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ORIGINAL RESEARCH

A Survey of the Incidence of Constipation in Patients with Chronic Non-cancer Pain Using Opioid Analgesics in Japan

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ABSTRACT

Introduction: Although opioids have potent analgesic properties, their use is associated with side effects, including opioid-induced constipation (OIC). This study investigated the incidence of OIC based on the Rome IV diagnostic criteria in patients using opioid analgesics for chronic non-cancer pain and to explore and compare the risk factors for the development of OIC in opioid analgesic users.

Methods: We surveyed patients aged 20 years or more living in Japan via the internet; who had been using opioid or non-opioid analgesics (N = 500 each) for at least 3 months for relief from chronic non-cancer musculoskeletal pain (low back pain or osteoarthritis); and who provided electronic consent to participate in and complete the survey. The groups were matched for age and sex.

Results: Of the patients using opioid analgesics, 89% were taking weak opioids. The proportion of patients perceiving constipation was comparable between the opioid and non-opioid analgesic groups (34% vs 29%, respectively); however, a significantly higher proportion of patients in the opioid group, compared to the non-opioid group, reported self-assessed constipation (40% vs 18%, respectively) after using an analgesic and fulfilled two or more symptoms of the Rome IV diagnostic criteria for constipation (28% vs 19%, respectively). A higher proportion of patients were taking prescribed medicine for constipation in the opioid group compared with the non-opioid group (33% vs 18%, respectively). Low back pain, but not opioid strength and scheduled dosing, was identified as a risk factor for OIC among various covariates assessed in the logistic regression analysis in 81 patients with OIC and Rome IV diagnosis vs 419 patients without OIC in the opioid group.

Conclusion: Use of opioid analgesics, including weak opioids, for treating chronic non-cancer musculoskeletal pain is associated with OIC. This finding highlights the need for appropriate treatment of constipation in patients with chronic non-cancer pain in Japan.

Trial Registration: UMIN000043985.

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Keywords: Analgesics; Constipation; Non-cancer; Chronic musculoskeletal pain; Weak opioids; Survey; Japan

Key Summary Points

To the best of our knowledge, this is the first study to investigate the incidence of OIC based on the Rome IV diagnostic criteria in patients who were primarily using weak opioid analgesics in a setting mirroring routine clinical practice.

Use of opioid analgesics for treating chronic non-cancer musculoskeletal pain was associated with OIC.

Furthermore, low back pain was identified as a risk factor for OIC among various covariates assessed in the logistic regression analysis in patients with OIC and Rome IV diagnosis vs patients without OIC.

The findings highlight the need for appropriate treatment of constipation along with chronic non-cancer pain during opioid therapy in Japan.

INTRODUCTION

Opioids have been the mainstay of cancer pain therapy for years [1]. Despite being originally developed for cancer pain, the use of opioids has also been extended to chronic non-cancer pain [2]. Opioids are potent analgesics but are associated with adverse effects, including physical dependence, sedation, gastrointestinal side effects and respiratory depression [3]. Gastrointestinal side effects are collectively referred to as opioid-induced bowel dysfunction (OIBD), which is characterized by dry mouth, increased gastric reflux, bloating, abdominal distension, hard and dry stools and incomplete defecation [3]. The most common symptom of OIBD is opioid-induced constipation (OIC) [3]. Opioids bind to the μ-opioid receptors in the enteric system, causing OIC [4]. Additionally, opioids block peristalsis of the fibre-increased bulk, which worsens abdominal pain and, in some cases, contributes to bowel obstruction [4]. OIC is a persistent condition [5]: it can negatively impact pain management [6, 7] and patient's health-related quality of life (QOL) [3, 8, 9] and can increase healthcare resource utilization [6]. The prevalence of OIC increases with increase in the duration of opioid treatment [10].

Weak opioids, such as codeine and tramadol, are mainly used in patients with chronic non-cancer pain in Japan [11]. Tramadol has non-opioid-mediated effects through modulation of serotonin and norepinephrine transmission [12]. Codeine, tramadol, tramadol/acetaminophen combination, transdermal formulation of buprenorphine, morphine, tamper-resistant controlled-release oxycodone and transdermal formulation of fentanyl are covered by healthcare insurance for the management of non-cancer pain in Japan. While the incidence of OIC in patients treated with opioids to alleviate cancer pain in Japan is documented [13], data on OIC in patients without cancer are lacking. Moreover, the overall incidence of constipation (based on the Rome IV diagnostic criteria used for OIC [14]), the QOL associated with constipation, risk factors and treatment of OIC in settings reflective of routine clinical practice in this patient population are inadequately studied. The objective of this study was to compare the incidence of constipation and bowel habits in patients using opioid analgesics vs those using non-opioid analgesics for chronic non-cancer pain, especially chronic musculoskeletal pain which is the most prevalent type of chronic pain [15], and to assess the risk factors for the development of OIC in opioid analgesic users.

METHODS

Study Population

An email requesting participation in an online preliminary survey on medication use was sent to potential research subjects registered in the Rakuten Insight Disease Panel, which included patients with intervertebral disc herniation, low

back pain, osteoarthritis and knee osteoarthritis. Patients responding to the survey were classified as those using opioid or non-opioid analgesics.

Patients who met the inclusion criteria in the preliminary survey were requested to complete a self-administered electronic survey form only once. In summary, patients aged 20 years or more and living in Japan; those who had been using opioid analgesics (strong or weak) or non-opioid analgesics for at least 3 months for relief from chronic pain; and those who provided electronic consent to participate in the survey and answered all survey questions were included in the study. Patients with a diagnosis of cancers or tumours were excluded.

Study Design

Rakuten Insights sent emails requesting participation and reported the results of data aggregation and analysis to Shionogi & Co., Ltd. in a deidentified manner. Endpoints assessed included the following: (1) proportion of patients who perceive a change in bowel habits and develop constipation after the use of their currently prescribed analgesics, (2) proportion of patients who have symptoms of constipation according to the Rome IV diagnostic criteria [14], (3) patients with OIC who fulfilled two or more symptoms of constipation according to the Rome IV diagnosis criteria with a change in defecation pattern after initiating opioid analgesic therapy and (4) mean scores on the four subscales (physical discomfort, psychosocial discomfort, worries/concerns and satisfaction) of the constipation-related patient assessment of constipation QOL (PAC-QOL) [16] and the mean overall PAC-QOL scores. The survey form is included in the supplementary material.

This study was approved by the ethics committee of Yoyogi Mental Clinic (SNG215), registered at the University Hospital Medical Information Network Clinical Trials Registry as UMIN000043985 and conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labour and Welfare, Japan. Since this research did not use human samples (such as blood, body fluids, tissues, cells, excrement, or DNA extracted from these specimens for research purposes), electronic consent was considered sufficient.

Analysis Population

Patients who met the inclusion criteria in the preliminary survey and answered all questions in the main survey were included in the analysis population. Survey responses were collected first from the respondents in the opioid analgesic group (target sample size, 500 patients; hereafter the opioid group) and then from age- and sex-matched respondents in the non-opioid analgesic group (hereafter the non-opioid group) to achieve 1:1 matching between the two groups (Fig. 1).

Codeine and tramadol were categorized as weak opioids, whereas morphine, oxycodone, fentanyl and buprenorphine were categorized as strong opioids, as defined in the previous studies [17], on the basis of their potency relative to morphine [18] and Japanese clinical guidelines for cancer pain management [19].

Statistical Analyses

Summary statistics were calculated for quantitative data for each question asked in the questionnaire; frequencies and proportions were calculated for qualitative data for the

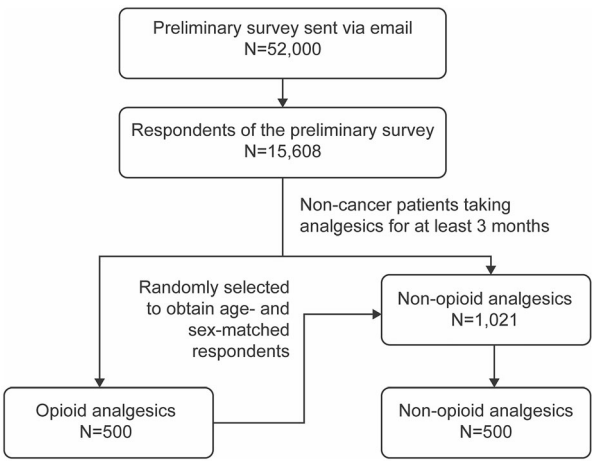

Fig. 1 Patient flow

Table 1 Baseline demographic and clinical characteristics

Characteristic	Opioid group (N = 500)	Non-opioid group (N = 500)	P value
Sex			
Male	366 (73)	366 (73)	1.000
Female	134 (27)	134 (27)	
Age (mean ± SD)	56.5 ± 10.5	56.4 ± 10.5	0.938
Diseases[a]			
Low back pain	319 (64)	340 (68)	0.182
Intervertebral disc herniation	262 (52)	180 (36)	< 0.001
Osteoarthritis	60 (12)	53 (11)	0.549
Knee osteoarthritis	54 (11)	79 (16)	0.025
Timing of administration[a]			
Scheduled dosing	396 (79)	141 (28)	< 0.001
When pain occurs (taken as needed)	161 (32)	386 (77)	< 0.001
Other	1 (0.2)	2 (0.4)	1.000

Data are expressed as n (%) or mean ± SD. Fisher's exact test (sex, diseases, timing of administration) and Welch's t test (age) were used for comparison between the groups

[a]Patients were allowed to provide multiple answers

opioid and the non-opioid groups separately and were compared using Fisher's exact test, Welch's t test, Mann–Whitney U test or chi-square test. The effects of differences in demographic characteristics and bowel habits at baseline on the endpoints were investigated. By using logistic regression, we calculated odds ratios (OR, odds of an event relative to the reference event) for risk factors for OIC using various covariates, including age (continuous), sex (male/female), presence of herniation, low back pain, osteoarthritis, knee osteoarthritis, use of a strong opioid analgesic and a scheduled dosing regimen for analgesic use. Statistical analysis was performed using Bellcurve® for Excel (version 3.21, Social Survey Research Information Co., Ltd., Tokyo, Japan), whereas Microsoft Excel was utilized for developing the figures. Values of $P < 0.05$ were considered significant.

RESULTS

Baseline Demographic and Clinical Characteristics

Overall, 1000 patients were included: 73% were male and 95% were aged 40 years or more (Tables 1, S1 in the supplementary material). In both opioid and non-opioid groups, most had low back pain (64% and 68%, respectively) or intervertebral disc herniation (52% and 36%, respectively; Table 1). Of the patients using opioid analgesics, 89% were taking weak opioids and tramadol was the most commonly used medication with or without combination with acetaminophen (70% or 22%, respectively; Table 2). Among patients using non-opioid analgesics, loxoprofen was the most commonly used analgesic as tablets (44%) or transdermal products (50%; Table 2). Most (79%) patients in

Table 2 Details of medications used by the patients in the opioid and non-opioid groups

Opioid group (N = 500)	
Oral	
Tramadol/acetaminophen	349 (70)
Tramadol	112 (22)
Codeine	8 (2)
Oxycodone	5 (1)
Morphine	4 (0.8)
Transdermal	
Fentanyl	33 (7)
Buprenorphine	15 (3)
Opioid classification (N = 500)	
Weak opioid	443 (89)
Strong opioid	57 (11)
Non-opioid group (N = 500)	
Oral	
Loxoprofen	220 (44)
Acetaminophen	63 (13)
Celecoxib	40 (8)
Pregabalin	40 (8)
Diclofenac	26 (5)
Duloxetine	11 (2)
Mirogabalin	9 (2)
Neurotropin®[a]	4 (0.8)
Transdermal	
Loxoprofen	251 (50)
Ketoprofen	172 (34)
Esflurbiprofen	17 (3)

Data are expressed as n (%). Patients were allowed to choose multiple responses within each analgesic group. Patients using both opioid and non-opioid analgesics were classified as those taking opioid analgesics; in the opioid classification, patients using both strong and weak opioids were classified as those using strong opioids. Oxycodone, morphine, fentanyl and buprenorphine were classified as strong opioids, whereas tramadol/acetaminophen, tramadol and codeine were classified as weak opioids, as described in the "Methods" section

[a]An extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus

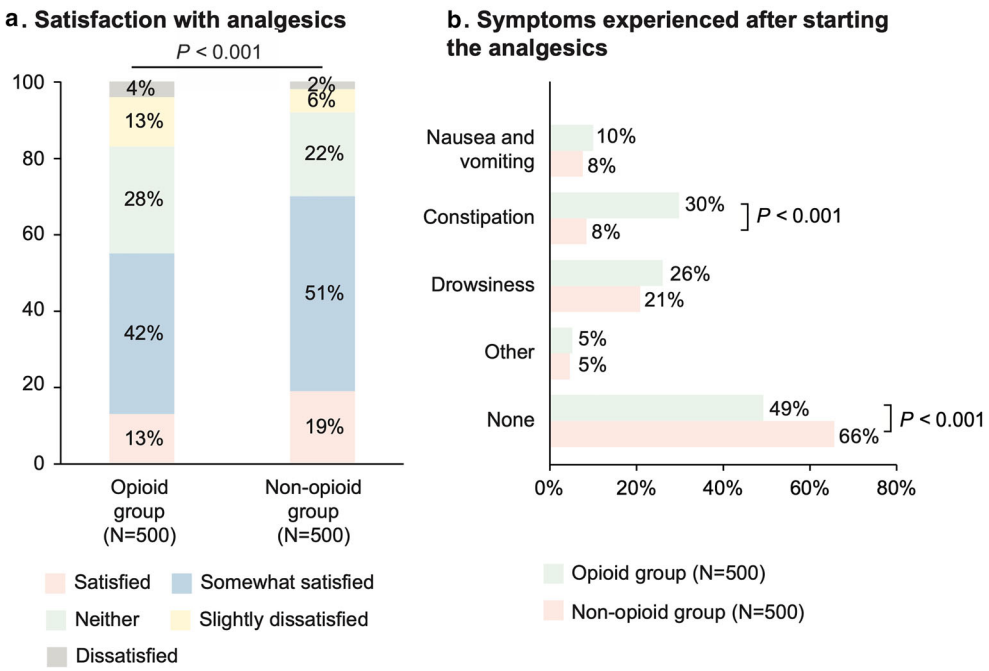

Fig. 2 Proportion of patients with **a** satisfaction with analgesics and **b** symptoms experienced after starting the analgesics. **a** Mann–Whitney *U* test with continuity correction and **b** Fisher's exact test were used for comparison between the groups

Table 3 Changes in the defecation pattern after initiating analgesic therapy and consultation with a healthcare provider as reported by the patients in the opioid and non-opioid groups

	Opioid group (*N* = 500)	Non-opioid group (*N* = 500)	*P* value
A change in defecation pattern after initiating analgesic therapy	186 (37)	82 (16)	< 0.001
Consultation with a healthcare provider upon a change in defecation pattern	133 (72)	48 (59)	–

Data are expressed as *n* (%). Fisher's exact test was used for comparison between the groups

the opioid group reported scheduled consumption of the prescribed medications, while 77% of those in the non-opioid group reported consumption of prescribed medications only when needed (Table 1). Overall, 55% and 70% of patients in the opioid and non-opioid groups, respectively, were at least somewhat satisfied with their medications (Fig. 2a, Table S2 in the supplementary material).

Constipation was experienced in significantly more patients in the opioid group compared with the non-opioid group (30% vs 8%), whereas other symptoms experienced, namely, drowsiness, nausea and vomiting, were comparable between the groups (Fig. 2b, Table S3 in the supplementary material).

A change in defecation pattern after analgesic use was reported by significantly more patients in the opioid group compared with the non-opioid group (37% vs 16%; Table 3). Among them, 72% and 59% of patients in opioid and non-opioid groups, respectively, had a consultation with a healthcare provider about a change in their defecation patterns (Table 3). Furthermore, only 46% and 16% of patients in the opioid and non-opioid groups, respectively,

Table 4 Explanation and queries about constipation by healthcare provider at the time of and after analgesic prescriptions as reported by the patients in the opioid and non-opioid groups

	Opioid group (N = 500)	Non-opioid group (N = 500)
Explanation of constipation provided by healthcare provider at the time of analgesic prescription	230 (46)	78 (16)
Queried by healthcare providers about constipation after the analgesic prescription	205 (41)	89 (18)

Data are expressed as n (%)

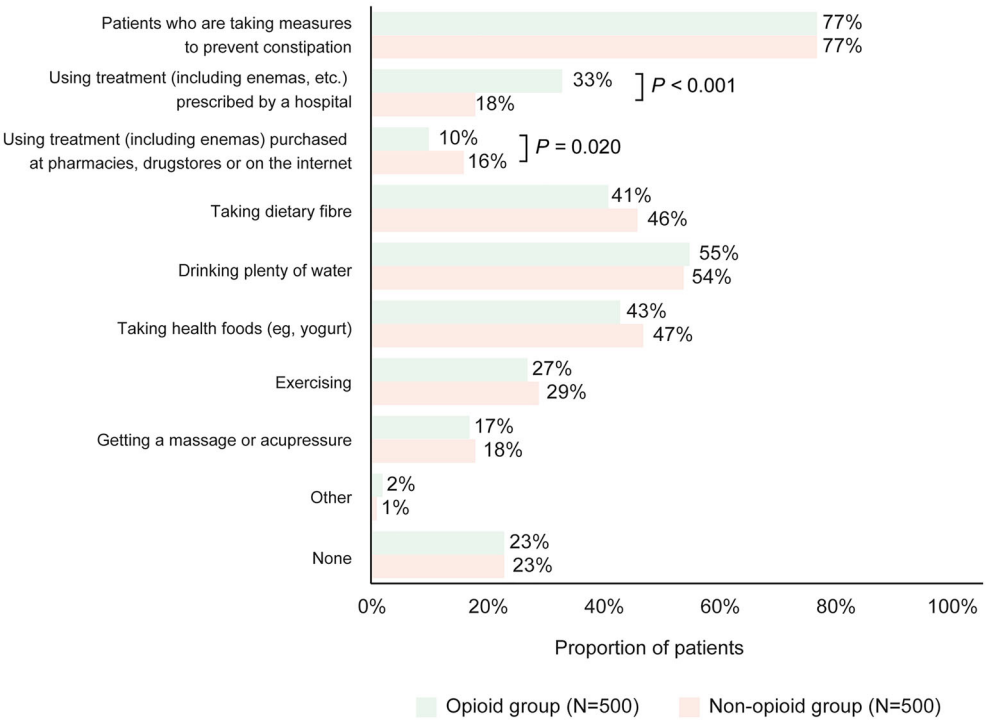

Fig. 3 Measures taken to prevent constipation. Fisher's exact test was used for comparison between the groups

were told about constipation by their healthcare providers at the time of analgesic prescription, and only 41% and 18% of patients, respectively, were asked about constipation by their healthcare providers at a follow-up visit after the prescription of analgesics (Table 4).

In both the groups, 77% of patients reported taking measures to prevent constipation, which included exercise, massage or acupressure, intake of fluids, fibre, yogurt, and other health foods and use of over-the-counter medications before initiating analgesic therapy (Fig. 3). A significantly higher proportion of patients took the prescribed medicine for constipation in the opioid vs non-opioid group (33% vs 18%, respectively; Fig. 3, Table S4 in the supplementary material). Magnesium oxide was most commonly prescribed. Overall, 75% of patients in the opioid group started taking the prescribed medicine for constipation simultaneously or immediately after the prescribed analgesic (Table S5 in the supplementary material), and 20% were satisfied and 39% were somewhat satisfied with them (Fig. 4). A

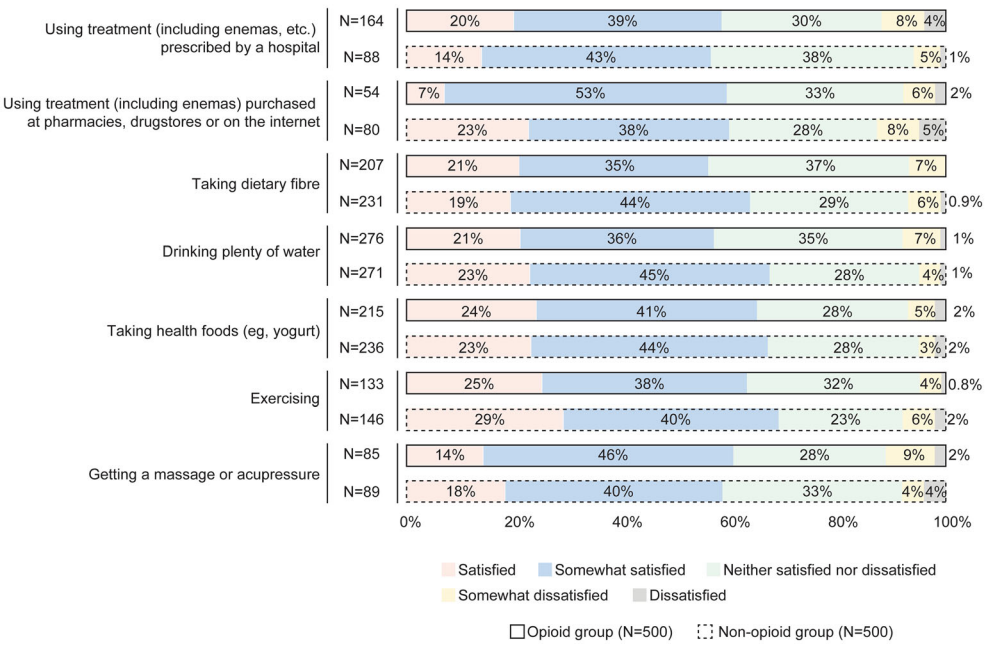

Fig. 4 Degree of satisfaction with the measures taken to prevent constipation as measured by the proportion of patients at least somewhat satisfied with their measures in the opioid and non-opioid analgesic groups

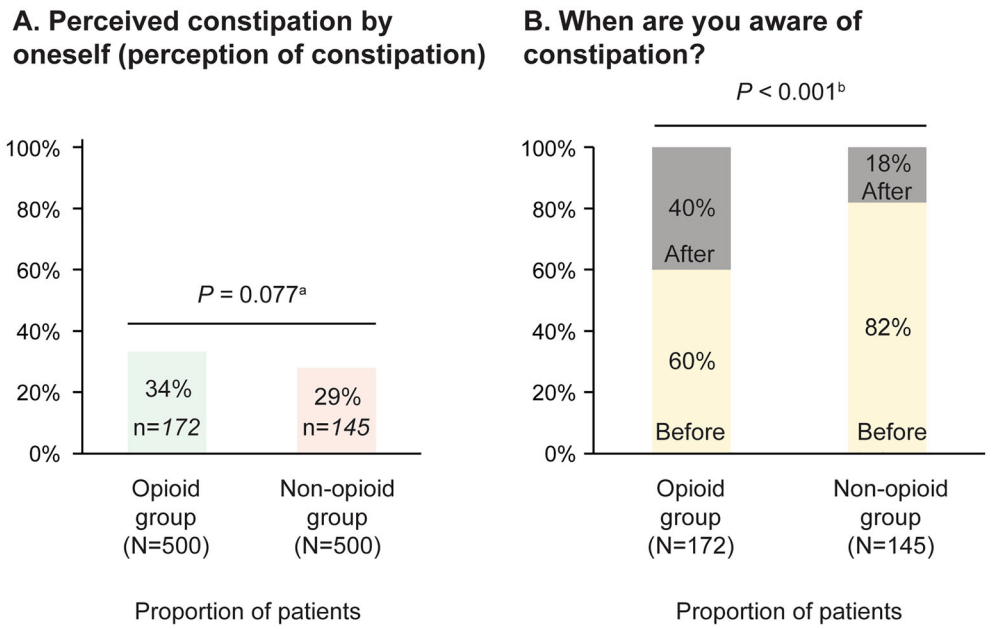

Fig. 5 Subjective awareness of constipation and timing of onset. [a]Fisher's exact test; [b]chi-square test. **A** The proportion of patients who currently self-perceive constipation. Opioid group, 34% (n = 172); non-opioid group, 29% (n = 145). **B** The timing of awareness of constipation among patients who currently self-perceived the constipation. "After" implies the timepoint post-analgesic therapy, and "before" implies the timepoint pre-analgesic therapy

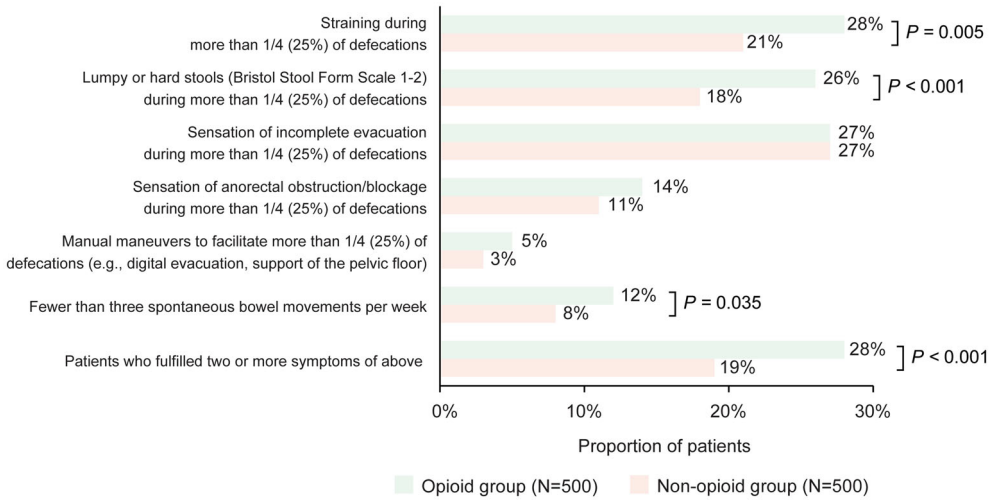

Fig. 6 Symptoms of constipation based on the Rome IV diagnostic criteria. Fisher's exact test was used for comparison of symptoms of constipation between the groups

comparable degree of satisfaction was observed for non-medical measures, such as dietary fibre intake, drinking water, taking health foods and exercises (Fig. 4, Table S4 in the supplementary material).

Although the two groups had comparable proportion of patients who were currently aware of constipation (34% vs 29%, respectively, Fig. 5A, Table S6 in the supplementary material), the proportion of patients who reported self-assessed constipation after initiating analgesic therapy was significantly higher in the opioid group than in the non-opioid group (40% vs 18%, respectively; Fig. 5B, Table S6 in the supplementary material). Significantly more patients in the opioid group fulfilled two or more symptoms of the Rome IV diagnostic criteria for constipation compared with the non-opioid group (28% vs 19%, respectively; Fig. 6, Table S7 in the supplementary material). The overall mean PAC-QOL scores were significantly lower in the opioid group compared with the non-opioid group (Table S8 in the supplementary material). However, PAC-QOL scores were comparable among patients who fulfilled two or more symptoms of Rome IV criteria, regardless of the analgesic used (Table 5).

Low back pain was the only risk factor for OIC among various covariates assessed in the logistic regression analysis for risk factors for OIC, based on 81 patients who were diagnosed with OIC (fulfilled two or more symptoms of the Rome IV diagnosis criteria with a change in defecation pattern after initiating opioid analgesic therapy) vs 419 patients without OIC in the opioid group (Table 6). Use of a strong opioid analgesic and/or scheduled dosing did not directly impact the odds of developing OIC among patients using opioid analgesics.

DISCUSSION

This study showed a substantially higher incidence of constipation among patients who were using opioid analgesics on the basis of the symptoms of Rome IV diagnostic criteria and a significantly higher awareness of constipation after starting analgesics in opioid users relative to non-opioid analgesic users. This finding conforms with the previously published data from a cross-sectional survey assessing the safety and efficacy of opioids in patients with chronic pain in Japan, in which 64% of the participants experienced constipation [20]. Notably, constipation was common despite 89% of patients using weak opioids in our study. This is unsurprising—even tramadol can be associated with constipation in up to 45% of patients based on the formulation and doses, as noted in a narrative review of 15 studies [21]. Results of regression analysis from our study

Table 5 PAC-QOL scores of those who fulfilled two or more symptoms of the Rome IV diagnostic criteria for constipation

	Opioid group (N = 138)	Non-opioid group (N = 94)	P value
All	1.06 ± 0.67	1.03 ± 0.56	0.682
Physical discomfort	1.36 ± 0.88	1.32 ± 0.78	0.707
Mental discomfort	0.83 ± 0.84	0.85 ± 0.77	0.841
Anxiety/concern	1.06 ± 0.88	1.00 ± 0.72	0.518
Degree of satisfaction	1.18 ± 0.63	1.14 ± 0.61	0.654

Data are expressed as mean ± SD. Welch's t test was used for comparison between the groups
PAC-QOL Patient Assessment of Constipation Quality of Life

Table 6 Results of multivariate logistic regression analysis for risk factors for OIC based on 81 patients with OIC vs 419 patients without OIC

Risk factors	OIC (N = 81)	Non-OIC (N = 419)	OR (95% CI)	P value
Mean age, years	56.2	56.5	0.99 (0.97–1.02)	0.650
Sex, male	60 (74)	306 (73)	0.98 (0.55–1.74)	0.943
Intervertebral disc herniation	45 (56)	217 (52)	1.57 (0.92–2.68)	0.096
Low back pain	65 (80)	254 (61)	3.17 (1.70–5.94)	< 0.001
Osteoarthritis	10 (12)	50 (12)	1.24 (0.58–2.65)	0.574
Knee osteoarthritis	5 (6)	49 (12)	0.75 (0.27–2.02)	0.563
Use of a strong opioid	9 (11)	48 (11)	0.99 (0.45–2.20)	0.981
Scheduled dosing for analgesic	68 (84)	328 (78)	1.54 (0.80–2.99)	0.198

Data for both groups are expressed as n (%) unless stated otherwise. Results of logistic regression are adjusted for sex (male vs female), age (continuous), intervertebral disc herniation (presence vs absence), low back pain (presence vs absence), osteoarthritis (presence vs absence), knee osteoarthritis (presence vs absence), use of a strong opioid (presence vs absence) and scheduled dosing for analgesic (used vs not used)
OIC opioid-induced constipation, *OR* odds ratio

also showed that OIC development does not depend on strength and dosing regimen of the opioids and reinforce that all opioids, regardless of their classification, are bothersome with respect to the overall burden of OIC. Indeed, results from a survey in five European countries showed that OIC symptoms were deemed bothersome by a comparable proportion of weak- and strong-opioids users (38% vs 40%) in an international survey [17]. Notably, low back pain was the only risk factor associated with OIC (OR 3.17, 95% CI 1.70–5.94). This finding is in agreement with the report that multiple gastrointestinal symptoms were significantly associated with back pain among women of all age groups in a cross-sectional analysis of survey data from the Australian Longitudinal Study on Women's Health [22]. It suggests that patients with low back pain tend to get constipation and therefore may be prone to get OIC after initiating opioid treatment. Intervertebral disc herniation is one of the causes of radicular low back pain. The OR was 1.57 but not significant. In a retrospective cohort study using a real-world national database, no difference in the likelihood of constipation was noted among adults with radicular and non-radicular low back pain for constipation [23], leading to speculation

that intervertebral disc herniation could also be a potential factor associated with OIC, similar to low back pain. Given the lack of reports about the role of pain site in OIC development, further studies assessing the association between these factors are required.

The proportion of patients who had intervertebral disc herniation or knee osteoarthritis was significantly different between the opioid and non-opioid groups. However, the number of patients who recognized their constipation before initiating analgesic therapy was comparable between the opioid and non-opioid groups (n = 119 vs n = 103, Fig. 5 and Table S6). These findings suggest that comorbid diseases and other background factors did not affect the development and/or perception of constipation before the analgesic therapy. In addition, the proportion of patients who received scheduled dosing was significantly higher in the opioid group compared with the non-opioid group. Although the dosing regimen did not affect the development of OIC in the opioid group in regression analysis, it may affect the development of constipation between the opioid and non-opioid groups after initiating analgesic therapy.

There were no significant differences between the opioid vs non-opioid groups in the proportion of patients who self-reported constipation or QOL among patients who fulfilled symptoms based on the Rome IV diagnostic criteria. The results may suggest difficulty in differentiating OIC and normal constipation when solely based on symptoms and bother scores of patients in clinical practice. However, constipation is one of the most common adverse effects associated with the opioid analgesic use. Therefore, the possibility of OIC should be considered when diagnosing and treating patients with pain that require opioid analgesics. Notably, less than 50% of patients taking opioids were informed about the potential of OIC at the time of opioid prescription and queried about constipation after the opioid prescription, suggesting that healthcare providers in Japan did not fully appreciate the burden of OIC symptoms and its impact on patient QOL. This finding is not unique to Japan: almost 60% of healthcare professionals did not adequately counsel patients about constipation being a common side effect of opioid as reported in a European multi-country questionnaire-based study [17]. It is also plausible that patients may forget or hesitate to ask their healthcare providers until OIC symptoms become prominent and bothersome. Therefore, healthcare providers should be encouraged to actively ask patients about OIC at every follow-up visit [24]. To that effect, educating healthcare providers and patients about the burden of OIC and the overall benefit-to-risk ratios of opioid analgesics is important.

Over 70% of patients in our study consulted a healthcare provider after experiencing constipation, which was higher than that reported in a Sweden-based study [9], suggesting patients' intent to get professional medical treatment for their bothersome constipation in Japan. Despite a high number of patients seeking medical help, most patients relied on self-management measures such as use of over-the-counter laxatives, dietary fibre intake and supplements, which is in alignment with the findings of a previous study in which only 12% of patients took prescribed medications for their constipation [9]. More importantly, patients rarely develop tolerance to the constipating effects of opioids. Consequently, OIC does not resolve over time on its own [3]. Therefore, the use of opioid treatment necessitates appropriate additional therapy for OIC. The current therapy for constipation is symptomatic and non-specific. Osmotic laxatives such as magnesium oxide and polyethylene glycol and stimulant laxatives, such as bisacodyl, are commonly used to treat OIC [25]. While laxatives increase stool bulk, distend the colon and stimulate peristalsis [4], they do not target the underlying mechanism of μ-opioid receptor-mediated OIC, rendering laxatives ineffective in many patients [26, 27]. Indeed, despite the use of laxative, OIC incidence is estimated to range from 15% to 90% in clinical trials and observational studies of patients using opioids, and from 40% to 64% in patients treated with opioids for chronic non-cancer pain [5]. In a prospective longitudinal study conducted in the USA, Canada, Germany and UK, 96% of patients taking one laxative and 38% taking two laxatives had

inadequate relief from OIC despite sufficient laxative use [5]. Effective treatment strategies to manage OIC are therefore required.

The role of peripheral μ-opioid receptors in tramadol-induced constipation is adequately described in a preclinical study in rodents [28]. Consequently, the co-administration of a peripherally acting μ-opioid receptor antagonist with negligible systemic availability, such as methylnaltrexone, naldemedine and naloxegol, presents a novel approach for selectively and locally antagonizing the gastrointestinal effects of opioids without compromising systemic analgesia [29, 30] and is strongly recommended by the American Gastroenterological Association Institute guidelines on the medical management of OIC [31]. Such pharmacological treatment of OIC will support a holistic multidisciplinary approach with a combination of medications, exercise and psychotherapy for the management of chronic pain.

Strengths and limitations of our study should be mentioned, too. Although we included patients with musculoskeletal pain, one of the most prevalent types of chronic pain [32], the study does not cover all patients with other types of chronic pain. Survey is a useful tool for collecting qualitative and quantitative information, and specifically an internet-based survey that can be completed in respondents' familiar space within a short period of time is expected to reduce the response bias wherein the respondents choose the desirable responses. However, sampling issues related to a study design may still apply. For instance, the characteristics of participants in online communities may not be representative of the routine clinical practice population [33]. Moreover, low response rates are characteristic of online surveys, as many potential responders may consider such invitations emails as spam [33], and potential bias is also related to voluntary participation [34]. We also acknowledge that lack of information on other treatments or clinical aspects other than opioid use that can cause constipation may further confound our results. These factors need to be considered while interpreting the results. Despite the limitations, as the first study to assess the occurrence of OIC in people with chronic non-cancer musculoskeletal pain in Japan, it provides insights into clinical management of OIC in people with chronic non-cancer pain.

CONCLUSION

Results from the present study show that use of opioid analgesics, including weak opioids, for the management of non-cancer musculoskeletal pain is associated with OIC. The findings highlight the need for appropriate treatment of constipation along with chronic non-cancer pain in Japan.

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Compliance with Ethics Guidelines. This study was approved by the ethics committee of Yoyogi Mental Clinic (SNG215), registered at the University Hospital Medical Information Network Clinical Trials Registry as UMIN000043985 and conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labour and Welfare, Japan [35]. Since this research did not use human samples (such as blood, body fluids, tissues, cells, excrement or DNA extracted from these specimens for research purposes), electronic consent was considered sufficient.

Data Availability . The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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