Brief Report

DOI: 10.5582/ddt.2026.01040

Disproportionality analysis of opioid-related urinary retention using the JADER database: Focus on the lack of signal for transdermal fentanyl

Yusuke Tanaka[1,2], Masahiko Kimura[1,2], Naohito Ide[2], Ken-ichi Sako[2], Tomoji Maeda[2,*]

[1] Department of Pharmacy, Jichi Medical University Saitama Medical Center, Saitama, Japan;
[2] Department of Clinical Pharmacy, Nihon Pharmaceutical University, Saitama, Japan.

SUMMARY: Urinary retention is a known adverse effect of opioids, but limited information is available on how this adverse event varies among individual opioids. This study evaluated disproportionality signals between major opioids and urinary retention using the Japanese Adverse Drug Event Report database (JADER). We performed a disproportionality analysis of reports submitted between April 2004 and October 2025. Signals were assessed using reporting odds ratios (RORs), 95% confidence intervals (CIs), and the Information Component (IC). Adverse events were identified using the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J) term "urinary retention." A sensitivity analysis was conducted using a broader definition of urinary dysfunction that also included "Dysuria." Time to onset was calculated from the start of opioid administration to event onset, and daily doses were converted to oral morphine equivalents. Significant signals were detected for morphine, oxycodone, tramadol, and codeine. Transdermal fentanyl was the only opioid without a detectable signal, even under the broader definition of urinary dysfunction. Among opioids with detected signals and available dose information, urinary retention was reported even at relatively low morphine-equivalent doses, suggesting the need for careful monitoring at the start of opioid therapy. The absence of a signal for transdermal fentanyl may reflect a lower reporting frequency in JADER, but not a lower clinical risk, of urinary retention. Given the limitations of spontaneous reporting systems, these findings are hypothesis-generating and are insufficient to guide opioid selection or switching.

Keywords: Adverse drug reaction, reporting odds ratio, signal detection, spontaneous reporting system

1. Introduction

Urinary retention is a recognized adverse drug event (ADE) associated with opioid use, but drug-specific information remains limited. Despite its clinical importance, reports on this condition remain limited, and current guidelines provide only general management strategies, offering little guidance on opioid selection from the perspective of urinary adverse events (*1*). We encountered a patient who developed urinary retention after initiating oral morphine therapy and subsequently showed improvement following a switch to a fentanyl patch (*2*). Although this single case cannot establish differences in clinical risk among opioids, it raised a clinical question as to whether urinary retention is reported differently among individual opioids in a spontaneous reporting database. However, although urinary retention has been included among opioid-related adverse events in previous JADER studies, detailed assessments of urinary retention reporting patterns across individual opioids remain limited. In addition, the rarity of this ADE makes conventional epidemiological studies difficult.

The Japanese Adverse Drug Event Reporting Database (JADER), maintained by the Pharmaceuticals and Medical Devices Agency (PMDA), is a large-scale spontaneous reporting system that collects adverse event reports from clinical practice in Japan. It has been widely used to evaluate drug safety signals, particularly for rare ADEs, using measures such as the reporting odds ratio (ROR) (*3-5*).

This study aimed to evaluate disproportionality signals for urinary retention associated with major opioids in JADER. These findings are intended to provide hypothesis-generating information for further evaluation and clinical monitoring, rather than to guide opioid selection.

2. Materials and Methods

2.1. Data source

This study included cases registered in the JADER between April 2004 and October 2025. The database was obtained from the Pharmaceuticals and Medical Devices Agency (PMDA) website. (*https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0003.html*).

JADER consists of four data tables: DEMO, DRUG, REAC, and HIST. Duplicate entries were identified and removed using the case identification numbers in the DEMO table. The DEMO, DRUG, and REAC tables were then linked using these identification numbers, and the analysis was conducted on the merged dataset. For each case, the contribution of administered drugs to adverse drug events (ADEs) was classified into three categories: "suspected drug," "concomitant medication," and "interaction." Only drugs classified as "suspected drug" were included in the analysis.

The DEMO table includes patient characteristics such as sex and age. In sex-specific analyses, cases with missing or unknown sex were excluded. Age was categorized into younger (< 60 years) and older (≥ 60 years) groups; records with ambiguous age categories were excluded.

2.2. Drugs included in the analysis

The drugs included in this analysis were morphine, fentanyl, oxycodone, hydromorphone, tramadol, and codeine phosphate hydrate. To minimize the influence of postoperative urinary retention, administration routes with a higher associated risk were excluded. Accordingly, fentanyl was limited to transdermal patch formulations, whereas the other opioids were restricted to oral formulations.

2.3. Extraction of adverse events

Adverse events were identified using the MedDRA/J (Medical Dictionary for Regulatory Activities, Japanese version; version 28.1) preferred term "urinary retention" (PT: 10046555). In addition, a sensitivity analysis was conducted to allow a broader assessment of urinary dysfunction by including the preferred term "Dysuria" (PT: 10013990).

2.4. Time to onset

For the time-to-onset analysis, cases with unknown start dates of drug administration or unknown dates of adverse event onset were excluded. Cases in which only the year was recorded, or in which the day was missing despite the availability of the month and year, were also excluded. Time to onset was defined as the interval from the start of drug administration to the onset of the adverse event, with 1 day added to the calculated duration.

2.5. Daily dose

For the daily dose analysis, cases with unknown dose information were excluded. The doses of opioids were converted to oral morphine equivalents. Specifically, 20 mg/day of oral oxycodone, 0.3 mg/day of transdermal fentanyl, 150 mg/day of oral tramadol, and 200 mg/day of oral codeine were considered equivalent to 30 mg/day of oral morphine (*6,7*).

2.6. Statistical analysis

The reporting odds ratio (ROR) and corresponding 95% confidence interval (CI) were calculated as measures of association. A signal was considered present when the lower limit of the 95% CI exceeded 1.

The ROR was calculated based on a two-by-two contingency table, defined as follows: a, cases with the target ADE associated with the suspected drug; b, non-cases associated with the suspected drug; c, cases with the target ADE associated with other drugs; and d, non-cases associated with other drugs. The ROR was calculated as (a×d) / (b×c). The RORs and corresponding 95% CIs were calculated using unrounded values.

Because no zero cells were present in the contingency table, no continuity correction was applied, and the ROR was calculated without adjustment. Drug definitions, including routes of administration, were kept consistent between the ROR and IC analyses.

In the primary analysis, the information component (IC), a Bayesian disproportionality measure, was calculated to assess the robustness of the signals. A signal was considered present when the lower limit of the 95% credibility interval of the IC (IC_{025}) exceeded 0. The IC was calculated using the Bayesian confidence propagation neural network method, and IC_{025} was defined as the lower limit of the 95% credibility interval of the IC.

For the analysis of time to ADE onset, the number of reports was limited; therefore, Weibull distribution analysis was not performed, and the median time to onset was calculated instead. All statistical analyses were performed using JMP® Student Edition 19.0.5.

2.7. Ethical considerations

Ethical approval was not required for this study because it was based on a secondary analysis of anonymized data from a publicly available database. The JADER database contains no personally identifiable patient information; therefore, informed consent was not applicable. In addition, the Ethics Committee of Nihon Pharmaceutical University determined that ethical review was not required for this study.

3. Results and Discussion

3.1. Patient characteristics

A comparison between all urinary retention reports (*n*

= 5,011) and reports in which opioids were reported as suspected drugs (n = 150) is shown in Table 1. Female patients accounted for 31.6% of all urinary retention reports and 45.3% of opioid-related urinary retention reports. Because tramadol accounted for a large proportion of the opioid-related reports, an additional descriptive analysis was conducted in a subgroup of strong opioids, excluding tramadol and codeine. In this subgroup, female patients accounted for 46.3% (19/41), showing a similar pattern.

Older adults aged ≥ 60 years accounted for 63.5% of all urinary retention reports and 71.3% of opioid-related urinary retention reports. These findings suggest that older adults represented a large proportion of urinary retention reports regardless of opioid involvement. However, because potential confounding factors could not be fully evaluated in JADER, these descriptive findings should be interpreted with caution.

3.2. Disproportionality analysis by drug

Based on these patient characteristics, disproportionality analyses were performed for each opioid. In the primary analysis, ROR-based signals for urinary retention were detected for morphine, oxycodone, tramadol, and codeine, whereas no ROR-based signal was detected for transdermal fentanyl or hydromorphone (Table 2). The IC analysis showed consistent results, with IC_{025} values exceeding 0 for morphine (0.10), oxycodone (0.01), tramadol (2.42), and codeine (1.10), but not for transdermal fentanyl (−1.14) or hydromorphone (−0.85).

The sensitivity analysis using a broader definition that included urinary retention and dysuria is presented in Table 3. ROR-based signals were detected for all target opioids except transdermal fentanyl. Thus, no disproportionality signal for transdermal fentanyl was detected in either the primary or sensitivity analysis. These findings should be considered hypothesis-generating and require further validation in clinical studies with detailed patient-level information.

3.3. Interpretation of the findings for transdermal fentanyl

Among the opioids examined, no disproportionality signal was detected for transdermal fentanyl. This finding should be interpreted cautiously and should not be taken as evidence of no association or a lower clinical risk of urinary retention. Several pharmacological and clinical observations may be relevant to urinary dysfunction. Opioid-induced urinary retention has been attributed to μ-receptor-mediated inhibition of bladder sensory input and the micturition reflex, as well as increased bladder outlet resistance (*8*). In previous non-JADER studies, intrathecal fentanyl produced milder and shorter bladder relaxation than intrathecal morphine in dogs, and urinary retention was reported less frequently with fentanyl

Table 1. Characteristics of all urinary retention reports and opioid-related urinary retention reports in the JADER database

Factor *n*	Total UR Reports (*n* = 5,011)	Opioid-related UR (*n* = 150)	Morphine (*n* = 11)	Fentanyl (*n* = 16)	Oxycodone (*n* = 12)	Hydromorphone (*n* = 2)	Tramadol (*n* = 98)	Codeine (*n* = 11)
Sex, *n* (%)								
Male	3,171 (63.3)	80 (53.3)	6 (54.5)	11 (68.8)	4 (33.3)	1 (50)	52 (53.1)	6 (54.5)
Female	1,581 (31.6)	68 (45.3)	5 (45.5)	5 (31.3)	8 (66.7)	1 (50)	46 (46.9)	3 (27.3)
Unknown	259 (5.2)	2 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (18.2)
Age group, *n* (%)								
Older adults (≥ 60 years)	3,181 (63.5)	107 (71.3)	5 (45.5)	11 (68.8)	11 (91.7)	0 (0)	76 (77.6)	4 (36.4)
Non-elderly (< 60 years)	732 (14.6)	26 (17.3)	2 (18.2)	3 (18.8)	1 (8.3)	1 (50)	14 (14.3)	5 (45.5)
Unknown	1,098 (21.9)	17 (11.3)	4 (36.4)	2 (12.5)	0 (0)	1 (50)	9 (9.2)	2 (18.2)

Abbreviations: JADER, Japanese Adverse Drug Event Report database; UR, urinary retention. Note: Data are presented as *n* (%). Opioid-related UR was defined as UR reports in which a target opioid was reported as a suspected drug. Fentanyl refers to transdermal fentanyl.

Table 2. Disproportionality analysis of urinary retention signals associated with individual opioids in the JADER database

Drug	Suspected drug		Other drugs		ROR	95% CI	IC	IC_{025}
	a (cases)	b (non-cases)	c (cases)	d (non-cases)				
Morphine	11	1077	5000	986660	2.02	1.11–3.65	0.94	0.10
Fentanyl	16	4324	4995	983413	0.73	0.45–1.19	-0.44	-1.14
Oxycodone	12	1300	4999	986437	1.82	1.03–3.22	0.81	0.01
Hydromorphone	2	154	5009	987583	2.56	0.63–10.33	0.96	-0.85
Tramadol	98	2786	4913	984951	7.05	5.75–8.64	2.71	2.42
Codeine	11	480	5000	987257	4.53	2.49–8.25	1.95	1.10

Abbreviations: CI, confidence interval; IC, information component; IC_{025}, lower limit of the 95% credibility interval; ROR, reporting odds ratio. Note: Data are presented as a two-by-two contingency table (a, b, c, and d), ROR with 95% CI, and IC values. The definitions of a, b, c, and d are as follows: a, cases with the target adverse event associated with the suspected drug; b, non-cases associated with the suspected drug; c, cases with the target adverse event associated with other drugs; d, non-cases associated with other drugs. A signal based on the ROR was considered present when the lower limit of the 95% CI exceeded 1. A signal based on the IC was considered present when IC_{025} exceeded 0. Fentanyl refers to transdermal fentanyl.

than with morphine in patients receiving intravenous patient-controlled analgesia (IV-PCA) after gastrectomy (*9,10*). However, differences in route of administration, study population, and outcome definitions limit direct comparison with the present analysis.

3.4. Interpretation of signals for other opioids

Another notable finding was the relatively high number of reports associated with tramadol. One possible explanation is its mechanism of action. In addition to its effects on opioid receptors, tramadol inhibits the reuptake of norepinephrine and serotonin (*11*), which may influence urinary function. Similar effects have been reported for antidepressants with comparable mechanisms (*5*). Increased norepinephrine activity may promote urethral sphincter contraction, thereby increasing the risk of urinary retention.

In addition, tramadol is not classified as a narcotic in Japan and is more widely prescribed than other opioids. It is commonly used for conditions prevalent in older adults, such as osteoarthritis and chronic non-cancer pain. These patients are more likely to have comorbidities such as benign prostatic hyperplasia, as well as age-related decline in renal function. These factors may have contributed to the higher number of reported cases.

For oxycodone, a significant signal was detected. A randomized controlled trial comparing intravenous morphine and oxycodone for postoperative pain management reported similar rates of opioid-related adverse events, including urinary retention (*12*), which is consistent with the present findings. However, the confidence interval in this study was close to 1, indicating marginal significance.

Codeine showed a significant signal in the primary analysis, whereas hydromorphone showed a signal only in the sensitivity analysis. Because the number of reports for these drugs was small, the precision of these estimates may be limited, and these findings should be interpreted with caution.

3.5. Time to onset and daily dose

To further characterize opioid-related urinary retention reports, we evaluated the time to onset and daily dose at the time of event onset. Morphine, oxycodone, and tramadol were included because ROR-based signals were detected and at least 10 events were reported, whereas transdermal fentanyl was included for descriptive purposes despite the absence of a disproportionality signal (Table 4). Fentanyl dose data were not interpreted as evidence of a dose-related association with urinary retention.

Among opioids with detected signals and available dose information, the mean morphine-equivalent daily doses at onset were 35.0 mg/day for morphine, 33.2 mg/day for oxycodone, and 16.2 mg/day for tramadol. These

Table 3. Sensitivity analysis of urinary retention and dysuria signals for individual opioids in the JADER database

Drug	Suspected drug		Other drugs		ROR	95% CI
	a (cases)	b (non-cases)	c (cases)	d (non-cases)		
Morphine	12	1076	5691	985969	1.93	1.09–3.42
Fentanyl	18	4322	5685	982723	0.72	0.45–1.14
Oxycodone	16	1296	5687	985749	2.14	1.31–3.51
Hydromorphone	5	151	5698	986894	5.74	2.35–13.98
Tramadol	111	2773	5592	984272	7.05	5.82–8.53
Codeine	11	480	5692	986565	3.97	2.18–7.22

Note: Cases were reports with urinary retention or dysuria. The definitions of a, b, c, and d are the same as described in Table 2. Fentanyl refers to transdermal fentanyl.

Table 4. Time to onset and daily dose at the onset of urinary retention associated with individual opioids

Opioid	n for onset	Time to Onset, days, median[mean]	n for dose	Dose at onset, mean OME mg/day
Morphine	8	1.5 [3.5]	7	35.0
Oxycodone	9	37.0 [34.6]	5	33.2
Fentanyl	10	4.0 [48.6]	7	81.6
Tramadol	43	7.0 [48.8]	56	16.2

Note: Time to onset was calculated from the start of opioid administration to the onset of urinary retention. OME, oral morphine equivalents. Cases with missing or incomplete date or dose information were excluded. Fentanyl refers to transdermal fentanyl.

descriptive findings suggest that urinary retention may be reported even at relatively low morphine-equivalent doses. However, because the number of available cases was limited and dose information was incomplete, these results should be interpreted with caution.

3.6. Limitations

This study has several limitations inherent to analyses based on spontaneous reporting systems. First, because JADER relies on spontaneous reports, it is subject to various reporting biases, including underreporting, overreporting, missing data, channeling bias, and event-competition or masking bias. Transdermal fentanyl may have been preferentially used in patients with specific clinical backgrounds, and its large number of total reports may have diluted the ROR for urinary retention because the ROR denominator includes non-target adverse events. Therefore, the lack of a signal for transdermal fentanyl should not be interpreted as evidence of a lower clinical risk. In addition, because the total number of patients exposed to each drug is unknown, the true incidence of adverse events cannot be determined.

Second, there are limitations related to data quality. In JADER, detailed information on patients' medical history and concomitant medications is often incomplete. Urinary retention, in particular, can be influenced by factors other than the drug itself, such as cancer stage, underlying conditions including benign prostatic hyperplasia, and concomitant use of medications with anticholinergic effects. These potential confounding factors could not be fully controlled for in the present analysis. Furthermore, comparisons among individual opioids should be interpreted cautiously because differences in drug characteristics, routes of administration, indications, and patient backgrounds may have influenced the observed reporting patterns. Therefore, the observed disproportionality signals do not necessarily represent differences in the intrinsic risk of urinary retention between opioids.

Third, caution is required in interpreting the statistical measures. The ROR is an indicator of disproportionality and does not directly reflect causal relationships or absolute risk. Therefore, the findings of this study should be interpreted as hypothesis-generating rather than confirmatory. Further validation through prospective studies with more detailed clinical information is warranted.

3.7. Conclusion

This hypothesis-generating study evaluated disproportionality signals for urinary retention among individual opioids using the JADER database. Transdermal fentanyl was the only opioid for which no signal was detected, even when a broader definition including dysuria was applied. In contrast, disproportionality signals were detected for morphine, oxycodone, tramadol, and codeine. Urinary retention was reported early after treatment initiation for some opioids and at relatively low morphine-equivalent doses in cases with available dose information, highlighting the need for careful monitoring during opioid therapy.

The absence of a disproportionality signal for transdermal fentanyl may reflect a lower reporting frequency in JADER, but it does not indicate a lower clinical risk of urinary retention. Given the limitations of spontaneous reporting systems and the potential

for channeling bias and event-competition bias, these findings should be regarded as hypothesis-generating and should not be used alone to guide opioid selection or switching. Prospective comparative studies with denominator data on drug exposure are required before any clinical recommendation can be made.

Acknowledgements

The authors thank all individuals who contributed to the data collection and management of the JADER database. The authors used an AI-based language editing tool to improve the English writing of this manuscript and take full responsibility for its content.

Funding: None.

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

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Received June 11, 2026; Revised July 27, 2026; Accepted August 15, 2026.

**Address correspondence to:*
Tomoji Maeda, Department of Clinical Pharmacy, Nihon Pharmaceutical University, 10281 Komuro, Ina-machi, Saitama 362-0807, Japan.
E-mail: t-maeda@nichiyaku.ac.jp

Released online in J-STAGE as advance publication August 21, 2026.