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Opioid-Related Respiratory Depression in Non-Cancer Patients, as Reported in the Japanese Adverse Drug Event Report Database

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Background: Opioid-induced respiratory depression (RD) is a potentially life-threatening adverse drug event. This study used the Japanese Adverse Drug Event Report (JADER) database to investigate the profile of opioid-related RD in non-cancer patients.

Methods: We analyzed data recorded in the JADER database between April 2004 and February 2020, which were downloaded from the Pharmaceutical and Medical Devices Agency website. Reporting odds ratios for RD were calculated for the 20 opioids approved in Japan, and daily dose and onset time were further analyzed for opioids used in chronic non-cancer pain (CNCP).

Results: Among the opioids, RD adverse event signals were detected for 22 combinations of opioids and administration routes in non-cancer patients. Of these combinations, transdermal buprenorphine and oral tramadol/acetaminophen were approved for CNCP and tended to be reported more frequently in elderly patients. The median daily doses of transdermal buprenorphine and oral tramadol/acetaminophen were 10.0 and 22.5 mg of daily oral morphine equivalent doses, respectively, which are within the standard range for starting dosage. The median time-to-onset of transdermal buprenorphine and oral tramadol/acetaminophen was 6.5 and 4.0 days, respectively, and 75% of cases were reported within 20 to 40 days after the start of treatment. The hazard type for both opioids was classified as early failure.

Conclusions: Our findings suggest that elderly CNCP patients should be closely monitored after the start of opioid treatment, especially during the first week and, if possible, for 1 month, even if starting doses are within ranges recommended by the manufacturer and guidelines.

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Key words: opioid, non-cancer patients, respiratory depression, Japanese Adverse Drug Event Report database, time-to-onset analysis

Introduction

Although opioid analgesics play an important role in the treatment of moderate to severe acute and chronic cancer and non-cancer pain, they are associated with adverse

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drug effects (ADEs) such as nausea, vomiting, constipation, sedation, and respiratory depression (RD). Opioid-induced RD, which is caused by opioid overdose or misuse, can be potentially fatal; thus, for safe opioid prescribing, careful titration of opioid dosages and continuous monitoring are required[1].

The current opioid epidemic is one of the most severe public health crises in the United States and other high-income countries, including Australia, Canada, and the United Kingdom[2–5]. In these countries, availability and use of opioids for cancer and chronic non-cancer pain (CNCP) has increased dramatically in the past few decades. Unfortunately, the increased availability of opioids has generated an enormous surplus of medication that was diverted for non-medical use[2]. Escalation of such opioid use for chronic pain and other conditions has led to serious health risks, including opioid-related RD and overdose deaths[1,3,5]. In Japan, deaths from opioid analgesic overdoses have not increased and are rarely reported[6].

CNCP is typically described as moderate or severe pain that persists for at least 6 months and is attributed to conditions such as neuropathic pain, rheumatoid arthritis, lower back pain, osteoarthritis, fibromyalgia, and a range of other conditions[5]. As summarized in the guidelines for prescribing opioid analgesics for CNCP edited by the Japan Society of Pain Clinicians, the objectives of treatment with opioid analgesics for CNCP are to relieve patients' pain without worsening quality of life from ADEs, and to improve the decrease in quality of life caused by pain[7].

In Japan, several formulations of opioids (transdermal buprenorphine, transdermal fentanyl, oral oxycodone, oral tramadol, and oral tramadol/acetaminophen) were approved for CNCP after 2010. Only doctors who have received e-learning and are approved can prescribe transdermal buprenorphine, transdermal fentanyl, and oral oxycodone. Although treatment with opioid analgesics has become more common, it may lead to an increase in the incidence of opioid-related RD and overdose. To our knowledge, there are no nationwide studies on reported opioid-related RD in non-cancer patients in Japan, especially CNCP patients.

In the present study, we used the Japanese Adverse Drug Event Report (JADER) database to investigate opioid-related RD in non-cancer patients in Japan. The JADER database, published by the Pharmaceutical and Medical Devices Agency, is a large spontaneous reporting system (SRS) that reflects the realities of clinical practice in Japan. Reporting odds ratios (ROR) in the JADER database are often used for pharmacovigilance assessment of ADEs[8–11]. Previously, we used the JADER database to analyse opioid-related RD in cancer patients[12]. In this study, we extend the analysis to non-cancer patients to obtain data to promote proper use of opioids for CNCP.

Materials and Methods

Data Source

Data recorded in the JADER database between April 2004 and February 2020 were obtained from the Pharmaceutical and Medical Devices Agency website (http://www.pmda.go.jp). The database consists of four data tables: patient demographic information (demo; n = 637,354 patients), drug information (drug; n = 3,664,828 pieces), ADEs (reac; n = 1,006,760 pieces), and primary disease (hist; n = 1,282,426 pieces). In each case, the contribution of prescribed medications to ADEs was classified into three categories: "suspected drug", "concomitant drug", and "interaction". Concomitant drugs were those for which the direct causal relationship with the ADE was unknown, and interaction was used to describe drugs that were affected by other drugs and for which the sole causal relationship was unknown. Therefore, we only extracted cases that were classified as a suspected drug from the "drug" table. Furthermore, we combined drug name data with route of administration data. In route of administration data, "subarachnoid" was included within "intrathecal", "intravenous (if not specified)" was included within "intravenous", and cases for which multiple routes were reported, or for which the route of administration was unknown, were included as "other". We eliminated duplicate data for each case in the "drug" and "reac" tables and combined them. The "demo" table was then joined to the combined table by using the ID number of each case for adverse event signal analysis.

In analysing the association with age, we extracted only cases of RD from the above combined data table. In addition, using age information classified by decade in the "demo" table, we defined "younger patients" as those described as "under 10," "10s," "20s," "30s," "40s," "50s," and "60s," and "elderly patients" as those in their "70s," "80s," "90s," and "100s." Cases reported as "adolescent," "adult," "elderly," "foetal," "infant," "newborn," "paediatric," "third trimester," and "unknown" were excluded from the analysis because their exact age was unknown.

As of February 2020, the drugs selected for this investigation were the 20 opioids approved in Japan (**Table 1**).

Table 1 Indications for Opioid Analgesics

Opioid	Dosage form	Indication		
		Chronic non-cancer pain	Cancer pain	Other
Buprenorphine	Injection, suppository	−	+	+
	Patch	+	−	−
Codeine	Powder, tablet	−	−	+
Dihydrocodeine	Powder	−	−	+
Eptazocine	Injection	−	+	+
Fentanyl	Injection	−	+	+
	Patch	+	+	−
	Transmucosal tablet, sublingual tablet	−	+	−
Fentanyl/droperidol	Injection	−	−	+
Hydromorphone	Injection, tablet, tablet (LA)	−	+	−
Methadone	Tablet	−	+	−
Morphine	Powder, tablet	−	−	+
	Injection	−	+	+
	Capsule (LA), powder (LA), solution, suppository, tablet (LA)	−	+	−
Opium	Powder, solution	−	−	+
Opium alkaloid	Injection, powder	−	−	+
Opium/ipecac	Powder	−	−	+
Oxycodone	Capsule (LA), injection, tablet, tablet (LA), powder	–*	+	−
Pentazocine	Injection	−	+	+
	Tablet	−	+	−
Pethidine	Injection	−	−	+
Pethidine/levallorphan	Injection	−	−	+
Remifentanil	Injection	−	−	+
Tapentadol	Tablet	−	+	−
Tramadol	Injection	−	+	+
	Tablet (LA), tablet	+	+	−
Tramadol/acetaminophen	Tablet	+	−	+

LA: long-acting. *: Oxycodone tablet approved for chronic non-cancer pain in October 2020.

The tamper-resistant formulation of oxycodone tablets was approved for CNCP in October 2020 in Japan; however, in the present study, we only included oxycodone as an indication for cancer pain, as the database only contains cases reported until February 2020.

Definition of RD

The ADEs in the "reac" table are coded according to preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA). The Standardized MedDRA Queries index consists of groupings of MedDRA terms, ordinarily at the PT level, that relate to a defined medical condition or area of interest. Ninety-six PTs were determined from the Standardized MedDRA Queries for acute central RD in the MedDRA (Ver. 23.0J) to detect RD.

Definition of Non-Cancer Patients

The primary diseases in the "hist" table were also based on PTs in the MedDRA. Cases with a primary disease not consistent with cancer-related PT were treated as non-cancer patients. From the following 10 Standardized MedDRA Queries in MedDRA (Ver. 23.0J), 1,692 PTs were determined after removing duplicated data to detect cancer patients: malignancy-related conditions, tumour markers, breast malignant tumours, ovarian malignant tumours, prostate malignant tumours, skin malignant tumours, uterine and fallopian tube malignant tumours, malignant lymphomas, haematological malignant tumours, and non-haematological malignant tumours, including gastric, colorectal, lung, and hepatic cancers. In addition, the "reason for use" data in the "drug" table were also checked, and cases that matched these PTs and those that included "cancer" or "malignancy" but not "prophylaxis" were defined as cancer patients and excluded.

Analysis of Daily Dose and Time-to-Onset

To analyse daily dose and time-to-onset, RD cases of non-cancer patients were extracted from the "reac" and "hist" tables and the data were combined. In addition, suspect drugs were extracted from the "drug" table and

joined with the combined data using ID numbers. Exclusion criteria were an unknown date of development of ADEs, when the year and month were indicated but the day was not, when only the year was indicated, when RD occurred in the daily dose analysis, cases with unknown dosages, and onset time more than 2 days after the latest administration day. Opioid doses were converted to the daily oral morphine equivalent such that oral tramadol/acetaminophen 37.5 mg (as tramadol) and transdermal buprenorphine 0.12 mg were converted to daily oral morphine equivalents of 7.5 mg and 10 mg, respectively. Daily morphine equivalents were calculated according to equianalgesic ratios recommended by the Australian and New Zealand College of Anesthetists[13]. For time-to-onset analysis, onset time was calculated by adding 1 to the time of the patient's first ADE appearance after the start of administration. We defined an onset time longer than 1 year as 365 days. Furthermore, cases with an unknown date of administration initiation were excluded.

Statistical Analysis

The adverse event signal index, ROR, was calculated by using the equation ROR = (a/b)/(c/d) = ad/bc, where a, b, c, and d were defined by cross-tabulation as: a: number of cases with an ADE after using the suspected drug, b: number of cases with all other ADEs after using the suspected drug, c: number of cases with an ADE after using all other drugs, and d: number of cases with all other ADEs after using all other drugs. Furthermore, we used Haldane-Anscombe 1/2 correction to correct for bias, as it is not possible to calculate ROR values from a cross-tabulation that contains zero in the columns[11].

Adverse event signals are considered significant when ROR estimates and the lower limits of the corresponding 95% confidence interval (CI) exceed 1. At least two cases are required to define a signal[14,15].

Time-to-onset duration of the data from the JADER database was calculated from the time of the patient's first prescription to the occurrence of ADEs. The median duration, quartiles, and Weibull shape parameters were used to evaluate the dates from administration to development of RD. The Weibull shape parameter test is used for statistical analysis of time-to-onset data and can describe a non-constant rate of ADE incidence[8,9,12]. In brief, the shape parameter β of the Weibull distribution indicates the hazard without a reference population. When β is equal to 1, the hazard is estimated to be constant over time. When β is greater than 1 and the 95% CI of β excludes 1, the hazard is considered to increase over time. When β is smaller than 1 and the 95% CI of β excludes 1, the hazard is considered to decrease over time. Data analyses were performed using JMP Pro 16. 0.0 (SAS Institute Inc., Cary, NC, USA).

The daily doses at the first appearance of an ADE were compared using the nonparametric Wilcoxon rank sum test between opioids. A p-value of < 0.05 was considered significant.

Results

Number of Reports and ROR for Opioid-Related RD in Non-Cancer Patients

Among 1,639,417 cases, 1,883 suspected drugs with administration routes were reported for RD in non-cancer patients. Among 20 opioids, 12 opioids were reported for RD in non-cancer patients. Among these opioids, 22 combinations of opioid and administration route were included for two or more reported cases and detected for a signal calculated using the ROR method (**Table 2**). Two or more cases of RD were reported for oral morphine and oral tramadol, but these opioids did not meet the criteria for signal detection. Buprenorphine (cutaneous, epidural, occlusive dressing technique, and parenteral), eptazocine (intramuscular), fentanyl (injection, sublingual, and endotracheal), hydromorphone (oral), morphine (intraarticular, periarticular, parenteral, and subcutaneous), opium (oral), oxycodone (intravenous and oral), pentazocine (subcutaneous), pethidine (intramuscular, parenteral, and subcutaneous), pethidine/levallorphan (intravenous and subcutaneous), remifentanil (injection, nasal, transplacental, and endotracheal), tapentadol (oral), and tramadol/acetaminophen (inhalation) were not reported for RD. Furthermore, fentanyl/droperidol, methadone, opium alkaloid, and opium/ipecac were not reported for any ADEs in the non-cancer patients.

Furthermore, we analysed 23,080 cases of RD (8,612 elderly patients and 14,468 younger patients) and found that the ROR and lower limit of the 95% CI exceeded 1 for only three formulations: transdermal buprenorphine, intravenous pethidine, and oral tramadol/acetaminophen (**Table 3**).

Daily Dose of Opioids for CNCP at the First Appearance of RD

A daily dose analysis of transdermal buprenorphine and oral tramadol/acetaminophen, which are not regulated as narcotics in Japan and have been approved for CNCP since 2011, was conducted in non-cancer patients (**Fig. 1**). The median daily doses at the first appearance

Table 2 Number of Reports and RORs of Respiratory Depression Associated with Opioids in Non-cancer Patients

Opioid	Administration route	a	b	c	d	ROR	95%CI
Buprenorphine	Cutaneous	0	1	24,815	1,614,601	21.69	0.88-532.40
	Epidural	0	10	24,815	1,614,592	3.10	0.18-52.87
	Intramuscular	2	15	24,813	1,614,587	10.49†	2.76-39.92
	Intravenous	10	75	24,805	1,614,527	9.05†	4.75-17.26
	Occlusive dressing technique	0	1	24,815	1,614,601	21.69	0.88-532.40
	Parenteral	0	2	24,815	1,614,600	13.01	0.62-271.06
	Rectal	1	59	24,814	1,614,543	1.64	0.32-8.29
	Transdermal	23	488	24,792	1,614,114	3.13†	2.07-4.74
	Other	3	46	24,812	1,614,556	4.90†	1.65-14.52
Codeine	Oral	7	196	24,808	1,614,406	2.48†	1.20-5.15
	Other	1	18	24,814	1,614,584	5.28	0.10-27.86
Dihydrocodeine	Oral	2	11	24,813	1,614,591	14.15†	3.60-55.54
	Other	0	5	24,815	1,614,597	5.91	0.33-106.97
Eptazocine	Intramuscular	0	3	24,815	1,614,599	9.29	0.48-179.95
Fentanyl	Epidural	11	52	24,804	1,614,550	14.26†	7.53-26.99
	Intradiscal	1	15	24,814	1,614,587	6.30	1.18-33.65
	Injection	0	1	24,815	1,614,601	21.69	0.88-532.40
	Intrathecal	5	8	24,810	1,614,594	42.11†	14.41-123.09
	Intravenous	82	644	24,733	1,613,958	8.35†	6.64-10.51
	Parenteral	1	16	24,814	1,614,586	5.92	1.11-31.47
	Oral	1	1	24,814	1,614,601	65.07	6.77-625.54
	Subcutaneous	1	3	24,814	1,614,599	27.89	4.12-188.84
	Sublingual	0	4	24,815	1,614,598	7.23	0.39-134.28
	Transdermal	26	472	24,789	1,614,130	3.65†	2.47-5.40
	Topical	1	7	24,814	1,614,595	13.01	2.25-75.12
	Transplacental	4	9	24,811	1,614,593	30.82†	10.04-94.63
	Endotracheal	0	5	24,815	1,614,597	5.91	0.33-106.97
	Other	63	351	24,752	1,614,251	11.78†	9.02-15.40
Hydromorphone	Oral	0	5	24,815	1,614,597	5.91	0.33-106.97
Morphine	Epidural	3	8	24,812	1,614,594	26.79†	7.72-93.04
	Intradiscal	1	3	24,814	1,614,599	27.89	4.12-188.84
	Intramuscular	3	9	24,812	1,614,593	23.97†	7.04-81.66
	intraarticular	0	1	24,815	1,614,601	21.69	0.88-532.40
	Intrathecal	2	1	24,813	1,614,601	108.45†	14.32-821.03
	Intravenous	4	55	24,811	1,614,547	5.28†	2.02-13.79
	Periarticular	0	1	24,815	1,614,601	21.69	0.88-532.40
	Parenteral	0	1	24,815	1,614,601	21.69	0.88-532.40
	Oral	2	79	24,813	1,614,523	2.05	0.58-7.21
	Subcutaneous	0	4	24,815	1,614,598	7.23	0.39-134.28
	Other	6	64	24,809	1,614,538	6.56†	2.93-14.69
Opium	Oral	0	1	24,815	1,614,601	21.69	0.88-532.40
Oxycodone	Intravenous	0	3	24,815	1,614,599	9.29	0.48-179.95
	Oral	0	36	24,815	1,614,566	0.89	0.05-14.52
	Other	1	12	24,814	1,614,590	7.81	1.44-42.47
Pentazocine	Intramuscular	8	76	24,807	1,614,526	7.23†	3.56-14.69
	Intravenous	16	165	24,799	1,614,437	6.49†	3.91-10.77
	Parenteral	1	1	24,814	1,614,601	65.07	6.77-625.54
	Oral	2	23	24,813	1,614,579	6.92†	1.88-25.50
	Subcutaneous	0	3	24,815	1,614,599	9.29	0.48-179.95
	Transplacental	5	4	24,810	1,614,598	79.54†	22.88-276.48
	Other	10	65	24,805	1,614,537	10.43†	5.44-20.02

Table 2 Number of Reports and RORs of Respiratory Depression Associated with Opioids in Non-cancer Patients (continued)

Opioid	Administration route	a	b	c	d	ROR	95%CI
Pethidine	Intramuscular	0	1	24,815	1,614,601	21.69	0.88-532.40
	Intravenous	24	58	24,791	1,614,544	27.27†	17.02-43.72
	Parenteral	0	1	24,815	1,614,601	21.69	0.88-532.40
	Subcutaneous	0	2	24,815	1,614,600	13.01	0.62-271.06
	Other	1	6	24,814	1,614,596	15.02	2.54-88.63
Pethidine/levallorphan	Intramuscular	1	2	24,814	1,614,600	39.04	5.16-295.56
	Intravenous	0	1	24,815	1,614,601	21.69	0.88-532.40
	Subcutaneous	0	2	24,815	1,614,600	13.01	0.62-271.06
Remifentanil	Epidural	3	11	24,812	1,614,591	19.80†	5.99-65.53
	Injection	0	1	24,815	1,614,601	21.69	0.88-532.40
	Intravenous	147	767	24,668	1,613,835	12.57†	10.54-15.00
	Nasal	0	2	24,815	1,614,600	13.01	0.62-271.06
	Parenteral	1	9	24,814	1,614,593	10.27	1.84-57.49
	Subcutaneous	1	1	24,814	1,614,601	65.07	6.77-625.54
	Transplacental	0	4	24,815	1,614,598	7.23	0.39-134.28
	Endotracheal	0	5	24,815	1,614,597	5.91	0.33-106.97
	Other	21	147	24,794	1,614,455	9.49†	6.04-14.92
Tapentadol	Oral	0	5	24,815	1,614,597	5.91	0.33-106.97
Tramadol	Oral	5	582	24,810	1,614,020	0.61	0.27-1.42
	Other	0	83	24,815	1,614,519	0.39	0.02-6.28
Tramadol/acetaminophen	Inhalation	0	3	24,815	1,614,599	9.29	0.48-179.95
	Oral	43	2,026	24,772	1,612,576	1.40†	1.03-1.89
	Other	2	95	24,813	1,614,507	1.70	0.49-5.98

a: respiratory depression (RD) by each opioid, b: other adverse drug events (ADEs) by each opioid, c: RD by other drugs, d: other ADEs by other drugs. ROR: reporting odds ratio. 95%CI: 95% confidence interval. †: met the criteria for signal detection (95%CI > 1 and a ≥ 2).

of RD for transdermal buprenorphine (n = 14) and oral tramadol/acetaminophen (n = 25) were 10.0 mg (interquartile range [IQR] 10.0 to 20.0 mg) and 22.5 mg (IQR 15.0 to 30.0 mg) in daily oral morphine equivalents, respectively. Although there were significant differences between these median values, they were all within the standard starting dose range and were not considered clinically significant. Transdermal fentanyl, which is regulated as a narcotic, has also been approved for CNCP since 2010, but no cases were available for analysis of the daily dose at onset, although a signal was detected.

Time-to-Onset of RD Associated with Opioid Treatment for CNCP

A histogram of time-to-onset in cases of RD between 0 to 365 days is shown in **Figure 2**. The median time-to-onset of transdermal buprenorphine (n = 14) and oral tramadol/acetaminophen (n = 24) was 6.5 days (IQR 2.0 to 16.8 days) and 4.0 days (IQR 2.0 to 37.5 days). The time-to-onset of RD associated with opioids was profiled using the Weibull distribution, and the parameters are summarized in **Table 4**. The β values of transdermal buprenorphine and oral tramadol/acetaminophen were <1, namely, 0.55 (95% CI: 0.36 to 0.76) and 0.45 (95% CI: 0.33 to 0.60), suggesting that time-to-onset of RD was the early failure type. There were no cases of transdermal fentanyl available for analysis in the time-to-onset analysis.

Discussion

In the present study, adverse event signals of RD were detected for 22 combinations of opioid and administration route in non-cancer patients. Of these combinations, transdermal buprenorphine, transdermal fentanyl, and oral tramadol/acetaminophen are opioid analgesics that have been approved for CNCP in Japan. Since these opioid analgesics are prescribed to inpatients and outpatients and may be self-administered by patients, patient education to prevent overdose is important. Furthermore, our study revealed that transdermal buprenorphine and oral tramadol/acetaminophen tended to be reported more frequently in elderly patients with respiratory depression, suggesting continued vigilance is needed to assess the use of these opioid analgesics and the risk of RD. Signals were also detected for codeine (oral), dihy-

Table 3 Number of Reports and RORs of Respiratory Depression Associated with Opioids in Elderly Non-cancer Patients

Opioid	Administration route	a	b	c	d	ROR	95%CI
Buprenorphine	Intramuscular	1	1	8,611	14,467	1.68	0.17-16.15
	Intravenous	4	6	8,608	14,462	1.16	0.35-3.87
	Rectal	0	1	8,612	14,467	0.56	0.02-13.75
	Transdermal	14	6	8,598	14,462	3.75†	1.49-9.47
	Other	1	1	8,611	14,467	1.68	0.17-16.15
Codeine	Oral	3	4	8,609	14,464	1.31	0.32-5.28
	Other	0	1	8,612	14,467	0.56	0.02-13.75
Dihydrocodeine	Oral	0	2	8,612	14,466	0.34	0.02-7.00
Fentanyl	Epidural	5	6	8,607	14,462	1.42	0.46-4.43
	Intradiscal	0	1	8,612	14,467	0.56	0.02-13.75
	Intrathecal	0	5	8,612	14,463	0.15	0.01-2.76
	Intravenous	26	55	8,586	14,413	0.80	0.50-1.27
	Oral	0	1	8,612	14,467	0.56	0.02-13.75
	Parenteral	0	1	8,612	14,467	0.56	0.02-13.75
	Subcutaneous	0	1	8,612	14,467	0.56	0.02-13.75
	Topical	0	1	8,612	14,467	0.56	0.02-13.75
	Transdermal	11	13	8,601	14,455	1.43	0.65-3.14
	Transplacental	0	4	8,612	14,464	0.19	0.01-3.47
	Other	17	35	8,595	14,433	0.83	0.47-1.47
Morphine	Epidural	2	1	8,610	14,467	2.80	0.37-21.20
	Intradiscal	0	1	8,612	14,467	0.56	0.02-13.75
	Intramuscular	3	0	8,609	14,468	11.76	0.61-227.77
	Intrathecal	0	2	8,612	14,466	0.34	0.02-7.00
	Intravenous	0	4	8,612	14,464	0.19	0.01-3.47
	Oral	0	2	8,612	14,466	0.34	0.02-7.00
	Other	0	5	8,612	14,463	0.15	0.01-2.76
Pentazocine	Intramuscular	5	3	8,607	14,465	2.64	0.69-10.09
	Intravenous	5	10	8,607	14,458	0.88	0.31-2.47
	Oral	1	0	8,611	14,468	5.04	0.21-123.74
	Parenteral	0	1	8,612	14,467	0.56	0.02-13.75
	Transplacental	0	2	8,612	14,466	0.34	0.02-7.00
	Other	1	9	8,611	14,459	0.27	0.05-1.48
Pethidine	Intravenous	20	4	8,592	14,464	7.67†	2.76-21.28
	Other	1	0	8,611	14,468	5.04	0.21-123.74
Pethidine/levallorphan	Intramuscular	0	1	8,612	14,467	0.56	0.02-13.75
Remifentanil	Epidural	0	3	8,612	14,465	0.24	0.01-4.65
	Intravenous	33	107	8,579	14,361	0.52	0.35-0.77
	Parenteral	0	1	8,612	14,467	0.56	0.02-13.75
	Subcutaneous	0	1	8,612	14,467	0.56	0.02-13.75
	Other	5	15	8,607	14,453	0.60	0.23-1.58
Tramadol	Oral	2	3	8,610	14,465	1.20	0.24-6.08
Tramadol/acetaminophen	Oral	28	14	8,584	14,454	3.31†	1.76-6.23
	Other	2	0	8,610	14,468	8.40	0.40-175.02

ROR = (a: number of reports of respiratory depression (RD) with the medicines in elderly patients) (d: number of reports of RD with all other medicines in younger patients) / (b: number of reports of RD with the medicines in younger patients) (c: number of reports of RD with all other medicines in elderly patients). ROR: reporting odds ratio. 95%CI: 95% confidence interval. †: met criteria for signal detection (95%CI > 1 and a ≥ 2).

drocodeine (oral), fentanyl (epidural, intrathecal, and intravenous), buprenorphine (intramuscular and intravenous), pethidine (intravenous), pentazocine (intramuscular and intravenous), morphine (epidural, intramuscular, intrathecal, and intravenous), and remifentanil (epidural and intravenous), which are conventional opioid analge-

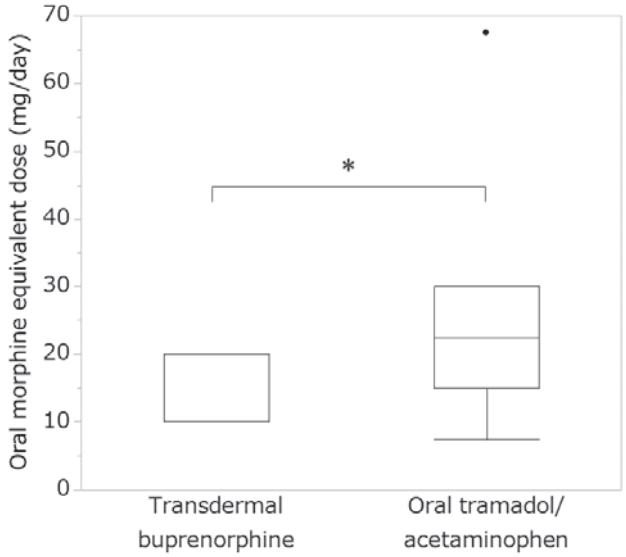

Fig. 1 Box Plot of Daily Dose for Opioids used in CNCP
Transdermal buprenorphine (n = 14) and oral tramadol/acetaminophen (n = 25) in non-cancer patients. The Y-axis represents the dose for each opioid as the daily oral morphine equivalent dose. Box plots represent the median (the horizontal line within the box), 25th, and 75th quantiles. The whiskers extend to the outermost data point that falls within the distances of 1.5 times the length of the inner quartiles. *: $p < 0.05$. Nonparametric Wilcoxon rank sum test is used.

sics used for antitussive, perioperative, and acute pain. Driver et al.[16] reported that postoperative respiratory depressive episodes are common and often multiple, making perioperative monitoring for ADEs important. Furthermore, signals were detected for fentanyl and pentazocine in the transplacental route of administration (e.g., indirect exposure to the foetus through the placenta by a drug administered to the parent in labour). Fentanyl and pentazocine are lipid-soluble drugs and are permeable to the placenta. In contrast, no signals were detected for opioid analgesics and routes of administration for non-cancer patients other than those listed above, but signal detection in the SRS may depend on the frequency of clinical use related to each indication and guideline recommendations; thus, these should be interpreted carefully.

We also intended to analyse the dosage and timing of onset of RD for transdermal buprenorphine, transdermal fentanyl, and oral tramadol/acetaminophen, which are indicated for CNCP. However, data on the dose and timing of onset of RD for transdermal fentanyl were missing and could not be analysed. This is a limitation of the SRS.

In the CDC guideline for prescribing opioids for chronic pain, Dowell et al.[17] reported that opioid-related overdose risks are dose-dependent: higher opioid doses are associated with greater overdose risk. The Japan Society of Pain Clinicians guidelines recommend that the dose of opioid analgesics for CNCP should be less than a daily morphine equivalent of 60 mg, and it is strongly recommended that the maximum dose should be a daily morphine equivalent of 90 mg[7]. However, in our study, the median daily doses of transdermal buprenorphine and oral tramadol/acetaminophen were within the standard ranges, and our results suggest that even low doses of opioids can be responsible for the risk of RD. Several studies report that a daily morphine equivalent of less than 50 mg may cause life-threatening respiratory or central nervous system depression[18] in patients with hepatic or renal impairment and in those concomitantly using central nervous system depressants such as benzodiazepines, antidepressants, and alcohol[19]. Our findings suggest that attention to RD is necessary even if opioid doses are within dose ranges recommended by the manufacturer or guidelines. Further investigation is needed to confirm associations with hepatic and renal dysfunction and concomitant medications in cases of RD at such low doses.

Previously, using the JADER database, we reported the onset profiles of opioid-related RD in cancer patients[12]. As was the case for oral morphine and transdermal fentanyl in cancer patients, transdermal buprenorphine and oral tramadol/acetaminophen exhibited early failure in non-cancer patients. Because opioids depress ventilation through their direct action on μ-opioid receptors expressed in the brainstem respiratory centers[20,21], opioid overdose can cause RD immediately after administration. Young et al.[22] reported that opioid-nontolerant patients had a 37% increased risk of being diagnosed with opioid poisoning in the first 7 days after initiation. In the present study, reporting peaks were within 10 days, and 75% of cases were reported within 20 to 40 days after the start of administration. These results suggest that patients need to be carefully monitored for opioid-related RD for at least 1 week after the start of administration. However, because of the small numbers of cases in the present study, it is necessary to collect further cases and analyse their onset profiles.

The present study had several limitations. First, we classified cases with a primary disease that did not match cancer-related PT as non-cancer patients, but further stratification by disease related to CNCP would be

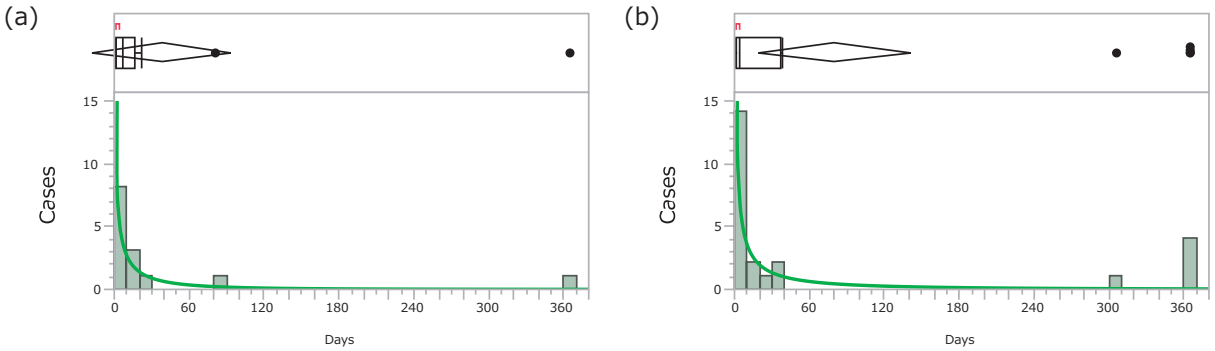

Fig. 2 Histogram and Weibull Shape Parameter of Respiratory Depression for Opioids used in CNCP
(a) Transdermal buprenorphine (n = 14, β = 0.55, 95% CI: 0.36-0.76), (b) oral tramadol/acetaminophen (n = 24, β = 0.45, 95% CI: 0.33-0.60) in non-cancer patients. Upper panel shows box plots, which represent the median (the horizontal line within the box), 25th, and 75th quantiles. The whiskers extend to the outermost data point that falls within the distances of 1.5 times the length of the inner quartiles. The confidence diamond contains the mean and the upper and lower 95% of the mean. The bracket outside of the box indentifies the shortest half, which is the densest 50% of all data.

Table 4 Median, Quartile, and Parameters of the Weibull Distribution and Failure Pattern for Opioids used in CNCP

Drug	Case reports	Median (day)	Lower quartile (day)	Upper quartile (day)	Minimum (day)	Maximum (day)	Scale parameter			Shape parameter		
							α	95%CI		β	95%CI	
Transdermal Buprenorphine	14	6.5	2.0	16.8	1.0	365.0	17.84	5.90	50.86	0.55	0.36	0.76
Oral Tramadol/acetaminophen	24	4.0	2.0	37.5	1.0	365.0	30.05	11.02	77.53	0.45	0.33	0.60

95%CI: 95% confidence interval.

necessary. Next, we analysed the dose and timing of onset of opioid-related RD, but caution should be exercised in interpreting the results. For example, reports from pain clinics and palliative care specialists might be rare and biased toward reports of mild cases occurring early at low doses from non-specialized health care providers. Furthermore, SRS, such as the JADER database, are subject to various biases, including over-reporting, under-reporting, missing data, exclusion of healthy individuals, lack of a denominator, and confounding factors such as concomitant medications and comorbidities[8–12]. Because of these limitations, disproportionality measures, such as ROR, do not allow for risk quantification. ROR provides a rough indication of signal strength and is only relevant to the hypothesis. Therefore, careful attention must be paid to the interpretation of the results from the JADER database. Considering the causality restraints of the present analysis, further validation by more robust epidemiological studies is needed.

In conclusion, this study is the first to use the JADER database to investigate the profiles of opioid-related RD in non-cancer patients. Adverse event signals of opioid-related RD were detected for 22 combinations of opioid/administration route in non-cancer patients. RD signals were detected in opioid analgesics recently approved for CNCP (transdermal buprenorphine, transdermal fentanyl, and oral tramadol/acetaminophen), in addition to conventional opioid analgesics used in the perioperative period and elsewhere, with transdermal buprenorphine and oral tramadol/acetaminophen tending to be reported more frequently in elderly patients. The daily doses of transdermal buprenorphine and oral tramadol/acetaminophen that were related to RD were within the standard ranges for starting doses and occurred relatively soon after the start of administration. Our results suggest that it is important to carefully monitor patients after the start of opioid treatment, especially during the first week and, if possible, for 1 month, even if opioid doses are consistent with doses recommended by the manufacturer and guidelines.

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