Use of Fentanyl Patch for Treatment of Moderate-to-severe Chronic Noncancer Pain: Postmarketing Surveillance of Medical Practice in Japan Using a Risk Minimization Action Plan

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Abstract

Objective: The purpose of this study was to discuss the safety, treatment profile, and clinical effectiveness of 12-month treatment with fentanyl patch (FP), a strong opioid, in medical practice in Japan under the risk minimization action plan (RMAP).

Methods: Patients with moderate-to-severe chronic noncancer pain who had switched to FP from another opioid were registered to take this survey to assess adverse drug reactions (ADRs), therapeutic effect, and pain intensity for up to 12 months.

Results: A total of 517 patients were enrolled, and 499 patients (male, 50.9%; mean [SD] age, 63.0 [15.4] years) were included in the safety population. During the 12-month observation period, an ADR occurred in 262 patients (52.5%); most frequent ADRs included nausea (24.2%), somnolence (22.4%), constipation (18.2%), vomiting (9%), and dizziness (4.6%). The prespecified priority survey items, including respiratory depression, drug dependence, and drug withdrawal syndrome, occurred in 2 (both nonserious), 3 (all serious), and 9 (all serious) patients, respectively. In 418 patients from the efficacy population, the response rate was 77.3%, the rate of achievement of the therapeutic goal was 64.5%, and the visual analog scale (VAS) scores for pain severity decreased by 22.3 (26.9) mm.

Conclusion: Our results identified a reasonable risk–benefit profile for the management of moderate-to-severe chronic noncancer pain in patients previously treated with opioids under long-term treatment with FP under the RMAP. Respiratory depression, drug dependency, and drug withdrawal were rarely observed even under the RMAP in Japan.

Key Words: chronic pain, opioids, long-term treatment, noncancer pain, fentanyl patch, adverse reaction, risk mitigation, Japan

INTRODUCTION

Patients with chronic pain are often treated with analgesics over a long period of time. Opioids have been used in patients with moderate-to-severe acute pain...
or chronic noncancer pain who do not respond to other analgesics, who have poor treatment tolerability, or in whom the benefits of opioid therapy exceed the risks. While the use of opioids in patients with chronic noncancer pain has increased rapidly since the late 1990s, abuse of opioids and opioid-related deaths became a social issue in the mid-2000s. It was strongly recognized that careful attention should be paid to avoid safety issues, dependency, and abuse with long-term opioid treatment in patients with chronic pain. The use of opioids for chronic pain is strictly controlled by regulatory bodies in Europe and the United States because of the potential concern of abuse and misuse. Several opioid use guidelines have been issued to ensure their controlled use.

In Japan, strong opioids have been used for the treatment of cancer pain in palliative care settings and postsurgical pain relief, but they have rarely been used to treat chronic noncancer pain compared with Europe and the United States because of the concern over abuse and/or dependency with long-term opioid use. In this socioclinical setting, a 3-day formulation of transdermal fentanyl patch (FP) was approved as a first-line strong opioid for chronic noncancer pain in 2010.

Fentanyl, a low-molecular-weight, highly lipophilic synthetic opioid with a potent analgesic effect, which is classified as a strong opioid, has a lower affinity for µ2 opioid receptors that cause motor inhibition of the gastrointestinal tract and respiratory depression, while having a higher affinity for µ1 opioid receptors that cause analgesia and euphoria. A 3-day formulation of FP enables a single application to maintain effective blood levels over 72 hours. It was formulated to be transdermally absorbed, to avoid a steep increase in plasma concentrations, which may increase the risks of respiratory depression and drug abuse—major adverse drug reactions (ADRs) of opioids.

However, the results of clinical registration trials were the only available evidence of FP use for chronic noncancer pain in Japan. Evidence from clinical trials greatly depends on trial conditions. Several prescribers (pain clinicians, orthopedists, or general practitioners), variations in assessment of patient conditions, and treatment of pain in real-world practice have the potential to impact the clinical risk–benefit profile of FP. Japanese healthcare and regulatory authorities are particularly concerned about increased safety risks in real-world practice, especially with regard to serious respiratory depression, abuse, and drug dependency with long-term use, because inadequate assessment of pain combined with casual use of opioid treatment may increase such risks.

With this background, we developed a risk minimization action plan (RMAP) for abuse and misuse of FP in consultations with the Pharmaceutical and Medical Device Agency (PMDA) before FP was commercially available. In this study, we describe the safety, treatment profiles, and clinical effectiveness of FP in managing chronic noncancer pain in medical practice under the RMAP, using data from postmarketing surveillance conducted immediately after FP marketing approval in Japan.

**METHODS**

**Study Design**

The protocol, including all ethical aspects, of this observational study was reviewed by an internal review board and approved by the PMDA. This was a prospective, multicenter, postmarketing surveillance study (UMIN registration ID: 000015898). Patients with moderate-to-severe chronic noncancer pain who had switched from another opioid and had never been treated with FP were registered within 14 days after the initiation of FP therapy. In Japan, the use of FP is prohibited for opioid-naïve chronic noncancer pain. The dose of FP was selected from 2.1-mg (5.25 cm²; 12.5 µg/hour), 4.2-mg (10.5 cm²; 25.0 µg/hour), 8.4-mg (21.0 cm²; 50.0 µg/hour), and 12.6-mg (31.5 cm²; 75 µg/hour) patches, according to the dose and administration of the previously used opioid based on package insert information. FP was applied to the chest, abdomen, upper arms, or thighs every 3 days. During the study period, there were no restrictions on concomitant drug therapy, physical therapy, or psychotherapy, which were administered according to the usual practice at the study sites. This surveillance was conducted in accordance with the Japanese regulation (Ministry of Health, Labour and Welfare Ministerial Ordinance No. 171) of Good Post-marketing Study Practice and commenced after execution of the contract between each site and Janssen Pharmaceutical K.K (JPKK, Tokyo Japan). As respiratory distress had been reported at a frequency of 3.9% and no respiratory depression had been reported during the clinical trial for the development of FP, respiratory distress was used for sample size calculation. The target sample size was set at 500 patients to detect respiratory distress in at least 5 patients with a probability of 95% or higher, assuming a 50% dropout rate.
Risk Minimization Action Plan

The RMAP developed by the pharmaceutical industry is defined as a strategic safety program for minimizing risks and maximizing benefits of postmarketing prescription drug products. JPKK, in consultation with the PMDA, designed and implemented the RMAP on misuse and abuse of FP after its approval in Japan. The RMAP includes, but is not limited to, the following: (1) prescription of FP restricted to physicians and pharmacists who have participated in a specially designed training session provided by JPKK on appropriate use of FP for chronic noncancer pain; (2) encouraging physicians to confirm treatment tolerability and reactivity (including potential abuse) to previous opioids at least 1 week before starting FP; (3) physicians issue a special “confirmation note” (valid for 1 year) that indicates a patient’s eligibility for FP use; (4) additional pharmacist-provided guidance for handling of narcotic drugs and obtaining written consent from patients; (5) pharmacists should prepare FP after verifying the confirmation note; and (6) physicians and pharmacists should perform monthly postprescription monitoring. This surveillance was conducted in a clinical setting while implementing the above RMAP.

Outcome Measures

Patient characteristics and medication history were collected at baseline. Adverse events (AEs) reported by physicians in charge during the observation period were recorded. The physicians were instructed at the beginning of the surveillance on classification of AEs. Events related to respiratory depression, drug dependence, and drug withdrawal syndrome were specified as priority survey items. Collected AEs were coded according to the Medical Dictionary for Regulatory Activity/Japanese (MedDRA/J) version 16.1. Subsequently, those AEs for which a causal relationship could not be ruled out (those where the physician indicated an unknown, possible, likely, or very likely relationship) were classified as ADRs and reported as safety outcome.

The effectiveness of FP was evaluated by the physician in charge and categorized as “effective,” “ineffective,” or “cannot be determined.” Patients in whom the therapeutic result was determined as “effective” were considered responsive to FP to calculate the response rate. In addition to the physician’s assessment, a patient-completed 100-mm visual analog scale (VAS) assessing intensity of pain in the last 24 hours was evaluated as well. In addition, patients reported achievement levels for self-set therapeutic goals of improvement in activities of daily living (ADLs), improvement in sleep, increase in physical activity, improvement in stress management, and pain relief. Using this record, the physician evaluated and categorized improvement in ADLs as “achieved,” “mostly achieved,” “not much achieved,” and “not achieved.” Patients who were determined by the physician to have “achieved” or “mostly achieved” improvement in ADLs were considered as those who achieved therapeutic goals to calculate the rate of achievement of the therapeutic goal.

Statistical Analyses

Among the outcome measures collected, categorical variables were summarized by frequency and proportion along with their corresponding 95% CIs; continuous variables were summarized as mean with SD, median, maximum, and minimum. Fisher’s exact test and the chi-square test were used to compare the incidence of ADRs between subgroups based on patients’ characteristics. The repeated-measures analysis of variance (ANOVA) was used to assess the changes in VAS scores from baseline. A set of post hoc paired t-tests was performed, followed by ANOVA. Missing values were imputed using the last observation carried forward (LOCF) and baseline observation carried forward (BOCF) methods, and results were reported in both ways. A 2-sided P value <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) and R version 3.1.0 (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

Between February 2010 and December 2011, a total of 517 patients were registered in 149 institutions across Japan. Of these, 499 patients were eligible for assessing the safety profile of FP (safety population), and 418 patients were eligible for assessing the clinical effectiveness (efficacy population) (Figure 1). In the safety population, 50.9% patients were male, and the mean age was 63.0 (15.4) years (Table 1). The baseline mean VAS score was 68.7 (22.3) mm. A majority of patients were treated in either an anesthesiology department or a pain clinic (78.0%), 32.1% had spinal stenosis, and...
82.0% had neuropathic pain (NeP). Sites of pain included lower extremities (50.5%), lumbar region (42.1%), and upper extremities (24.3%). Previous monotherapy opioids included codeine preparation (46.7%), morphine preparation (26.5%), tramadol/acetaminophen combination (10.8%), and other opioids (8.0%). Monotherapy with an opioid was provided in 93.8% patients, whereas only 9 patients (1.8%) received combination therapy with multiple opioids. Twenty patients had no history of opioid use; these were excluded from the efficacy population.

Treatment Status During the Observation Period

The initial application dose of FP was 2.1 mg in 89.0% patients (maximum dose: 16.8 mg), and the mean single-application dose was 3.8 (3.0) mg (Table 1). Another opioid analgesic was administered as rescue therapy after baseline application in 170 patients (34.1%). FP therapy was discontinued in 242 patients (48.5%) during the entire observation period. The primary reasons for discontinuation included patient’s request (31.4%), occurrence of AEs (including those for which causal relationship with FP was ruled out) (28.5%), changing hospital (9.1%), and missed visits (7.0%). Most discontinuations were reported in the initial time period after baseline: before Day 30: 82 patients; days 30 to 89: 81 patients; days 90 to 179: 33 patients; and days 180 to 359: 44 patients. Concomitant medication was administered to 472 (94.6%) patients, including 379 (76.0%) received an analgesic: pregabalin in 178 patients (47.0%), acetaminophen in 74 patients (19.5%), gabapentin in 68 patients (17.9%), loxoprofen in 62 patients (16.4%), an extract from cutaneous tissue of rabbit inoculated with vaccinia virus in 51 patients (13.5%), celecoxib in 48 patients (12.7%), and ketoprofen in 48 patients (12.7%). Overall, 172 patients (34.5%) used an anti-emetic, and the most frequently used anti-emetics included prochlorperazine in 93 patients (54.1%), domperidone in 46 patients (26.7%), and metoclopramide in 43 patients (25.0%). The laxatives magnesium oxide and sennoside were used in 190 (38.1%) and 115 (23.0%) patients, respectively.

Safety

A total of 604 ADRs (674 AEs) were reported in 262 of 499 patients (52.5% [95% CI: 48.0–57.0]) (Table 2). ADRs reported at a frequency of ≥ 3% were nausea (24.2%), somnolence (22.4%), constipation (18.2%), vomiting (9.0%), and dizziness (4.6%). Respiratory depression (not including respiratory distress), specified as a priority survey item, was reported by 2 patients (0.4%, both nonserious) and was relieved during continuation or by reducing the dose of FP (Table 3). Drug dependence occurred in 3 patients (0.6%, all serious); based on psychiatric consultation, 1 of these patients had morphine dependence (previous medication). The second patient had been experiencing emotional instability since baseline, which was relieved by continuing FP treatment and regular psychiatric consultations after onset. The last patient showed withdrawal syndromes after discontinuation of FP, which was consequently reported as drug dependence. Drug withdrawal syndrome was reported in 9 patients (1.8%, all serious), including sweating, cold sweat, trembling, chills, palpitations, malaise, pyrexia, and irritability that occurred after dose reduction or discontinuation. Except for 2 patients whose outcomes were unknown, withdrawal syndrome was relieved without requiring additional
Table 1. Patient characteristics and treatment status during the survey period in the safety and efficacy populations

| Parameter (%) | Safety population (n = 499) | Efficacy population (n = 418) |
|---------------|-----------------------------|-----------------------------|
| Male          |                             |                             |
| Age (years, mean ± SD) | 63.0 ± 15.4 | 62.8 ± 15.4 |
| Duration of chronic pain (years) | 5.5 ± 6.5 | 5.7 ± 6.9 |
| Opioid history (years) | 1.0 ± 2.0 | 1.0 ± 2.1 |
| Clinical setting  |                             |                             |
| Anesthesiology/pain clinic | 389 (78.0) | 324 (77.5) |
| Orthopedics | 84 (16.8) | 72 (17.2) |
| Other | 26 (5.2) | 22 (5.3) |
| Major diagnosis (multiple allowed) |                             |                             |
| Spinal stenosis | 160 (32.1) | 129 (30.9) |
| Post-therapeutic neuralgia | 69 (13.8) | 60 (14.4) |
| Complex regional pain syndrome | 53 (10.6) | 49 (11.7) |
| Disk herniation | 41 (8.2) | 35 (8.4) |
| Gonarthrosis | 35 (7.0) | 32 (7.7) |
| Rheumatoid arthritis | 25 (5.0) | 22 (5.3) |
| Spinal cord injury | 21 (4.2) | 20 (4.8) |
| Classification of chronic pain |                             |                             |
| NeP | 236 (47.3) | 205 (49.0) |
| NeP + NocP | 173 (34.7) | 138 (33.0) |
| NocP | 88 (17.6) | 74 (17.7) |
| Other | 2 (0.4) | 1 (0.2) |
| Past medical history |                             |                             |
| Present | 166 (33.3) | 136 (32.5) |
| Complication Present | 387 (77.6) | 328 (78.5) |
| Previous opioids |                             |                             |
| Present | 479 (96.0) | 418 (100.0) |
| Initial application dose (mg, mean ± SD) | 2.5 ± 1.5 | 2.5 ± 1.6 |
| 1.05 | 3 (0.6) | 2 (0.5) |
| 2.1 | 444 (89.0) | 373 (89.2) |
| 4.2 | 36 (7.2) | 29 (6.9) |
| > 6.3 | 16 (3.2) | 14 (3.3) |
| Mean single-application dose (mg, mean ± SD) | 3.8 ± 3.0 | 3.9 ± 3.2 |
| < 2.1 | 7 (1.4) | 3 (0.7) |
| 2.1-4.1 | 373 (74.7) | 309 (73.9) |
| 4.2-6.2 | 68 (13.6) | 60 (14.4) |
| > 6.3 | 51 (10.2) | 46 (11.0) |
| Concomitant therapy for chronic pain |                             |                             |
| Concomitant drug therapy | 472 (94.6) | 393 (94.0) |
| Rescue opioid analgesics | 170 (34.1) | 150 (35.9) |
| Concomitant nondrug therapy | 176 (35.3) | 148 (35.4) |

NeP, neuropathic pain; NocP, nociceptive pain.

The incidence of ADRs was 38.0% during the period after baseline and before Day 30, which gradually decreased after Day 30 (10.8% from days 30 to 59, 7.7% from days 60 to 89, and 11.4% from days 90 to 179) and subsequently became roughly constant until Day 360. There were no gender- or age-related differences in the incidence of ADRs (patients aged ≥ 65 years, 50.8%; patients aged < 65 years, 54.4%; Table 4). With regard to departments, the incidence of ADRs was higher in the anesthesiology department/pain clinic (58.1%) than in the orthopedic department (33.3%, P < 0.001). Furthermore, the incidence of ADRs was higher in patients diagnosed with NeP (57.2, P = 0.012) than in those diagnosed with nociceptive pain (NocP) alone (38.6%). Moreover, the incidence of ADRs was also high in patients with no past medical history of opioid use, no comorbidities, and no concomitant drug therapy. The incidence of ADRs by mean single-application dose was lowest in patients treated with a dose of 2.1 to 4.1 mg (48.5%) and significantly higher in those treated with a dose of 4.2 mg or higher (63.0%, P = 0.0061). With respect to concomitant drug therapy, including preventive and treatment drugs, the incidence of ADRs was the highest in patients using the anti-emetic prochlorperazine (n = 73 [78.5%]); the most frequently reported ADRs included nausea in 52 patients (55.9%) and somnolence in 37 patients (39.8%), which occurred more frequently than in patients using other concomitant drugs.

Clinical Effectiveness

In the 418 patients from the efficacy population, the response rate based on the therapeutic effect, as determined by the primary physician, was 77.3%, with no notable gender- or age-related differences (Table 4). The response rate was higher in patients with NocP (84.0%) than in those with NeP (70.2%). Most frequent primary diseases (n = 20 or more) with a response rate ≥ 80% included disk herniation (94.3%), gonarthrosis (84.4%), and rheumatoid arthritis (81.8%); those with response rates < 70% were spinal cord injury (65.0%) and complex regional pain syndrome (67.3%).

The rate of achievement of the therapeutic goal was 64.5% in 451 patients evaluable using the “pain treatment diary.” With regard to response rate, the rate of achievement of the therapeutic goal was higher in patients belonging to 30-39 age group than in those of 40-49 age group (69.9% vs. 68.0%, P = 0.0073). The repeated-measures ANOVA in 348 patients with VAS measurements (Figure 2) showed a significant temporal effect in both LOCF and BOCF populations (both P < 0.001). The VAS scores significantly decreased from 67.6 (22.4) mm at baseline to 45.0 (26.9) mm at the last observation period (−22.3 [26.9] mm, P < 0.001, paired t-test). Moreover, the
VAS scores decreased from 67.3 (22.5), 69.0 (22.3), and 64.0 (23.2) mm at baseline to 47.5 (26.4), 45.0 (27.8), and 37.6 (26.2) mm at the last observation in 170 patients with NeP, 104 with NeP + NocP, and 62 with NocP, respectively (by 19.8 [25.1], 24.0 [26.7], and 26.4 [31.7] mm, respectively, all P < 0.001, paired t-test).

**DISCUSSION**

This postmarketing surveillance study was conducted under the RMAP. Therefore, FP was only prepared in institutions where physicians and medical personnel could appropriately control and explain the risks of FP.
Table 4. Incidence of adverse drug reactions and response rates by patient characteristics

| Parameter (number of patients) | Safety population (n = 499) | Efficacy population (n = 418) |
|--------------------------------|-----------------------------|-----------------------------|
|                                | Number of patients in whom an ADR occurred (%) | Number of patients responding to FP (%) | P  |
| Gender                         |                             |                             |  |
| Male (254)                     | 127 (50.0)                  | 173 (75.9)                  | 0.282 |
| Female (245)                   | 135 (55.1)                  | 150 (79.0)                  | 0.199 |
| Age (< 40 [39])                | 21 (93.5)                   | 28 (82.4)                   | 0.012 |
| 40–49 [79]                     | 50 (63.3)                   | 53 (80.3)                   | 0.012 |
| 50–59 [64]                     | 29 (45.3)                   | 42 (76.4)                   | 0.707 |
| 60–69 [100]                    | 51 (51.0)                   | 62 (73.8)                   | 0.001 |
| 70–79 [155]                    | 84 (54.2)                   | 70–79 (126)                 | 0.001 |
| ≥ 80 [62]                      | 27 (43.6)                   | 44 (83.0)                   | 0.707 |
| Clinical setting               |                             |                             |  |
| Anesthesiology/PC (389)        | 226 (58.1)                  | 249 (76.9)                  | < 0.001 |
| Orthopedics (84)               | 28 (33.3)                   | 54 (75.0)                   | 0.276 |
| Other (26)                     | 8 (36.4)                    | 20 (90.9)                   | 0.276 |
| Classification of chronic pain | NeP (236)                   | NeP (205)                   | < 0.001 |
| NeP + NocP (173)               | 92 (53.2)                   | 144 (70.2)                  | 0.012 |
| NocP (88)                      | 34 (38.6)                   | 63 (85.1)                   | 0.012 |
| Past medical history           | Absent (333)                | Absent (282)                | 0.002 |
| Present (274)                  | 104 (38.0)                  | Present (136)               | 0.321 |
| Complications                  | Absent (112)                | Absent (90)                 | 0.571 |
| Present (387)                  | 49 (43.8)                   | Present (328)               | 0.571 |
| Mean single-application dose (mg) |                             |                             |  |
| < 2.1(7)                       | 6 (85.7)                    | 2 (66.7)                    | 0.001 |
| 2.1–4.1(373)                   | 181 (48.5)                  | 234 (75.7)                  | 0.069 |
| 4.2–6.2 (68)                   | 45 (66.2)                   | 49 (81.7)                   | 0.001 |
| ≥ 6.3 (51)                     | 30 (58.8)                   | ≥ 6.3 (46)                  | 0.001 |
| Concomitant drug               | Absent (27)                 | Absent (25)                 | 0.471 |
| Present (472)                  | 3 (11.1)                    | Present (393)               | 0.471 |

ADR, adverse drug reaction; FP, fentanyl patch; NeP, neuropathic pain; NocP, nociceptive pain; PC, pain clinic.

use to patients. Consequently, unlike the report that chronic pain is controlled under a pain specialist’s care in 2% of patients,10 in this study, 78.0% of patients were treated in anesthesiology departments/pain clinics. In addition, therapeutic intervention with FP was provided to group of patients with a mean VAS score of 68.7 (22.3) mm, which corresponds to a pain intensity qualified as moderate-to-severe. Unlike most similar articles, we report ADRs and not AEs. Some events may have been misclassified as drug related. The overall incidence of ADRs in this trial was 52.5%. This compares well to a systematic review of Moore and McQuay where they found an overall AE rate of 51.0%.11 The incidence of ADRs by order of frequency was fairly consistent with the results from a previous 52-week clinical trial.12 The discontinued rate of FP therapy was 48.5% (n = 242) during the entire observation period. This rate was fairly consistent with previous studies that also evaluated safety and effectiveness of opioids on managing chronic pain using a similar study design.13,14

The ADR incidence was the highest during the period after baseline and before Day 30 (38%), which rapidly decreased to 10.8% during the subsequent 30-day period and to approximately 10% thereafter. These results are consistent with the following data from previous studies: The incidence of ADRs was 67.2% during the period from Day 1 to Day 8, but <10% during the period from Day 9 to Day 22, and 35.3% (approximately 30% each for gastrointestinal disorders and constipation) during the period from Day 23 to Day 29 in the 4-week clinical registration trial in Japan.15 The incidence of somnolence, nausea, and constipation—most frequently reported ADRs in the clinical registration trial of long-term FP use—was high (55.7%, 48.1%, and 36.8%, respectively) during the initial 4 weeks and decreased notably thereafter.12 An anti-emetic was used in 34.5% patients, and nausea and/or vomiting were reported in a similar proportion (33.2%) of patients. On the other hand, the proportion of patients who reported constipation (18.2%) was lower than that of patients who used a laxative (51.1%). These results suggest that nausea and/or vomiting may not have been treated adequately, which should be improved. Future research should address the prevention of ADRs in patients who use concomitant drug therapy. The Japanese society of pain clinicians recommends that patients should visit their primary physician every week after opioid therapy is initiated or when the opioid dose is increased.16 As ADRs were frequently reported in the initial 30 days, active monitoring of the patients is particularly needed during this period for preventing occurrence of ADRs.
The incidence of serious events was 7.8%. This is higher than in other clinical trials; for example, Langford et al.\textsuperscript{13} reported a serious adverse event rate of 2.8%. A higher hospitalization rate in Japan or some misclassifications may explain the difference. The rank order of most frequent serious ADRs was nausea, somnolence, constipation, vomiting, and dizziness.

Two events of respiratory depression (both nonserious), specified as an identified important risk, were reported. There are no further details of these cases but it is of note that one of the reported events lasted for 25 days which is quite unusual for an opioid-induced respiratory depression.

There were 9 other cases of drug withdrawal syndrome events (all serious) reported, and the patients were confirmed to have recovered, except 3 patients who were lost to follow up. This is line with the findings of Langford et al.\textsuperscript{13} in Caucasian patients who used the short opiate withdrawal scale (SOWS) to assess the drug withdrawal after a 12-week treatment with transdermal fentanyl. They found that 2 to 6% of the patients rated any withdrawal symptom as severe.

There were three drug dependence cases reported, two of them preexisting before inclusion, respectively, at baseline and one which was specified as withdrawal symptom. Repeated dose escalations especially when dosages of a morphine equivalent dose of 200 mg daily or higher are used may be a marker for substance use disorder or diversion;\textsuperscript{5} as per the Japanese guidelines, the maximum morphine equivalent dose should be 120 mg daily.\textsuperscript{16} The aforementioned maximum doses are equivalent to 8.4 mg and 4.2 mg of FP per application, respectively.\textsuperscript{17} In this survey, FP therapy was initiated at a dose of 2.1 mg (less than a morphine equivalent dose of 45 mg daily) in approximately 90% of patients, and only 10% of patients initiated FP therapy at \( \geq 4.2 \) mg per application. In addition, the mean single-application dose of FP was \(< 4.2 \) mg in 76.2% patients. These findings confirm that FP was used in accordance with the Japanese guidelines in most patients. The incidence of ADRs was lowest in patients treated at a mean single-application dose of 2.1 to 4.1 mg; this suggests the necessity of a thorough assessment of risks and benefits along with regular follow-ups, particularly when FP is prescribed at a dose of 4.2 mg or higher.

The overall response rate based on clinical effectiveness, as determined by the primary physician, was 77.3\%, and the rate of achievement of therapeutic goal was 64.5\%. These results imply that a majority of physicians and patients should experience a clinical benefit when using FP to manage moderate-to-severe chronic pain. The VAS scores significantly decreased by 22.3 mm from baseline to the last observation. Ostelo and de Vet suggested that the minimally clinically important decrease in VAS should be at least 20 mm from baseline to the last observation. Ostelo and de Vet suggested that the minimally clinically important decrease in VAS should be at least 20 mm for patients with subacute or chronic lower back pain.\textsuperscript{18} Although this study used a single-arm observational design and the effectiveness of FP should thus be interpreted with caution, we consider the above information to be supportive of the positive clinical effectiveness of FP.
There were no significant gender- or age-related differences regarding the incidence of ADRs. The incidence of ADRs was higher in patients diagnosed with NeP (55.5%) than in those diagnosed with NocP alone (38.6%). Moreover, the VAS scores largely decreased in patients diagnosed with NocP. The efficacy evaluation at Week 4 in the clinical trial for the development of FP also showed that the response rate was higher by approximately 10% in patients with a diagnosis of NocP, although it was not statistically significant. The mean single-application doses were relatively similar among patients diagnosed with NeP, NeP + NocP, and NocP (3.8 ± 3.0, 3.7 ± 2.7, and 3.8 ± 3.0 mg, respectively); however, the median and maximum single-application doses were 2.8 and 32.0, 2.8 and 23.0, and 2.3 and 15.7 mg, respectively. Furthermore, the higher incidence of ADRs in patients visiting anesthesiology departments/pain clinics appears to reflect that patients with NeP were treated more often by specialized physicians. The present study did not find any significant factor for explaining these differences regarding ADR occurrences. However, we hypothesize that different types of medical practice including number of hospital visits might affect these differences. Future studies focusing on the association between pain types and adverse events are needed.

The present study has several limitations. First, because of the nature of a postmarketing surveillance study, the present study was not conducted with intensive study monitoring and source data verification that are routinely conducted in clinical registration trials. Consequently, the data, especially for the incidence of ADRs, highly reflect the original case reports from each study site and are not directly comparable with the results of other clinical trials. Although consistencies and similar trends with previous clinical trials for the incidence of ADRs were observed, the interpretation should be made with caution. Second, this study was not designed to specifically evaluate the effectiveness of RMAP. Therefore, the causal relationship between the RMAP and the incidence of ADRs could not be derived. Future study is strongly needed to derive the evidence of effectiveness regarding the RMAP. Similar to the interpretation of RMAP, this study was not designed to evaluate the efficacy of FP in chronic pain management. The causation between treatment and efficacy outcomes could not be derived.

In conclusion, our results suggest that respiratory depression, drug dependency, and drug withdrawal under long-term use of FP were rarely observed even under the RMAP in Japan. Nonpain clinicians should be kept informed on the appropriate use of strong opioids to manage severe chronic pain. In addition, our results further advanced the literature pool of clinical effectiveness of FP for managing moderate-to-severe chronic pain. Finally, it is considered that the use of FP, especially under the RMAP, should be a useful treatment option for moderate-to-severe chronic pain in patients previously treated with an opioid.

ACKNOWLEDGEMENTS

The authors would like to show their deep appreciation to the physicians and patients who participated in this survey.

DISCLOSURE

This study was funded by Janssen Pharmaceutical K.K. of Johnson & Johnson in Japan. All authors are employees of Janssen Pharmaceutical K.K of Johnson & Johnson in Japan. This study was previously presented at the 21st Annual Meeting of the Japanese Society of Lumbar Spine Disorders, 2013.

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