

Use of immediate-release opioids as supplemental analgesia during management of moderate-to-severe chronic pain with buprenorphine transdermal system

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Background: The buprenorphine transdermal system (BTDS) is approved in the US for the management of chronic pain. Due to its high affinity for μ -opioid receptors with a slow dissociation profile, buprenorphine may potentially displace or prevent the binding of competing μ -opioid-receptor agonists, including immediate-release (IR) opioids, in a dose-dependent manner. Health care professionals may assume that the use of IR opioids for supplemental analgesia during BTDS therapy is not acceptable.

Materials and methods: This post hoc analysis evaluated the use of IR opioids as supplemental analgesia during the management of moderate-severe chronic pain with BTDS at 52 US sites (BUP3015S, NCT01125917). Patients were categorized into IR-opioid and no-IR-opioid groups. At each visit of the extension phase, adverse events, concomitant medications, and information from the Brief Pain Inventory (BPI) were recorded.

Results: The most common supplemental IR opioids prescribed during BTDS treatment (n=354) were hydrocodone-acetaminophen and oxycodone-acetaminophen. The mean daily dose of IR opioids (morphine equivalents) for supplemental analgesia was 22 mg. At baseline, BPI – pain intensity and BPI – interference scores were higher for patients in the IR-opioid group. In both treatment groups, scores improved by week 4, and then were maintained throughout 6 months of the open-label extension trial. The incidence of treatment-emergent adverse events was similar in both groups.

Conclusion: Patients who were prescribed IR opioids reported lower scores for BPI pain intensity and pain interference to levels similar to patients receiving BTDS without IR opioids, without increasing the rate or severity of treatment-emergent adverse events. Patients prescribed concomitant use of IR opioids with BTDS had greater treatment persistence. The results of this post hoc analysis provide support for the concomitant use of IR opioids for supplemental analgesia during the management of moderate-severe chronic pain with BTDS.

Keywords: buprenorphine transdermal system, ER opioids, chronic low-back pain, chronic noncancer pain, Butrans, supplemental analgesia, breakthrough pain

Introduction

Chronic pain conditions affect approximately 100 million adults in the US.¹ The US Food and Drug Administration guidance has noted that prescription opioids are an important component of modern pain management.² Opioid medications can be classified as immediate-release (IR) or extended-release (ER)/long-acting (LA) opioid formulations on the basis of their duration of action. Usually, IR opioids are short-acting, intended for use every 3–6 hours, and are more appropriate for transient pain types,

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such as acute, breakthrough, or intermittent pain.^{3,4} Common IR opioids (eg, morphine, hydromorphone, oxycodone, codeine, fentanyl, tramadol, tapentadol, oxycodone, and hydrocodone) may be available as single entity or in combination with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs). Due to associated risks of hepatic and gastrointestinal toxicity with acetaminophen or NSAIDs, the maximum daily amount of these combination therapies may be limited.⁴ On the other hand, ER/LA opioids have a prolonged half-life and deliver a dose over a longer period of time (greater than 8 hours), which makes them appropriate for patients with persistent chronic pain that requires stable, around-the-clock dosing.^{3,4} Generally, ER/LA opioids are intended to result in less frequent administration than IR-opioid formulations.⁵

Buprenorphine hydrochloride was introduced in the US for pain management in a parenteral form in 1981.⁶ Transdermal formulations for pain management were launched in Europe in 2001, which led to renewed interest in the use of buprenorphine to treat cancer pain and chronic nonmalignant pain.^{7,8} In 2010, the buprenorphine transdermal system (BTDS; Butrans®, Purdue Pharma LP, Stamford, CT, US) was approved in the US for the management of chronic pain.^{9–11} The BTDS is a transdermal patch that delivers an average of 5, 7.5, 10, 15, or 20 µg/h of buprenorphine over 7 days. It is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.⁹ Several studies have demonstrated that the BTDS is effective, safe, and generally well tolerated among adults with moderate–severe chronic pain.^{10–19}

Buprenorphine is a lipophilic, semisynthetic opioid derived from thebaine that is classified as a schedule III controlled substance.^{9,20} Buprenorphine demonstrates high binding affinity for μ -, κ -, and δ -receptors and low affinity for ORL1 (nociceptin).²¹ Buprenorphine demonstrates different intrinsic activities as a partial agonist at μ -opioid receptors and at ORL1 receptors, an antagonist at κ -receptors, and an agonist at δ -opioid receptors *in vitro*.^{9,22,23} The analgesic effects of buprenorphine appear to derive largely (if not solely) from its actions at the μ -opioid receptor,²⁴ while the contributions of actions at the other opioid receptors are unclear.⁹ The slow dissociation of buprenorphine from μ -opioid receptors may contribute to its long duration of activity.^{6,25}

Due to its high affinity and slow dissociation from opioid receptors, buprenorphine given at higher doses may

effectively inhibit the binding of concomitantly administered opioids. In the higher-dose sublingual buprenorphine formulations, this results in a dose-related protective effect that is useful when treating opioid dependence in patients with higher opioid requirements.²⁶ Because buprenorphine at higher doses may inhibit concomitantly administered opioids, it has been assumed that IR opioids are generally less effective when used for supplemental analgesia during therapy with lower-dose buprenorphine formulations, such as the BTDS.

The risks of treating chronic pain with opioids should always be carefully assessed in each patient, and there are many patient- and drug-specific factors to consider. The BTDS shares the common side effects of opioid therapy, such as nausea, headache, dizziness, constipation, and somnolence, and also may cause application-site reactions, such as pruritus, erythema, and rash. Additionally, the risk of respiratory depression is greatest when initiating therapy or when increasing the dose. Although respiratory depression can occur at recommended doses, the risk of death due to overdose is linked to higher opioid doses.^{27,28} Specific patient populations may be at greater risk of respiratory depression, including elderly, cachectic, or debilitated patients and those with preexisting pulmonary diseases, taking concomitant central nervous system depressants, or impaired renal or hepatic function. Because buprenorphine is highly metabolized by CYP3A4, there is a risk of drug interactions with CYP3A4 inhibitors, leading to increased buprenorphine plasma concentrations and increased or prolonged opioid effects. Misuse, abuse, and addiction to opioids can also occur, even at recommended doses.⁹

Breakthrough pain, usually presenting as incident pain or episodic pain, describes exacerbations of pain occurring in the background of adequately managed chronic pain.²⁹ Incorporating principles of the multimodal approach to pain management, it is common to manage breakthrough pain utilizing nonopioid or combination IR opioid–nonopioid products for supplemental analgesia.³⁰ As a balanced approach to pain management for some patients with chronic pain, IR opioids may be used to supplement ER/LA-opioid therapy. However, there is limited guidance and discussion on optimal treatment strategies for add-on therapy of IR opioids to ER/LA-opioid therapy to treat breakthrough pain.³⁰ The objective of this post hoc analysis is to describe the efficacy, safety, and tolerability of the BTDS when used concomitantly with IR opioids as supplemental analgesia during the management of moderate–severe chronic pain.

Materials and methods

Study population and design of open-label extension

Data in the current analysis were collected from the open-label extension phase (BUP3015S, NCT01125917) of a 12-week, randomized double-blind clinical trial of the BTDS in patients with moderate–severe chronic low-back pain (BUP3015, NCT00313014).¹⁰ The open-label, long-term study was conducted from June 2004 to September 2005. Ethical approvals were obtained, and consent processes for the clinical trials used in this research were followed. The data from the clinical trials is freely available (ClinicalTrials.gov).

All patients, regardless of treatment, who had entered the double-blind period and who completed or discontinued due to lack of efficacy were eligible to enroll in the open-label extension phase of this study. Opioid-experienced patients (receiving 30–80 mg/day of oral morphine or equivalent) with moderate–severe chronic low-back pain who had received either the BTDS or IR oxycodone for up to 12 weeks in the double-blind study were eligible to be enrolled in the open-label, long-term study. IR opioids for supplemental analgesia were not permitted after the first week of the double-blind study.¹⁰

Regardless of their dose level at the completion of the double-blind trial, all patients began the extension phase with BTDS 5 µg/h, and the dose was titrated to BTDS 10 µg/h or further to BTDS 20 µg/h if necessary. The maximum BTDS dose allowed was 20 µg/h, and patients with adequate analgesia were allowed to withdraw from the study. BTDS 7.5 and 15 µg/h were not available at the time this study was conducted. Titration to the next dose level occurred at the minimum titration interval of 3 days, when plasma concentrations were at a steady state. Downward titration was also permitted. Patients were able to titrate to their optimal dose, and at any given time could wear only one 5, 10, or 20 µg/h patch.

Enrolled patients were allowed non-sponsor-supplied supplemental analgesic medications, such as IR opioids and NSAIDs. Extended-release opioids, including transdermal fentanyl, were not allowed during the entire study course (ie, neither the core nor the extension).

At each visit of the extension phase, information recorded included adverse events (AEs), concomitant medication, and study-medication changes. Patients also completed an eleven-item Brief Pain Inventory – short form (BPI-SF), a self-administered questionnaire developed to assess the severity of pain and the interference of pain on daily functioning. The BPI pain-intensity scale measures, 1) pain at its worst in the last 24 hours, 2) pain at its least in the last 24 hours, 3) pain on average, and 4) pain right now. The BPI

pain-interference scale measures how pain interferes with the patient's general activity, mood, walking ability, work, relations with others, sleep, and enjoyment of life during the last 24 hours. Pain intensity was scored on an 11-point scale where 0 = “no pain” and 10 = “pain as bad as you can imagine”, while pain interference was scored as 0 = “does not interfere” and 10 = “completely interferes”.

Analysis

In this retrospective post hoc analysis, patients were categorized into two groups: 1) the IR-opioid group (those who were prescribed IR opioids as supplemental analgesia at least once during the extension trial), and 2) the no-IR-opioid group (those who were not prescribed IR opioids as supplemental analgesia during the extension trial). For each patient in the IR-opioid group, the average daily IR-opioid dose (in morphine equivalents) was calculated. The equianalgesic ratios used to convert from other opioids to morphine were those published in recent guidelines, where 30 mg of oral morphine per day equates to 30 mg per day of hydrocodone or 20 mg per day of oxycodone.³¹

Pain scores from the BPI-SF (pain intensity and pain interference) were tabulated and plotted by group at baseline and at weeks 4, 12, 16, 20, and 24 of the extension phase. Baseline scores were the patient's BPI scores at the end of the double-blind period, and were defined as the measurement at week 0 of the extension phase. *P*-values for BPI pain intensity and pain interference were generated from an analysis of covariance with treatment included (IR-opioid group/no-IR-opioid group) and adjusted by baseline. Because this study was terminated early for administrative reasons unrelated to safety or efficacy, BPI pain intensity and BPI interference were analyzed only for the 6-month period.

Treatment-emergent AEs (TEAEs) were tabulated for the entire extension phase for both the IR-opioid group and the no-IR-opioid group. The incidence of TEAEs was further calculated in a manner where patients in the IR-opioid group were separated by whether they were on IR opioids or not. TEAEs in patients who were on IR opioids were those that occurred within a 7-day period after reporting the use of a concurrent IR opioid. TEAEs in patients who were not on IR opioids were those that occurred outside the 7-day period of concurrent IR-opioid use. Total TEAEs in the IR-opioid group were also summarized, and included all TEAEs that occurred during the 24-week treatment period, regardless of concurrence of IR-opioid usage. The calculation for total TEAEs in the IR-opioid group may be numerically less than the sum of TEAEs during periods on IR opioids or not on

IR opioids, since it removed any TEAEs that may have been reported twice (eg, when a patient was on IR opioids, then again when the patient was not). Since this was a post hoc analysis of an open-label, observational study, only minimal inferential analyses were performed, and the results presented are mainly descriptive.

Results

Patient characteristics

A total of 354 patients were enrolled in the extension trial, with 181 patients in the IR-opioid group and 173 patients in the no-IR-opioid group (Table 1). Patient characteristics were similar between the IR-opioid group and the no-IR-opioid group: mean age 50.9 years vs 51.5 years, sex 56% male vs 55% male, race 98% white vs 90% white, respectively. Of the 354 patients, 213 were exposed to the BTDS for at least 6 months, including 54 patients exposed for at least 1 year. Patients in the IR-opioid group remained in the extension phase a mean of 164 days compared with 122 days for patients in the no-IR-opioid group.

IR-opioid use as supplemental analgesia

The most common IR opioids prescribed for supplemental analgesia during BTDS treatment were hydrocodone–acetaminophen and oxycodone–acetaminophen. The mean daily dose of IR opioids (reported in morphine equivalents, using a morphine:hydrocodone potency ratio of 1:1 and a morphine:oxycodone potency ratio of 3:2) prescribed for supplemental analgesia was 22 mg. Mean supplemental IR-opioid use was relatively consistent throughout the 24-week study period (Figure 1). The median daily IR-opioid dose was 12 mg.

Pain scores

At baseline (end of core study), scores were higher ($P<0.05$) for both BPI pain intensity (rating of 4) and BPI interference

(rating of 3.8) in patients in the IR-opioid group versus patients in the no-IR-opioid group (BPI scores of 3.4 and 3.16, respectively; Figures 2 and 3). By the first scheduled visit after baseline at week 4, BPI pain intensity and BPI interference had improved for patients in the IR-opioid group, and in the 5 months thereafter remained similar to the no-IR-opioid group. The number of patients with a completed BPI assessment at baseline and at weeks 4, 12, 16, 20, and 24 was 175, 154, 116, 94, (84 for BPI pain intensity, 85 for BPI interference), and 85 for the IR-opioid group and 167, 150, 108, 88, 72, and 72 for the no-IR-opioid group, respectively. Reasons for discontinuations in each group were not evaluated for this post hoc analysis.

Treatment-emergent adverse events

In general, the incidence of TEAEs was similar in patients on IR opioids compared with patients in the no-IR-opioid group during the study (Table 2). The BTDS was well tolerated in both groups, with no remarkable increase in TEAEs in the IR-opioid group. In the IR-opioid group, 72.4% had a TEAE compared to 69.4% in the no-IR-opioid group. The

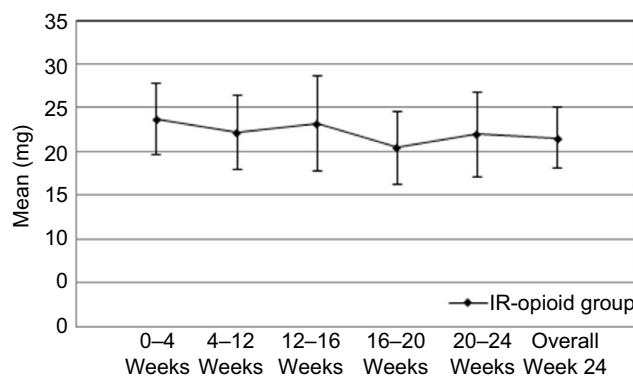
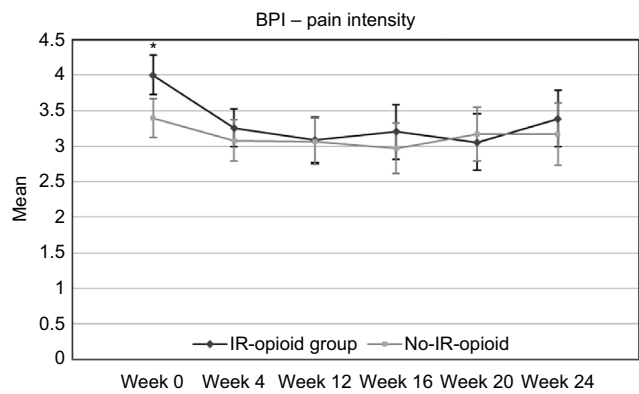


Figure 1 Mean supplemental opioid use over time (in milligrams of morphine equivalents) for patients in the IR-opioid group.
Abbreviation: IR, immediate-release.

Table 1 Comparative characteristics, enrolled extension-trial population

	IR-opioid group (n=181)	No-IR-opioid group (n=173)
Mean age, years (SD)	50.9 (12.49)	51.5 (12.49)
Minimum, maximum age, years	24, 84	24, 82
Sex, n (%)		
Male	102 (56)	95 (55)
Female	79 (44)	78 (45)
Race, n (%)		
White	178 (98)	156 (90)
Black	2 (1)	12 (7)
Asian	0	2 (1)
Other	1 (0.6)	3 (2)
Mean days in extension trial	164	122

Abbreviations: IR, immediate-release; SD, standard deviation.

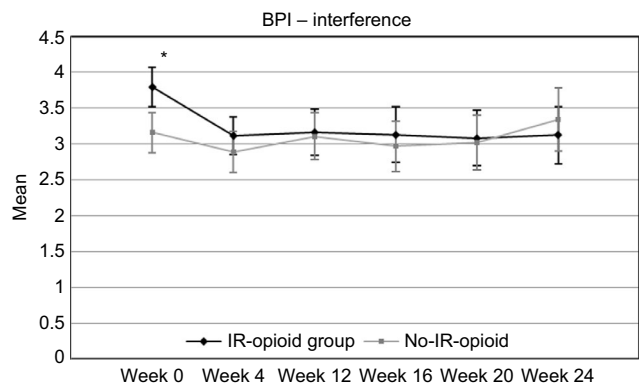


	Start of extension	Week 4	Week 12	Week 16	Week 20	Week 24
IR-opioid, n	175	154	116	94	84	85
No-IR-opioid, n	167	150	108	88	72	72

Figure 2 Mean pain-intensity scores for patients in the IR-opioid and no-IR-opioid groups.

Notes: *P<0.05; error bars represent 95% CIs.

Abbreviations: IR, immediate-release; CIs, confidence intervals; BPI, Brief Pain Inventory.



	Start of extension	Week 4	Week 12	Week 16	Week 20	Week 24
IR-opioid, n	175	154	116	94	85	85
No-IR-opioid, n	167	150	108	88	72	72

Figure 3 Mean pain-interference scores at each assessment point for patients in the IR-opioid and no-IR-opioid groups.

Notes: *P<0.05; error bars represent 95% CIs.

Abbreviations: IR, immediate-release; CIs, confidence intervals; BPI, Brief Pain Inventory.

most common TEAE was headache: 14% in the IR-opioid group compared with 16.8% in the no-IR-opioid group.

The incidence of serious AEs (SAEs) reported during this extension study was 5% (19 of 354). Of the 19 patients who experienced SAEs, eleven were in the IR-opioid group and eight the no-IR-opioid group. One patient in the IR-opioid group experienced a fatal SAE (sudden cardiac death of a 74-year-old male). The majority of SAEs, including the one death, were

considered by the investigator to be unrelated to BTDS use. One additional SAE was reported after study discontinuation.

Discussion

While more rigorous studies are needed, the results of this post hoc analysis provide support for the acceptable use of IR opioids for supplemental analgesia during BTDS therapy. Compared with the no-IR-opioid group, the IR-opioid group reported higher BPI pain and interference scores at the start of the open-label period, suggesting patients with a higher pain score required additional analgesia. While the use of IR opioids remained consistent throughout the 24-week period, BPI scores stabilized after the first visit/week 4 and were similar to those reported in the no-IR-opioid group for the remainder of the 24-week analysis period. These findings suggest that the use of IR opioids with the BTDS lowered BPI scores to levels comparable with BTDS use alone. The reporting of TEAEs in patients on IR opioids was similar to patients in the no-IR-opioid group.

Data for this post hoc analysis were obtained from an open-label clinical study, which introduces some inherent limitations, such as patient self-reporting of medication use, pain scores, and AEs. The division of patients into the IR-opioid group and no-IR-opioid group was based on investigator documentation of prescribing concomitant medications. The actual dose taken by the patient during the study was not verified. While the mean daily dose of IR opioids prescribed for supplemental analgesia was 22 mg of morphine equivalents, due to the trial design and methodology, it is not possible to confirm that all prescribed doses of supplemental opioid analgesic were actually taken by the patients in the IR-opioid group. This introduces a potential inconsistency between the prescribed dose and the dose of IR opioids actually taken by the patient for supplemental analgesia. This analysis should thus be considered exploratory research.

Consistent with most open-label trial designs, additional medical therapies deemed appropriate for the subject's medical condition were permitted during the extension phase at the discretion of the investigator, with the exception of long-acting opioid analgesics. The addition of other medical therapies may impact the results of this analysis. In an open-label, usual-care study design, such as this one, investigators are generally allowed to individualize treatment for chronic pain, using their own clinical judgment regarding a target pain score balanced with safety considerations. Although AEs were evaluated, this post hoc analysis did not evaluate reasons for discontinuation by patients. Patients with inadequate analgesia could have discontinued from the extension study.

Table 2 Incidence of TEAEs ($\geq 5\%$) during BTDS treatment for moderate–severe chronic pain: IR-opioid group vs no-IR-opioid group

	IR-opioid group (n=181)						No-IR-opioid group (n=173)	
	On IR opioid		Not on IR opioid		Total		n	%
	n	%	n	%	n	%		
Any TEAE	131	72.4	43	23.8	144	79.6	120	69.4
Headache	25	13.8	4	2.2	29	16	29	16.8
Application-site erythema	18	9.9	4	2.2	22	12.2	17	9.8
Application-site pruritus	17	9.4	5	2.8	22	12.2	17	9.8
Application-site rash	14	7.7	6	3.3	20	11	15	8.7
Arthralgia	17	9.4	3	1.7	20	11	9	5.2
Nausea	13	7.2	4	2.2	17	9.4	17	9.8
Back pain aggravated	10	5.5	2	1.1	12	6.6	5	2.9

Abbreviations: TEAEs, treatment-emergent adverse events; BTDS, buprenorphine transdermal system; IR, immediate-release.

Despite the stated limitations, previous studies on both buprenorphine pharmacology and clinical experience with the BTDS further corroborate that the supplemental use of IR opioids during BTDS therapy is appropriate for some patients (Table 3).^{6–8,17,23,25,32–48} Although buprenorphine is considered a partial agonist at the μ -opioid receptor in vitro and an antagonist at the κ -opioid receptor, studies have shown that buprenorphine can be expected to produce pharmacological effects similar to those of full μ -agonists, especially at the comparatively lower buprenorphine doses delivered by the BTDS.^{9,7,22,25} It has been reported that buprenorphine behaves like a full μ -opioid agonist at analgesic doses, and the partial agonistic property, high affinity binding, or slow dissociation of buprenorphine does not have a negative effect on the availability of μ -opioid receptors or on its interaction with full μ -opioid agonists.^{23,25} In animals pretreated with an analgesic dose of buprenorphine, the addition of morphine, oxycodone, or hydromorphone results in an additive or synergistic effect.²⁵

Buprenorphine exhibits dose-dependent receptor occupancy. Due to its high affinity for μ -opioid receptors, buprenorphine may inhibit or displace other μ -opioid receptor agonists at higher concentrations. Receptor inhibition is likely dependent on the dose of buprenorphine or concentration of buprenorphine at the receptor.^{49–54} However, the buprenorphine doses provided by the BTDS in the US are relatively low. For example, the systemic buprenorphine-delivery rate from the BTDS averages 5, 7.5, 10, 15, and 20 $\mu\text{g}/\text{hour}$ over 7 days. Since transdermal administration of buprenorphine bypasses the gastrointestinal tract and first-pass metabolism, bioavailability is 100% of the dose delivered. The BTDS doses in the US correspond to average daily buprenorphine doses of approximately 0.12 mg, 0.18 mg, 0.24 mg, 0.36 mg, and 0.48 mg.^{9,13} In the US, the sublingual and buccal buprenorphine products indicated for

the treatment of opioid dependence are available in higher-dosage strengths than the BTDS, ranging 1.4–11.4 mg with naloxone and 2–8 mg without naloxone,^{55–58} and may have less than 100% bioavailability, since some of the dose is swallowed.^{59,60} At higher sublingual buprenorphine doses (2–32 mg), opioid receptors approach saturation, as evidenced in a study evaluating positron-emission tomography brain scans.⁶¹ Buprenorphine produces analgesia in humans at less than full receptor occupancy.⁶² Therefore, at lower doses of buprenorphine, such as those elicited by the BTDS, opioid receptors are unsaturated, which allows for the concomitant binding of other opioids to unoccupied receptors for effective analgesia for breakthrough pain.

To support the pharmacological perspective, we sought to understand the clinical perspective further, and conducted literature searches in the Medline, Embase, and Derwent Drug File databases, using search terms for use of IR opioids for breakthrough pain or supplemental analgesia during transdermal buprenorphine therapy (Table 3). We found numerous studies that reported the use of supplemental opioid analgesics, including codeine, morphine, tramadol, fentanyl, and buprenorphine, during transdermal buprenorphine therapy for chronic pain. Many of the studies identified included a higher-dose transdermal formulation of buprenorphine available in Europe that provides 35, 52.5, or 70 $\mu\text{g}/\text{hour}$ of buprenorphine,⁶³ corresponding to average daily buprenorphine doses of 0.84 mg, 1.26 mg, and 1.68 mg.⁶⁴ Few studies were designed to evaluate the safety and efficacy of supplemental IR-opioid use along with transdermal buprenorphine.^{34,37,41} The studies that did, reported the efficacious use of an IR opioid along with transdermal buprenorphine with an AE profile that was generally acceptable, and similar to that produced by opioids and transdermal systems. The results of this literature search indicate vast clinical experience with the concomitant use of IR opioids and buprenorphine, even at

Table 3 Published studies where IR opioids were used as supplemental analgesia during transdermal buprenorphine therapy for chronic pain

Study	Reported pain condition(s)	IR opioids used as supplemental analgesia	Reported dose of IR opioid
Aurilio et al ³²	Chronic cancer pain	Oral morphine	Mean 4–34 mg/day
Böhme and Likar ³³	Severe chronic pain of malignant or nonmalignant origin	Sublingual buprenorphine (Europe)*	Mean 0.3–0.4 mg/day
de Barutell and Gonzalez-Escalada ³⁴	Any type of chronic pain	Oral tramadol or oral morphine	Mean tramadol range 60–114 mg/day; mean morphine range 13–17 mg/day
Freye et al ³⁵	Pain of different origins	Oxycodone, oral morphine, sublingual buprenorphine (Europe)*	Doses not reported
Gordon et al ¹⁶	Moderate or greater chronic low-back pain	Oral codeine 30 mg and APAP 300 mg	Mean 1.8±2.6 tabs/day
Likar et al ⁸	Cancer and noncancer patients with moderate–severe chronic persistent pain	Sublingual buprenorphine (Europe)*	41% took 0 tabs (0.2 mg), 25% took 1 tab, 23% took >1 but ≤3 tabs, 11% took > 3 tabs
Menten et al ³⁶	Radiotherapy-related pain in head and neck cancer	Oral tramadol, sublingual buprenorphine (Europe),* oral morphine	Not reported
Mercadante et al ³⁷	Episodic pain in cancer patients	IV morphine	Mean 6.1 mg/day
Mercadante et al ³⁸	Cancer patients	Oral morphine	Not reported
Mercadante et al ³⁹	Cancer patients	Oral morphine	Not reported
Mordarski ⁴⁰	Noncancer pain in hemodialysis patients	Oral tramadol	Mean dose 61–149 mg/day
Nadezhda et al ⁴¹	Moderate–severe chronic cancer pain	Oral tramadol or IM buprenorphine	Mean tramadol dose 61–147 mg/day; IM buprenorphine up to 0.6 mg/day
Pace et al ⁴²	Chronic cancer pain	Oral tramadol	Up to 200 mg/day
Poulain et al ⁴³	Severe cancer pain	Sublingual buprenorphine (Europe)*	Mean 1±1 tab/day
Ruggiero et al ⁴⁴	Moderate–severe cancer related pain in pediatric patients	Oral tramadol	Not reported
Setti et al ⁴⁵	Postoperative pain from gynecologic surgery	IV morphine	Mean up to 7.2±4.6 mg/day
Sittl et al ⁴⁶	Chronic severe pain due to cancer and other conditions	Sublingual buprenorphine (Europe)*	Mean 0.3 mg/day
Sorge and Sittl ⁴⁷	Severe chronic cancer or noncancer pain	Sublingual buprenorphine (Europe)*	Mean up to 1.1 mg/day
Zarth ⁴⁸	Chronic pain due to breast and bone cancer	Oral morphine, transmucosal fentanyl, sublingual buprenorphine (Europe)*	Not reported

Note: *Sublingual buprenorphine available in Europe as a 0.2 mg dosage strength.

Abbreviations: IR, immediate-release; APAP, *N*-acetyl-*para*-aminophenol (acetaminophen); IM, intramuscular; IV, intravenous.

higher transdermal buprenorphine doses than those approved in the US (Table 3).^{8,17,32–48}

Conclusion

The results of this post hoc analysis provide support for the use of IR opioids as an acceptable choice for supplemental analgesia during the management of moderate–severe chronic pain with the BTDS. In this study, patients who were concomitantly prescribed IR opioids with the BTDS reported lowered scores for BPI pain intensity and pain interference to levels similar to patients receiving the BTDS only. Patients concomitantly prescribed BTDS treatment with supplemental IR opioids did not report substantial increases in the rate or severity of TEAEs compared with BTDS use alone. Patients

prescribed concomitant IR opioids with the BTDS remained in the study for a longer period of time than patients receiving the BTDS alone. Pharmacologic evidence and extensive published medical literature corroborate the clinical findings of this post hoc analysis, and together provide evidence and rationale to health care professionals regarding the acceptability of prescribing IR opioids for breakthrough pain during BTDS therapy.

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Author contributions

All authors were involved in study design and data collection, and participated in data analysis, data interpretation, and writing the article. The authors had full access to all data, and had final responsibility for the decision to submit for publication.

Disclosure

MJC, MK, and SRR are full-time employees of Purdue Pharma LP. SS is a speaker/consultant for Purdue Pharma and other companies. RBR is a speaker, consultant, and basic-science investigator for several pharmaceutical companies involved in analgesics research, but receives no royalty from the sale of any product. The abstract of this paper was presented at the American Pharmacists Association Annual Meeting and Exposition, March 9–12, 2012, New Orleans, LA as an abstract with interim findings, and then at the following conferences as posters: Pain Week, September 6–10, 2012, Las Vegas, NV; American Academy of Pain Management 23rd Annual Clinical Meeting, September 20–23, 2012, Phoenix, AZ.

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