregabalin and mirogabalin on somnolence occurrence, a multivariable logistic regression analysis was conducted. The analysis dataset comprised patients reporting pregabalin (13,160 patients) and mirogabalin (960 patients) use. Sex and age were included as adjustment factors, and the groups were categorized as "under 10s," "10s," "20s," "30s," "40s," "50s," "60s," and "elderly" (70s, 80s, 90s, and 100s) by referencing prior studies (Kato et al. 2015; Mukai et al. 2019).

2.6. Signals of somnolence and respiratory depression

Table 2 presents the ICs of somnolence and respiratory depression reported as AEs with pregabalin and mirogabalin use. Signals for somnolence were detected with the use of both drugs (ICs [95% CIs]: pregabalin, 2.89 [2.70 to 3.08]; mirogabalin, 2.50 [1.85 to 3.16]). Additionally, when evaluating respiratory depression, a signal was observed with pregabalin use but not with mirogabalin use (ICs [95% CIs]: pregabalin, 1.28 [0.83 to 1.73]; mirogabalin, -0.15 [-2.20 to 1.89]).

Table 2: ICs for pregabalin and mirogabalin for somnolence and respiratory depression

	N_{11}	N_{10}	N_{01}	N_{00}	ICs [95%CIs]
Somnolence					
Pregabalin	262	12,898	1,754	752,704	2.89 [2.70 to 3.08]
Mirogabalin	19	941	1,997	764,661	2.50 [1.85 to 3.16]
Respiratory depression					
Pregabalin	42	13,118	932	753,526	1.28 [0.83 to 1.73]
Mirogabalin	1	959	973	765,685	-0.15 [-2.20 to 1.89]

N_{11}, N_{10}, N_{01}, N_{00} each represent the corresponding cell name in table2, which is represented by two-by-two contingency tables. ICs, Information components; CIs, confidence intervals.

2.7. Multivariable logistic regression analysis for determining the effect of concomitant use of strong opioid analgesics on somnolence occurrence

Multivariable analysis revealed that the use of strong opioid analgesics resulted in the increased occurrence of somnolence

Table 3: Multivariable logistic regression analysis for the occurrence of somnolence.

	Odds ratio	95%CIs	*p*-values
Pregabalin			
Opioid use	1.62	1.17–2.24	0.004
Female	1.51	1.17–1.94	0.001
Elderly (≥ 70s)	0.91	0.71–1.17	0.457
Milogabalin			
Opioid use	1.60	0.45–5.73	0.471
Female	2.13	0.76–6.00	0.153
Elderly (≥ 70s)	1.19	0.46–3.09	0.728

CIs, confidence intervals.

when they were used in combination with pregabalin ($p = 0.004$) but not when used in combination with mirogabalin (Odds ratio [95% CIs]: pregabalin, 1.62 [1.17–2.24] and mirogabalin, 1.60 [0.45–5.73]) (Table 3).

3. Discussion

Gabapentinoids are extensively utilized for managing neuropathic cancer pain. Treatment typically involves the use of a combination of adjuvant analgesics such anticonvulsants and antidepressants, alongside opioids. However, robust evidence supporting their efficacy and safety in neuropathic cancer pain remains limited (Jongen et al. 2013; Matsuoka et al. 2022). Concurrent use of gabapentinoids and opioids may alter the risk of AEs associated with opioid use (Kardas et al. 2020).

In the present study, we evaluated the AE signals of somnolence and respiratory depression associated with pregabalin and mirogabalin use. Signals for somnolence were observed with the use of both drugs. However, multivariable analysis indicated that the use of strong opioid analgesics increased somnolence occurrence when combined with pregabalin but not when it was combined with mirogabalin. Previous retrospective studies have highlighted the concomitant use of pregabalin and strong opioids as a significant risk factor for somnolence and dizziness incidence. This suggests that combining pregabalin with opioids may elevate AE rates, necessitating careful attention, particularly in neuropathic cancer pain treatment (Kato et al. 2015; Ohishi et al. 2015). Nevertheless, our database-driven study indicates a need for further investigation into the influence of mirogabalin and opioid use on AEs.

The 2023 American Geriatrics Society Beers Criteria® caution against combining opioids with gabapentinoids (gabapentin and pregabalin) in older adults due to the potential risk of severe sedation-related AEs, including respiratory depression and death (the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel 2023). Additionally, concurrent use of opioids with gabapentinoids has been reported to be associated with an increased risk of mortality, as evidenced by an analysis of death registrations in the United Kingdom (Chen et al. 2022). In the present study, when evaluating the signal of respiratory depression, a typical and serious AE associated with opioid analgesics, a signal was detected with pregabalin use but not with mirogabalin use. This raises the possibility that pregabalin and mirogabalin may exhibit different degrees of AEs, which warrants consideration from a pharmacological perspective.

The efficacy of pregabalin and mirogabalin in treating neuropathic pain stems from their modulation of glutamate release from hyperexcited neurons via binding to the α2δ subunit. Pregabalin binds nonselectively to both α2δ-1 and α2δ-2 subunits, leading to unwanted CNS adverse effects. In contrast, mirogabalin selectively binds to α2δ-1 and α2δ-2 subunits, with a longer dissociation half-life from α2δ-1 compared to α2δ-2. This suggests mirogabalin may have fewer AEs than pregabalin (Kato et al. 2021; Itaya et al. 2023).

This study has some limitations. First, spontaneous reporting systems such as JADER are passive and prone to biases such as under-reporting, over-reporting, and confounding by comorbidities. Second, the number of AEs associated with mirogabalin use reported in the JADER database is relatively low due to its recent approval in 2019. Further investigations, such as cohort studies involving patients with neuropathic cancer pain, are warranted to compare the safety of mirogabalin and pregabalin use.

In conclusion, while the safety of concomitant mirogabalin and opioid administration remains debated, caution is advised when combining opioids with pregabalin for neuropathic pain management, compared to that for mirogabalin.

4. Experimental

4.1. Statistical analysis

Statistical significance was considered at p-values < 0.05. Analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a modified version of R Commander, serving as a graphical interface for R version 4.2.2, developed by the R Foundation for Statistical Computing, Vienna, Austria (Kanda 2013).

4.2. Ethical approval

Ethical approval and consent to participate were not required because this study used an open-access database.

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References

American Geriatrics Society Beers Criteria® Update Expert Panel (2023) American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc 71: 2052-2081.

Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, Dale O, De Conno F, Fallon M, Hanna M, Haugen DF, Juhl G, King S, Klepstad P, Laugsand EA, Maltoni M, Mercadante S, Nabal M, Pigni A, Radbruch L, Reid C, Sjogren P, Stone PC, Tassinari D, Zeppetella G (2012) Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 13: e58–68.

Chen TC, Knaggs RD, Chen LC (2022) Association between opioid-related deaths and persistent opioid prescribing in primary care in England: A nested case-control study. Br J Clin Pharmacol 88: 798–809.

Goodman CW, Brett AS (2017) Gabapentin and pregabalin for pain - is increased prescribing a cause for concern? N Engl J Med 377: 411–414.

Guan J, Tanaka S, Kawakami K (2016) Anticonvulsants or antidepressants in combination pharmacotherapy for treatment of neuropathic pain in cancer patients: a systematic review and meta-analysis. Clin J Pain 32: 719–725.

Hahn J, Jo Y, Yoo SH, Shin J, Yu YM, Ah YM (2022) Risk of major adverse events associated with gabapentinoid and opioid combination therapy: A systematic review and meta-analysis. Front Pharmacol 13: 1009950.

Itaya T, Sano M, Kajiwara I, Oshima Y, Kuramochi T, Kim J, Ichimaru Y, Kitajima O, Masamune A, Ijichi H, Ishii Y, Suzuki T (2023) Mirogabalin improves cancer-associated pain but increases the risk of malignancy in mice with pancreatic cancer. Pain 164: 1545–1554.

Jongen JL, Huijsman ML, Jessurun J, Ogenio K, Schipper D, Verkouteren DR, Moorman PW, van der Rijt CC, Vissers KC (2013) The evidence for pharmacologic treatment of neuropathic cancer pain: beneficial and adverse effects. J Pain Symptom Manage 46: 581–590.e1.

Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48: 452–458.

Kardas P, Urbański F, Lichwierowicz A, Chudzyńska E, Czech M, Makowska K, Kardas G (2020) The prevalence of selected potential drug-drug interactions of analgesic drugs and possible methods of preventing them: lessons learned from the analysis of the real-world national Database of 38 million citizens of Poland. Front Pharmacol 11: 607852.

Kato H, Miyazaki M, Takeuchi M, Tsukuura H, Sugishita M, Noda Y, Yamada K (2015) A retrospective study to identify risk factors for somnolence and dizziness in patients treated with pregabalin. J Pharm Health Care Sci 1: 22.

Kato J, Inoue T, Yokoyama M, Kuroha M (2021) A review of a new voltage-gated Ca^{2+} channel $\alpha_2\delta$ ligand, mirogabalin, for the treatment of peripheral neuropathic pain. Expert Opin Pharmacother 22: 2311–2322.

Kim JY, Abdi S, Huh B, Kim KH (2021) Mirogabalin: could it be the next generation gabapentin or pregabalin? Korean J Pain 34: 4–18.

Matsuoka H, Clark K, Fazekas B, Oyamada S, Brown L, Ishiki H, Matsuda Y, Hasuo H, Ariyoshi K, Lee J, Le B, Allcroft P, Kochovska S, Fujiwara N, Miyaji T, Lovell M, Agar M, Yamaguchi T, Satomi E, Iwase S, Phillips J, Koyama A, Currow DC (2022) Phase III, international, multicentre, double-blind, dose increment, parallel-arm, randomised controlled trial of duloxetine versus pregabalin for opioid-unresponsive neuropathic cancer pain: a JORTC-PAL16 trial protocol. BMJ Open 12: e050182.

Mukai R, Hasegawa S, Umetsu R, Nakao S, Shimada K, Uranishi H, Masuta M, Suzuki H, Nishibata Y, Nakamura M (2019) Evaluation of pregabalin-induced adverse events related to falls using the FDA adverse event reporting system and Japanese Adverse Drug Event Report databases. J Clin Pharm Ther 44: 285–291.

Noguchi Y, Murayama A, Esaki H, Sugioka M, Koyama A, Tachi T, Teramachi H (2021) Angioedema caused by drugs that prevent the degradation of vasoactive peptides: a pharmacovigilance database study. J Clin Med 10: 5507.

Ohishi A, Chisaki Y, Hira D, Nagasawa K, Terada T (2015) Opioid analgesics increase incidence of somnolence and dizziness as adverse effects of pregabalin: a retrospective study. J Pharm Health Care Sci 1: 30.

Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F (2012) Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol 23 Suppl 7: vii139-154.

Taylor CP, Angelotti T, Fauman E (2007) Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res 73: 137–150.

World Health Organization (1996) Cancer pain relief (2nd edn.), Geneva.