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ORIGINAL RESEARCH ARTICLE

Assessment of Transdermal Buprenorphine Patches for the Treatment of Chronic Pain in a UK Observational Study

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Abstract

Background Opioids provide effective analgesia for moderate-to-severe, chronic pain. Transdermal buprenorphine (TDB) is available in the UK as weekly, lower-dose (5–20 μg/h) patches and twice-weekly, higher dose (35–70 μg/h) patches. This prospective, observational, multicenter study of patients with various chronic pain conditions assessed the safety, perceptions, and discontinuation of treatment with TDB in a real-world, non-interventional setting (ClinicalTrials.gov study ID: NCT01225861).

Methods Patients aged ≥18 years who were already receiving or initiating treatment with TDB were recruited in the UK during routine clinical visits and were followed for 6 visits or 9 months (whichever came first). Self-reported treatment adherence, patient satisfaction, and safety data were collected at each study visit.

Results Of 465 patients, 272 were already receiving 7-day TDB at the study start (TDB experienced), 146 were TDB naïve, and 47 were prescribed twice-weekly TDB. Most patients were female (72.9 %) and overweight/obese (body mass index ≥25: 75.3 %). The median age was 67 years, and the mean duration of pain was 11.1 years. Arthritis/other musculoskeletal disorders (39.6 %) were the most common causes of pain. Mild adverse events were commonly reported. Skin irritations, which were most frequent in 7-day TDB-experienced patients (45.6 %), rarely resulted in treatment discontinuation (8.8 %). Nearly all patients used TDB in accordance with treatment recommendations. Most patients reported that TDB was 'effective'/'very effective' at relieving pain and were 'satisfied'/'very satisfied' with TDB therapy.

Conclusion In everyday clinical practice, TDB was well tolerated and patients were satisfied with their therapy. Self-reported adherence to TDB was very high, and adverse events rarely resulted in treatment discontinuation. Opportunities were identified to limit common adverse events associated with TDB.

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Key Points for Decision Makers

Chronic pain is a highly debilitating condition commonly associated with physical and psychosocial impairments and a significant socioeconomic burden. Effective management often necessitates long-term treatment, which can be associated with suboptimal compliance and relapse.

This prospective, observational study indicates that real-world use of transdermal buprenorphine (TDB) in the UK is largely in accordance with the prescribing information.

Although many patients receiving TDB experienced at least one adverse event, these rarely resulted in treatment discontinuation. Patients also reported a high level of satisfaction with TDB therapy.

1 Introduction

Moderate-to-severe, chronic pain affects approximately one fifth of adults in Europe and is particularly prevalent in the elderly, being reported to affect over 70 % of individuals aged >65 years [1, 2]. It impairs patients' physical and psychological well-being and places a large financial burden on individuals and society [1, 3, 4]. Pharmacological treatments for chronic pain include traditional analgesics such as paracetamol and non-steroidal anti-inflammatory drugs, with adjuvants such as antidepressants and anticonvulsants for neuropathic pain. The World Health Organization (WHO) analgesic ladder, developed for cancer-related pain, recommends a stepwise treatment approach, including step-2 weak opioid analgesics (e.g., codeine and tramadol) or more potent step-3 opioid analgesics (e.g., buprenorphine, morphine, and oxycodone) for selected patients with moderate-to-severe pain [5]. The evidence basis for managing non-cancer pain is less robust, with a recent meta-analysis reporting that paracetamol was ineffective for lower back pain and osteoarthritis [6]. Consequently, treatment guidelines for non-cancer pain generally support the WHO analgesic ladder [7, 8]. A large-scale survey of prescribing practices for opioid analgesics in the UK revealed that 83 % of general practitioners considered opioids to be effective for chronic, non-malignant pain, although many had reservations about prescribing opioid analgesics long term [9]. While many patients benefit from prolonged-release oral opioids, transdermal formulations combine the convenience of a long duration of action with a simplified administration regimen and may particularly suit individuals wanting to reduce their pill count and those with swallowing difficulties or impaired gastrointestinal function [10, 11].

In vitro receptor-activation assays indicate that buprenorphine, along with fentanyl and morphine, acts as a partial agonist of the μ-opioid receptor [12]. However, studies in healthy volunteers and heroin-dependent individuals reveal that oral buprenorphine at doses of 2 mg occupies approximately 30–50 % of μ-opioid receptors in the central nervous system, while oral doses of 16 mg and above occupy 79–95 % of these receptors [13, 14]. The slow dissociation of buprenorphine from μ-opioid receptors results in a long duration of analgesic action, while antagonism of κ-opioid receptors exerts an antihyperalgesic effect [15–17]. Clinically relevant doses of buprenorphine have no analgesic ceiling effect, immunosuppressive activity, or effect on gonadal hormones, and pharmacokinetic properties are unaltered in elderly patients and individuals with renal dysfunction [10, 15, 16, 18]. Furthermore, the ceiling effects of buprenorphine on respiratory depression do not translate into a ceiling effect on analgesia [19].

Lower-dose (5–20 mg; nominal release rate 5–20 μg/h) transdermal buprenorphine (TDB) patches, administered weekly, are indicated for moderate, chronic, non-cancer pain, while higher dose (20–40 mg; nominal release rate 35–70 μg/h), twice-weekly TDB patches are indicated for patients with moderate-to-severe cancer pain or severe pain that does not respond to non-opioid analgesics [20, 21]. TDB can also be combined with short-acting opioid analgesics as a rescue medicine for breakthrough pain [22, 23]. A cross-sectional, UK study of opioid-prescribing patterns in primary care revealed a marked increase in the prescribing of buprenorphine between 2000 and 2010 [24].

In common with all opioid analgesics, buprenorphine has addictive properties and, as a Scheduled Drug, it is subject to stringent controls regarding its prescription, storage, and distribution. It is noteworthy that the pharmacokinetic properties of buprenorphine, including the ceiling effect on substance-induced euphoria, gradual systemic exposure, and low peak plasma concentrations for effectiveness, limit the 'likeability' of buprenorphine for abuse in comparison with other opioid analgesics [19]. In addition, the transdermal matrix patch renders buprenorphine particularly difficult to extract for illicit purposes [19].

Clinical trials demonstrate that TDB provides superior analgesia to placebo [25–29]. Furthermore, lower-dose TDB provides equivalent pain relief to sublingual buprenorphine and is non-inferior to prolonged-release tramadol or co-codamol [30–32]. Common events (occurring in ≥10 % of patients) with TDB are typical of opioid analgesics and include constipation, dry mouth, nausea,

vomiting, headache, dizziness, and somnolence [20, 21]. While skin irritations at the site of transdermal patch application are reported, information is lacking regarding the frequency, nature, and impact of skin irritations in a wider setting [20, 21, 33].

The nature of chronic pain generally necessitates long-term treatment, but many patients discontinue long-term opioid therapy because of adverse events (AEs), dosing schedules, and attitudes of others towards opioids [34]. We conducted a prospective, observational study to assess TDB in patients with chronic pain in a real-world, non-interventional setting. The primary objective was to establish the incidence and severity of AEs and reasons for discontinuing treatment with TDB in patients with chronic pain already treated with TDB and in those initiating therapy. Secondary aims were to gain insights into skin irritations associated with TDB, and patient and physician perceptions of treatment, and to assess self-reported adherence and satisfaction with TDB treatment in real-world clinical settings.

2 Patients and Methods

2.1 Patients and Study Design

Patients already receiving or initiating treatment with TDB were recruited into this single-arm, prospective, observational study (ClinicalTrials.gov study ID: NCT01225861) in the UK during routine clinical visits at 51 primary care (general practitioner) and ten secondary care (pain specialist) centers. Participating physicians were recruited from 12 Strategic Health Authorities (SHAs) distributed across the UK (South West, South Central, East of England, South East Coast, London, Scotland, Wales, East Midlands, Yorkshire and Humberside, North East, North West, West Midlands). Each SHA covered several Primary Care Trusts incorporating general practitioners and at least one pain clinic. Patients aged <18 years or with a life expectancy of <6 months were excluded from the study. The first patient first visit and last patient last visit occurred in January 2011 and February 2014, respectively. The study comprised a baseline recruitment visit and six observational (follow-up) visits (or 9 months on-study, whichever came first), which were conducted during routine clinical consultations (Fig. 1).

The study was performed in accordance with the regulations and guidelines governing medical practice and ethics in the UK, following National Research Ethics Service approval. Local approval was obtained from the Research and Development Departments of the participating secondary care centers. For each primary care site, the responsible Clinical Commissioning Group or Primary Care Trust was notified and approval was obtained as necessary. All study documents were reviewed and approved by the appointed Research Ethics Committee, and all patients provided informed, written consent. No patient-identifiable data were collected.

2.2 Outcomes and Assessments

Data on AEs with TDB, self-reported treatment adherence, patient satisfaction, and perceptions of treatment were collected at regular intervals throughout the study via questionnaires. Patient demographic data and medical history were also assessed.

Patient Questionnaire A (completed at baseline) and Patient Questionnaire B (completed at each follow-up visit) evaluated the effectiveness, application/self-reported adherence, and satisfaction with 7-day TDB; various parameters of the Brief Pain Inventory assessment tool; and AEs, including skin irritations. Patient Questionnaire A also evaluated the medical history, prior treatments for pain, and personal circumstances/general well-being. Treatment switches (including reasons for switching) were captured in Patient Questionnaire B.

Physician Questionnaire A (completed at baseline) and Physician Questionnaire B (completed at each follow-up visit) evaluated the effectiveness of 7-day TDB; AEs, including skin irritations and serious AEs; and treatment switches (including the reasons for switching). Physician Questionnaire A also evaluated the medical history, comorbidities, prior treatments for pain, and satisfaction with 7-day TDB (See the Electronic Supplementary Material for further details of the Patient and Physician Questionnaires).

A separate Study Discontinuation Form was also completed if the patient discontinued TDB therapy, to evaluate the reasons for discontinuation, including the characteristics of AEs, the duration of TDB therapy, and follow-up treatments (Fig. 1).

2.3 Statistical Methods

The analyses were based on data collected in the Patient/Physician Questionnaires. Outcomes are described for all patients meeting the study inclusion criteria. Patients were stratified according to the type of TDB product: 7-day TDB [5 mg, 10 mg, or 20 mg patch strengths (equivalent to 5–20 μg/h)] or twice-weekly TDB [20 mg, 30 mg, or 40 mg patch strengths (equivalent to 35–70 μg/h)]. The 7-day TDB population was further stratified as treatment experienced (patients receiving 7-day TDB at study enrolment for >30 days) or treatment naïve (patients who had not received 7-day TDB prior to study onset for >30 days). Further analyses were conducted in patients

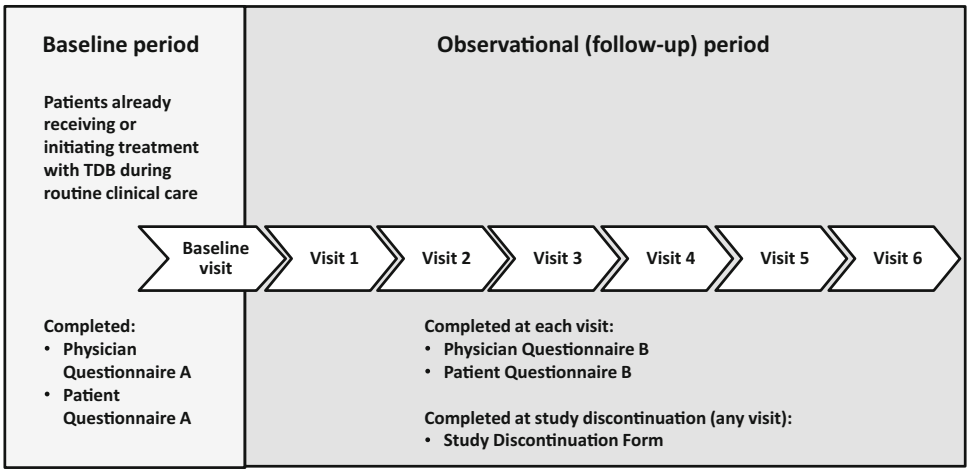

Fig. 1 The study comprised a baseline period [during which patients already receiving or initiating treatment with transdermal buprenorphine (TDB) were recruited during routine clinical care, and Physician Questionnaire A and Patient Questionnaire A were completed] and an observational (follow-up period) of 9 months or six follow-up visits (whichever came first). At each study visit, Physician Questionnaire B and Patient Questionnaire B were completed. A Study Discontinuation Form was completed at study discontinuation

who experienced skin irritation. Follow-up data are presented according to the date when TDB was initiated.

In addition to descriptive statistical approaches, continuous variables were compared using a Student's *t* test or a Mann–Whitney test (for normally and not-normally distributed data, respectively). Categorical variables were compared using chi-squared or Fisher exact tests, depending on the observations presented. An α value of 0.05 was applied as the significance level. No operational efforts were made to address for potential bias.

Incidence rates for AEs per 100 patient-years were calculated using the following formula:

$$\text{Incidence of specific AE} = \frac{\text{total number of episodes of specific AE} \times 100}{\text{total time of exposure to specific AE}}.$$

Because of the descriptive design of this study, missing values were not replaced (corresponding values were set to 'missing').

A sample size of 448 patients was required to estimate the prevalence of AEs (32–61 %) with a minimum precision of ± 0.0452 points.

3 Results

3.1 Patient Characteristics

Of 465 patients included in the analyses, 418 and 47 were prescribed 7-day TDB and twice-weekly TDB, respectively. Of the 7-day TDB cohort, $n = 272$ (65.1 %) had already been receiving TDB at study enrolment for >30 days and $n = 146$ (34.9 %) were TDB naïve. More patients were recruited by primary care physicians ($n = 381$) than by pain specialists ($n = 84$). The mean [standard deviation (SD)] durations of follow-up were 3.3 (3.5) months for all patients (range 0.0–16.7 months) and 5.0 (3.3) months for those with ≥1 follow-up visit ($n = 304$, range 0.2–16.7 months).

Demographic and disease characteristics were comparable for patients receiving 7-day and twice-weekly TDB (Table 1). Overall, most patients were female, of white ethnicity, and either overweight or obese. Patients had been receiving analgesic medication for a mean (SD) of 10.0 (10.0) years. The most common primary pain diagnosis was arthritis or another musculoskeletal inflammatory disorder, and the most common comorbidities were depression, constipation, drug hypersensitivity, and asthma ($n = 91$, 19.6 %). Constipation at baseline was most frequent in the twice-weekly TDB cohort ($n = 17$, 36.2 %) compared with TDB-experienced patients ($n = 80$, 29.4 %) and TDB-naïve patients ($n = 32$, 21.9 %). Other atopic allergic comorbidities included hay fever ($n = 25$, 5.4 %), rash or hives ($n = 17$, 3.7 %), and contact allergies ($n = 15$, 3.2 %). The main reasons for initiating TDB treatment were to reduce the number of oral medications (32.0 %), pain control (31.9 %), compliance (20.4 %), and failure on other analgesics (20.3 %).

Twice-weekly TDB was prescribed at a higher mean (SD) dose [30.2 (12.1) mg] than 7-day TDB. Patients who were 7-day TDB experienced were prescribed a higher mean (SD) dose of TDB than TDB-naïve patients [12.5 (6.8) mg versus 7.2 (4.1) mg]. Seven-day TDB 5 mg patches were more commonly prescribed for treatment-naïve

Table 1 Patient demographic and disease characteristics at baseline

Characteristic	7-day TDB ($n = 418$)	Twice-weekly TDB ($n = 47$)
Median age, years (range)	68 (22–99)	61 (31–96)
Female, *n* (%)	307 (73.4)	32 (68.1)
Body mass index, mean (SD)	29.4 (6.7)	29.3 (6.0)
Primary diagnosis, *n* (%)		
Arthritis or musculoskeletal inflammatory disease	172 (41.1)	12 (25.5)
Spinal/back pain condition or injury	147 (35.2)	13 (27.7)
Musculoskeletal pain or injury	50 (12.0)	9 (19.1)
Bone disease and related pain	19 (4.5)	2 (4.3)
Neurological disorder	17 (4.1)	3 (6.4)
Other[a]	13 (3.1)	8 (17.2)
Mean duration of chronic pain, years (SD)	11.2 (10.8)	10.7 (7.3)
Mean pain score on numerical analog scale[b] during previous 7 days (SD)	6.0 (2.1)	6.1 (2.3)
Mean duration of treatment for chronic pain, years (SD)	10.0 (10.3)	9.6 (7.3)
Common concomitant morbidities[c], *n* (%)		
Depression	131 (31.3)	14 (29.8)
Constipation	112 (26.8)	17 (36.2)
Drug hypersensitivity	111 (26.6)	8 (17.0)
Asthma	81 (19.4)	10 (21.3)
Autoimmune or chronic inflammatory disorder	47 (11.2)	6 (12.8)
Gait and balance disorder	44 (10.5)	6 (12.8)

SD standard deviation, *TDB* transdermal buprenorphine

[a] Other primary diagnoses included cancer (1.7 %), inflammatory diseases (1.1 %), dermatological conditions (1.1 %), renal and genitourinary disorders (0.4 %), and lymph/circulatory disorders (0.2 %)

[b] Numerical analog scale (from 0 = no pain to 10 = worst pain imaginable)

[c] Common concomitant morbidities occurring in ≥10 % of the total study population [other atopic allergic comorbidities included hay fever ($n = 25$, 5.4 %), rash or hives ($n = 17$, 3.7 %), and contact allergies ($n = 15$, 3.2 %)]

patients than for treatment-experienced patients (70.5 versus 22.4 %), while fewer treatment-naïve patients than treatment-experienced patients received 10 mg TDB patches (22.6 versus 42.6 %). Most patients (81.3 %) received concomitant analgesic medication in parallel with TDB during the study. The most frequently coprescribed analgesics were paracetamol (46.0 %), paracetamol combinations excluding psycholeptics (13.1 %), and tramadol (11.8 %). Amitriptyline was coprescribed in 13.1 % of patients.[1]

Overall, 80.9 % of the 465 patients continued treatment with TDB during the follow-up period. The discontinuation rate was higher in TDB-naïve patients (34.2 %) than in TDB-experienced patients (12.1 %) and those receiving twice-weekly TBD (12.8 %). In the overall population, the most common reason for discontinuing treatment was AEs ($n = 56$, 12.0 %; Fig. 2). Very few patients discontinued treatment because of self-reported lack of adherence (i.e., the patient stopped using TDB: $n = 3$, 0.6 %). At treatment discontinuation, the mean (SD) twice-weekly and 7-day TDB doses were 68.1 (24.3) mg and 11.4 (9.5) mg, respectively, and 7-day TDB-experienced patients were receiving a numerically lower mean (SD) patch strength [9.7 (5.8) mg] than TDB-naïve patients [12.5 (11.2) mg, $p = 0.564$].

3.2 Safety: Excluding Skin Irritations

AEs, excluding skin irritations, were experienced by 50.1 % of patients, the most common events being constipation (28.0 %), nausea (16.6 %), dizziness (10.3 %), sleeping disorder (10.1 %), and vomiting (3.9 %). The incidence rates per 100 patient-years were 20.6, 12.9, 7.7, 7.4, and 3.5 for constipation, nausea, dizziness, sleeping disorder, and vomiting, respectively.

A higher proportion of 7-day TDB-experienced patients than TDB-naïve patients reported constipation (30.9 versus 20.5 %, $p = 0.0237$), which also persisted for longer in

[1] Amitriptyline may have been prescribed for analgesia, depression, or both conditions (31.2 % of patients had depression as a comorbidity).

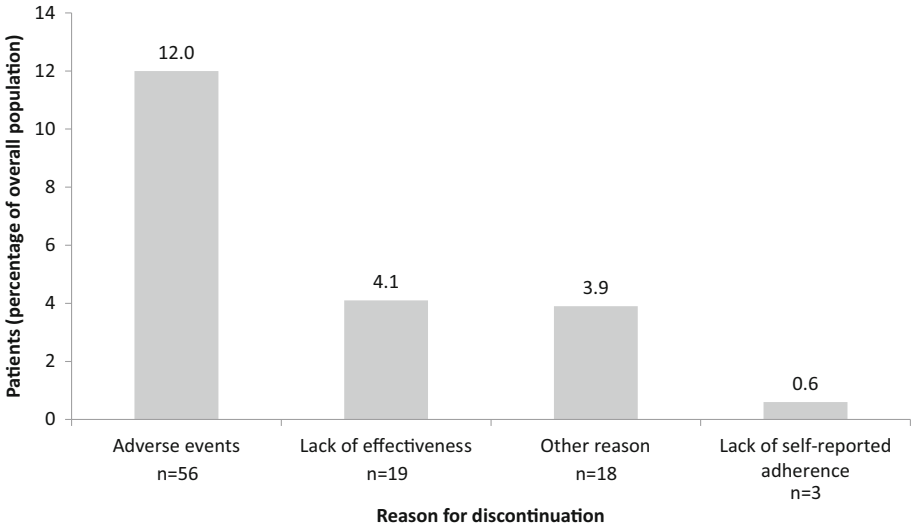

Fig. 2 The reasons for discontinuing treatment with transdermal buprenorphine in the overall population ($n = 465$) were adverse events (12.0 %), lack of effectiveness (4.1 %), other reasons (3.9 %), and lack of self-reported adherence (0.6 %)

treatment-experienced patients [mean (SD) 233.7 (361.1) versus 50.5 (49.2) days, $p = 0.0154$]. Constipation was generally rated as moderate (47.7 %) or mild (33.3 %). Dizziness was less frequent in TDB-experienced patients than in TDB-naïve patients (7.4 versus 17.1 %, $p = 0.0021$), but, when present, it persisted for longer in TDB-experienced patients [mean (SD) 168.4 (363.7) versus 15.6 (17.9) days, $p = 0.0192$]. Nausea, vomiting, and sleep disturbance were experienced by similar proportions of treatment-experienced and treatment-naïve patients. Nausea and dizziness were most frequently rated as mild (46.6 and 45.5 %, respectively), sleep disturbance was most frequently rated as moderate (72.0 %), and vomiting was most frequently rated as severe (56.0 %). Concomitant medications were received by 68.4, 50.0, 40.8, 24.4, and 15.6 % of patients experiencing constipation, vomiting, nausea, sleep disorders, and dizziness, respectively, to manage these events.

3.3 Safety: Skin Irritations

Skin irritation was the most frequently reported AE, being more common in 7-day TDB-experienced patients (45.6 %) than in treatment-naïve patients (32.9 %). However, very few patients experiencing skin irritation discontinued TDB therapy because of the skin irritation (8.8 %, Fig. 3). Overall, 41.1 % of patients receiving TDB experienced an average of 1.3 skin irritations. Skin irritations (Table 2) were generally short lasting (80.6 %), mild (53.3 %), or moderate (33.0 %) in severity and were described as an itching sensation (60.7 %) or a burning sensation (18.8 %). Almost all skin irritations were limited to within the patch area (98.4 %), and TDB therapy was suspected to be the cause of skin irritation in 97.0 % of cases. The 7-day TDB-experienced group with skin irritation experienced significantly more erythema than the TDB-naïve group (76.6 versus 54.2 %, $p = 0.0038$) and had numerically fewer patients with 'no evidence of skin irritation' (21.8 versus 35.4 %, $p = 0.0659$). Overall, 25.7 % of patients experiencing skin irritation received treatment. Hydrocortisone was most commonly used by patients receiving 7-day TDB, while emollients/protectives were used most frequently by patients receiving twice-weekly TDB. Most patients who received treatment for skin reaction considered it to be at least 'somewhat effective' (77.6 %).

Analyses performed only in 7-day TDB patients revealed that skin irritations tended to be more common in patients who reported a history of certain allergies, including skin reactions to food (no skin reaction 2.2 % versus $\geq$1 skin reaction 15.1 %, $p = 0.0028$) and skin reactions to perfumes, cosmetics, and washing powder (15.7 versus 37.0 %, $p = 0.002$). There was no significant difference in the incidence of skin irritations according to patient-reported asthma, hay fever, or skin reaction to pets. However, the physician-reported data showed that skin irritations were more common (no skin reaction versus $\geq$1 skin reaction) in patients with hay fever (3.3 versus 8.7 %, $p = 0.0158$). A numerically greater incidence of skin irritations was also seen in patients with physician-reported drug hypersensitivity (23.6 versus 30.8 %, $p = 0.0992$) or psoriasis (3.3 versus 7.0 %, $p = 0.0791$), while skin irritations were less common in patients with autoimmune/chronic inflammatory disorders (13.8 versus 7.6 %, $p = 0.0461$).

Approximately half of the patients (45.8 %) who experienced skin irritation reported that they took no action. Of the actions taken, the most frequent was to remove the TDB patch and apply a new patch to a different skin location (32.9 %; Fig. 3).

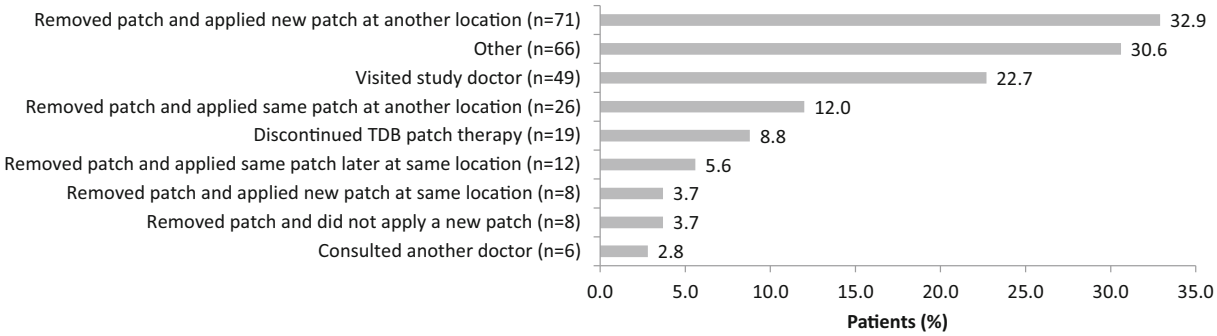

Fig. 3 The most common patient-reported actions ($n = 216$) with transdermal buprenorphine (TDB) patches in response to skin irritation (a multiresponse question) were 'removed patch and applied a new patch to another location' (32.9 %), 'other' response (including 'cream applied', 'kept patch on, no action', 'reduced dosage', 'scratch', 'took antihistamines', and 'washed and dried site'; 30.6 %), and 'visited study doctor' (22.7 %)

Some events of skin irritations reported by physicians were not reported by patients: 48 of 222 and 10 of 25 physician-reported skin irritation AEs were not reported by patients in the 7-day TDB and twice-weekly TDB groups, respectively.

3.4 Self-Reported Adherence and Treatment Satisfaction

Seven-day TDB-naïve and TDB-experienced patients wore patches for a median of 7 days (95 % CI 6.7–6.9), and twice-weekly TDB patients wore patches for a median of 3.5 days (95 % CI 3.5–4.3). Patients had applied patches to a median of four different skin locations in the previous 4 weeks. Almost all patients did not remove and reapply patches during the dosing interval (97.2 %) or cut the patches (98.5 %). During the previous 4 weeks, 3.1 % of patients said they had applied more patches than they were prescribed and 6.4 % said they had forgotten to apply a patch. There were no significant differences in measures of self-reported adherence for 7-day TDB-naïve versus TDB-experienced patients.

Treatment satisfaction data are available for a longer length of time than the study observation period, as some patients were receiving TDB therapy prior to study enrolment. Most patients reported that 7-day TDB was 'effective' or 'very effective' in relieving their pain (Fig. 4a). Patients were more likely to find 7-day TDB 'not very effective' during the first 3 months of therapy (approximately one third), and 'effective'/'very effective'with increasing time on therapy. Most patients 'fully agreed' or 'agreed' that their skin tolerated TDB patches well across the entire study period [from 55.6 % (in month 15) to 87.5 % (in month 36); Fig. 4b]. Most patients were also satisfied overall with TDB therapy; satisfaction rates remained above 70 % for the entire treatment duration assessed (Fig. 4c). Treatment satisfaction was also high in patients experiencing at least one skin irritation: 62.9 % (in month 15) to 93.5 % (in month >36) of this patient group were satisfied overall with TDB. More than 65 % of patients also favored TDB above their previous analgesic medication throughout the follow-up period. There were no consistent differences in treatment satisfaction parameters between treatment-naïve and treatment-experienced patients.

4 Discussion

This observational, prospective, multicenter study describes the AEs, reasons for treatment discontinuation, satisfaction, self-reported adherence, and characteristics of 465 patients receiving TDB in the UK healthcare system. Since the study sites were well distributed throughout the UK, these findings are likely to be representative of the wider UK population.

This study suggests that UK patients are receiving TDB in accordance with the prescribing information [20, 21]. For example, patients were experiencing chronic pain (average duration 11 years), which was predominantly non-cancer in origin and of moderate-to-severe intensity. The patients receiving TDB in this study largely reflected the wider UK population with chronic pain [35]. Most patients were older (median age 67 years), and over half had a primary pain diagnosis of arthritis or a musculoskeletal inflammatory disease, or a spinal/back pain condition or injury. Physician-reported baseline allergic conditions were common in patients in this study and included drug sensitivities (25.6 %) and asthma (19.6 %). The observation that most patients (81.3 %) prescribed TDB were also receiving concomitant analgesic medications is in line with the WHO stepwise analgesic ladder [5]. However, because of the non-interventional design of this study, we cannot ascertain the impact of these concomitant medications on the AEs observed.

Skin irritation was the most frequently reported AE (41.1 %) reported with TDB, followed by constipation (28.0 %) and nausea (16.6 %). The high incidence of

Table 2 Skin irritations occurring during treatment with transdermal buprenorphine (TDB): patients with ≥1 skin irritation during follow-up[a]

Parameter	7-day TDB experienced	7-day TDB naïve	Twice-weekly TDB
Intensity of skin irritation, *n* (%)[b]			
No evidence of irritation	27 (21.8)	17 (35.4)	5 (26.3)
Erythema	95 (76.6)	26 (54.2)	17 (89.5)
Erythema and papules	25 (20.2)	13 (27.1)	7 (36.8)
Erythema, papules and vesicle	6 (4.8)	3 (6.3)	1 (5.3)
Strong reaction spreading beyond test site	0	3 (6.3)	0
Median duration of skin irritation, days (range)[c]	94 (1–2481)	23 (1–405)	167 (1–1716)
Severity of skin reaction, *n* (%)[d]			
Mild	74 (56.9)	27 (49.1)	12 (44.4)
Moderate	40 (30.8)	17 (30.9)	13 (48.1)
Severe	16 (12.3)	11 (20.0)	2 (7.4)
Progression of skin reaction, *n* (%)[b]			
Short lasting	104 (83.9)	33 (68.8)	17 (89.5)
Long lasting	23 (18.5)	12 (25.0)	3 (15.8)
Long lasting and worsening over time	4 (3.2)	4 (8.3)	0
Skin reaction suspected to be treatment related, *n* (%)[e]	139 (95.9)	57 (100.0)	27 (96.4)
Pathogenic nature of skin reaction, *n* (%)[b]			
Allergic	22 (17.7)	12 (25.0)	5 (26.3)
Irritant	69 (55.6)	21 (43.8)	12 (63.2)
Toxic	11 (8.9)	3 (6.3)	1 (5.3)
Infectious	0	1 (2.1)	0
Unclear	26 (21.0)	10 (20.8)	3 (15.8)
Received treatment for skin irritation, *n* (%)[b]	28 (22.6)	14 (29.2)	7 (36.8)
Treatment received for skin irritation, *n* (%)[f]			
Emollient and protectives	7 (25.0)	4 (28.6)	7 (100.0)
Hydrocortisone	16 (57.1)	9 (64.3)	0
Betamethasone	1 (3.6)	0	1 (14.2)
Clobetasol propionate	3 (10.7)	0	0
Beclomethasone	3 (10.7)	0	0
Fexofenadine	0	3 (21.4)	0
Effectiveness of treatment for skin irritation, *n* (%)[f]			
Completely effective	8 (28.6)	5 (35.7)	2 (28.6)
Very effective	4 (14.3)	2 (14.3)	1 (14.3)
Somewhat effective	10 (35.7)	4 (28.6)	2 (28.6)
Not very effective	2 (7.1)	1 (7.1)	1 (14.3)
Not at all effective	3 (10.7)	2 (14.3)	0

[a] 124 7-day TDB-experienced patients (45.6 %), 48 7-day TDB-naïve patients (32.3 %), and 19 twice-weekly TDB patients (40.4 %) experienced ≥1 skin irritation during follow-up

[b] Assessed in 124, 48, and 19 7-day TDB-experienced, 7-day TDB-naïve, and twice-weekly TDB patients, respectively (progression of skin reaction was a multiresponse question)

[c] Assessed in 97, 44, and 20 7-day TDB-experienced, 7-day TDB-naïve, and twice-weekly TDB patients, respectively

[d] Assessed in 130, 55, and 27 cases of skin irritation in 7-day TDB-experienced, 7-day TDB-naïve, and twice-weekly TDB patients, respectively

[e] Assessed in 145, 57, and 28 cases of skin irritation in 7-day TDB-experienced, 7-day TDB-naïve, and twice-weekly TDB patients, respectively (patient-reported, multiresponse question)

[f] Assessed in 28, 14, and seven 7-day TDB-experienced, 7-day TDB-naïve, and twice-weekly TDB patients, respectively (percentages calculated with the number of patients prescribed treatment for skin irritation as the denominator; type of treatment was a patient-reported, multiresponse question; data on treatment effectiveness are missing for one 7-day TDB-experienced patient and one twice-weekly TDB patient)

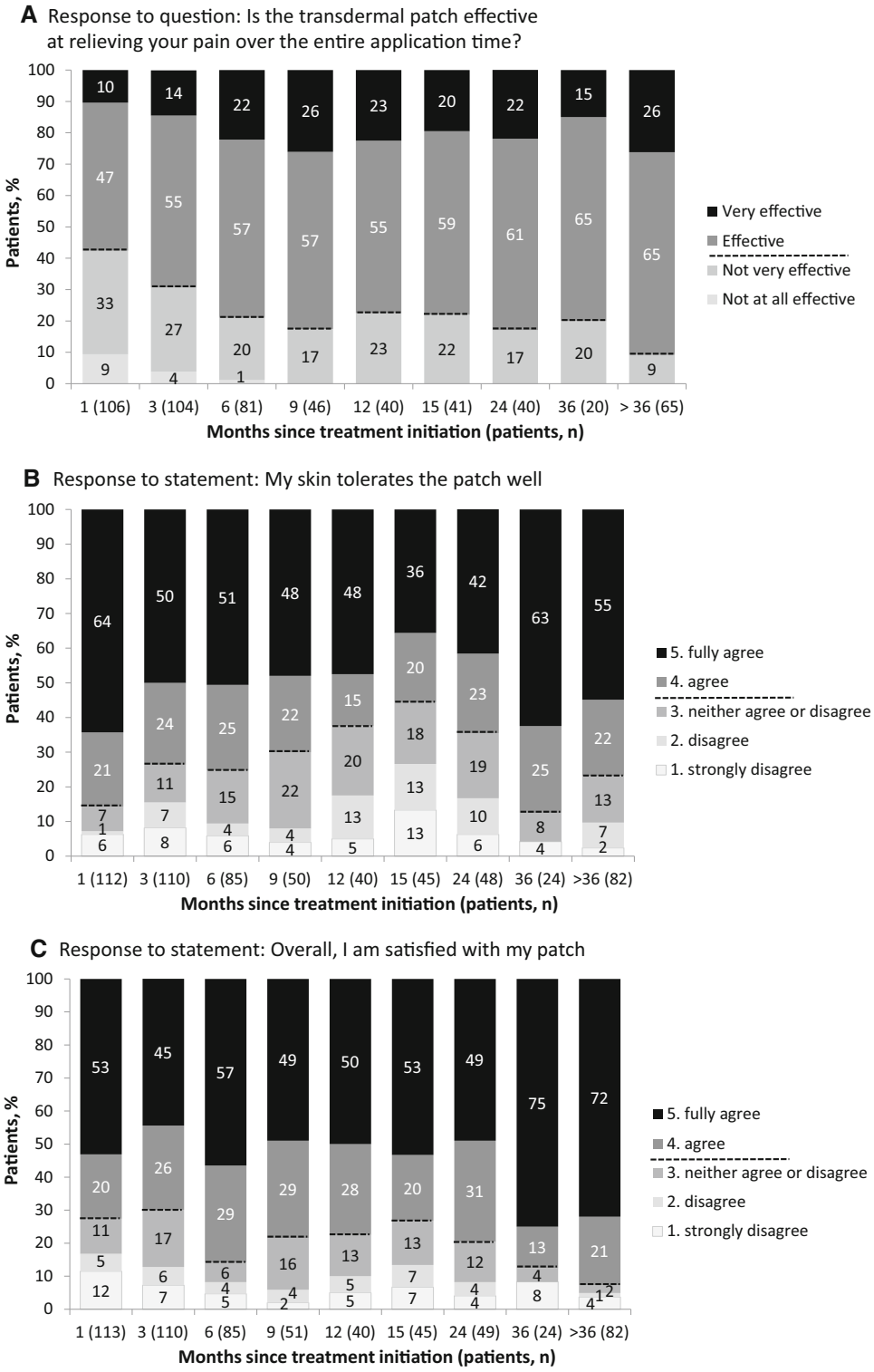

Fig. 4 Patient-reported satisfaction with transdermal buprenorphine patches (in all patients with available data). **a** Overall treatment effectiveness (only in patients receiving 7-day TDB). **b** Skin tolerability of treatment. **c** Overall satisfaction with treatment

constipation at study baseline, including 21.9 % of TDB-naïve patients, is worth noting. While constipation is a common class effect of opioid analgesia, arising from the interaction of opioids with μ-opioid receptors present throughout the gastrointestinal tract, other factors may also contribute to constipation—for example, reduced mobility and dietary factors [36, 37]. Furthermore, some commonly used drugs—for example, selective serotonin reuptake inhibitors—are also associated with an increased incidence of constipation [38].

Skin irritancy appears to be a class effect for transdermal delivery of opioid. A systematic review including five studies of transdermal fentanyl identified skin irritation at the application site to be the only AE that was not observed in patients receiving opioid analgesia via other modes of delivery [39]. Skin irritations reported in the present study were generally mild or moderate in severity and were restricted to the application site. Furthermore, very few patients discontinued TDB therapy because of this AE. However, only one quarter of patients experiencing skin irritations received treatment to manage these symptoms. Given that most patients reported that the interventions were at least somewhat effective, physicians are likely missing opportunities to manage skin irritations associated with TDB. It is the authors' clinical experience that advising patients to wash the affected area with soap and water after removing the TDB patch can help to ameliorate minor skin irritations, along with application of a low-dose steroid cream for a few days if symptoms persist. Another observation from this study, which may assist clinicians to optimize TDB therapy, was that skin irritations tended to be more common in patients with a history of skin reactions to certain foods, perfumes, cosmetics, and washing powder. Proactive questioning about skin irritations and their management appears to be particularly relevant for these patients. Furthermore, the higher incidence rates of constipation and skin irritations reported in TDB-experienced patients highlight the need for physicians to proactively address these common AEs, particularly in individuals receiving long-term therapy. It is possible that the ≤9-month duration of treatment for treatment-naïve patients may not been of a sufficient duration for some AEs to develop.

In comparison with a prior 12-month, retrospective cohort study of nearly 5000 UK patients prescribed low-dose TDB by primary care physicians, the incidences of constipation, nausea, vomiting, and dizziness were largely similar, while skin irritations were 5- to 30-fold more frequent in the present study [40]. The reason for this discrepancy is unclear, although it may reflect the different designs of the studies. For example, the larger study utilized information obtained from the General Practice Research Database, while data were obtained from study-specific questionnaires completed at regular intervals during the present study and included some patients who were already receiving 7-day TDB at study entry [40].

Despite the occurrence of AEs, discontinuation of TDB therapy was rare. Over 80 % of patients continued treatment throughout the follow-up period, with just 12.0 % discontinuing because of AEs. Discontinuation was also uncommon in patients who experienced skin irritations. This suggests that the benefits of TDB outweigh the AEs, which patients generally tolerate. While direct comparisons between studies of differing designs cannot be made, the rate of treatment discontinuation due to AEs was lower than those reported in randomized, controlled trials of low-dose TDB (approximately 36 %), was similar to those observed in studies of transdermal fentanyl (approximately 12 %), and compares favorably with those in studies of oral opioid analgesics (approximately 23 %) [30, 32, 39]. Other studies of low-dose TDB have also demonstrated high rates of treatment continuation, which were significantly greater than those observed with codeine, dihydrocodeine, and tramadol [40].

This study was designed to capture both patients' and physicians' perceptions of treatment with TDB. Approximately one fifth of skin irritation events reported by physicians were not also reported by patients. While this discrepancy between patient- and physician-reported AEs may be due to the design of this study, it underscores the importance of discussing AEs during consultations. It is also worth noting that the TDB patch strength tended to increase over the course of treatment, suggesting that some physicians do not reduce the buprenorphine dosage prior to discontinuation in order to ameliorate AEs.

This study also indicates that in real-world settings, most patients use 7-day TDB patches in accordance with treatment recommendations. Most patients wore each patch for the recommended duration and were rotating the skin site for patch application. Very few patients forgot to apply the patch, applied more patches than were prescribed, cut the patch, or applied a new patch before the previous one was removed. The high rate of self-reported adherence to treatment in this study is an important observation, given that patients who are prescribed self-administered medications typically take only about half of their prescribed doses, and few data are available to provide insight into how adherence can be improved to realize the full health benefits of medicines [41–43]. The high rates of self-reported adherence tallied with the observation that most patients were 'satisfied' or 'very satisfied' with TDB therapy, including those who experienced skin irritations. Treatment satisfaction rates appeared to increase over time, with 92.7 % of patients who used the patch for ≥36 months reporting high satisfaction.

The advantages of transdermal opioids include slow, continuous release into the circulation over a prolonged period and the avoidance of first-pass hepatic metabolism [15]. Low-dose TDB also has the convenience of once-weekly administration and reduces the overall pill burden, which may be particularly important for older patients with chronic conditions who are commonly taking multiple medications [32]. However, patch therapy is associated with some limitations, including less flexible dosage adjustment in comparison with oral opioid formulations [10].

While this study was designed to inform on the effectiveness, AE profile, self-reported adherence, and perceptions of treatment with TDB in routine clinical practice, because of the observational, non-intervention design, the efficacy of TDB cannot be compared with that of other treatments. Other limitations included potential patient selection bias and lack of validation of outcome measures.

5 Conclusion

This UK observational study indicated that in everyday clinical practice, TDB was well tolerated by patients with a variety of chronic pain conditions and comorbidities. Most patients reported that TDB therapy was effective and were satisfied with their treatment. Self-reported adherence to TDB was also very high, with nearly all patients applying the patches per treatment recommendations. Although many patients receiving TDB experienced at least one AE, these were tolerable, as AEs rarely resulted in treatment discontinuation. This study also identified potential missed opportunities to ameliorate or reduce the intensity of common AEs experienced by patients treated with TDB.

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Compliance with Ethical Standards

All authors contributed to the analysis and/or interpretation of data, as well as critical revision of the manuscript for important intellectual content, and approved the submitted draft.
All study documents were reviewed and approved by the appointed Research Ethics Committee, and all patients participating in this study provided informed, written consent.

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Potential conflicts of interest Mick Serpell was the Principal Investigator for the study. He received support from Mundipharma Research GmbH & Co. KG to travel to meetings to discuss the findings of this study and discuss manuscript preparation. He has also received honoraria from Astellas, Grünenthal Ltd, Sanofi-Pasteur MSD, Napp Pharmaceuticals and Pfizer to present at educational meetings. Sabine Scherzinger and Shiva Tripathi acted as study investigators. Shiva Tripathi has received honoraria from Mundipharma Research GmbH & Co. KG, Napp Pharmaceuticals, Astellas and Pfizer for speaking at scientific meetings. Sabine Scherzinger has no potential conflicts of interest to declare. Sònia Rojas-Farreras, an employee of IMS Health at the time of the study, was responsible for statistical analysis of the data and preparation of the study report, funded by Mundipharma Research GmbH & Co. KG. Alexander Oksche, an employee of Mundipharma Research GmbH & Co. KG, acted as the responsible clinician for the study sponsor and contributed to the design of the study. Margaret Wilson, an employee of Mundipharma Research Ltd, also contributed to the design of the study. As corresponding author, Margaret Wilson acts as the guarantor of the manuscript.

Statement of human rights All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research ethics committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

References

1. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10:287–333.
2. Helme RD, Gibson SJ. The epidemiology of pain in elderly people. Clin Geriatr Med. 2001;17:417–31.
3. Strine TW, Hootman JM, Chapman DP, et al. Health-related quality of life, health risk behaviors, and disability among adults with pain-related activity difficulty. Am J Public Health. 2005;95:2042–8.
4. Allen H, Hubbard D, Sullivan S. The burden of pain on employee health and productivity at a major provider of business services. J Occup Environ Med. 2005;47:658–70.
5. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician. 2010;56:514–5.
6. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2015;350:h1225.
7. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10:113–30.
8. Pergolizzi J, Boger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an international expert panel with focus on the six clinically most often used World Health Organization step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract. 2008;8:287–313.
9. McCracken LM, Velleman SC, Eccleston C. Patterns of prescription and concern about opioid analgesics for chronic non-malignant pain in general practice. Prim Healthc Res Dev. 2008;9:146–56.
10. Plosker GL, Lyseng-Williamson KA. Buprenorphine 5, 10 and 20 mug/h transdermal patch: a guide to its use in chronic non-malignant pain. CNS Drugs. 2012;26:367–73.
11. Hadley G, Derry S, Moore RA, et al. Transdermal fentanyl for cancer pain. Cochrane Database Syst Rev. 2013;(10):CD010270.
12. Livingston KE, Traynor JR. Disruption of the Na+ ion binding site as a mechanism for positive allosteric modulation of the mu-opioid receptor. Proc Natl Acad Sci USA. 2014;111:18369–74.
13. Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-

dependent volunteers. Neuropsychopharmacology. 2003;28:2000–9.
14. Zubieta J, Greenwald MK, Lombardi U, et al. Buprenorphine-induced changes in mu-opioid receptor availability in male heroin-dependent volunteers: a preliminary study. Neuropsychopharmacology. 2000;23:326–34.
15. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. Eur J Pain. 2009;13:219–30.
16. Pergolizzi J, Aloisi AM, Dahan A, et al. Current knowledge of buprenorphine and its unique pharmacological profile. Pain Pract. 2010;10:428–50.
17. Guetti C, Angeletti C, Marinangeli F, et al. Transdermal buprenorphine for central neuropathic pain: clinical reports. Pain Pract. 2011;11:446–52.
18. Aurilio C, Ceccarelli I, Pota V, et al. Endocrine and behavioural effects of transdermal buprenorphine in pain-suffering women of different reproductive ages. Endocr J. 2011;58:1071–8.
19. Pergolizzi JV Jr, Scholten W, Smith KJ, et al. The unique role of transdermal buprenorphine in the global chronic pain epidemic. Acta Anaesthesiol Taiwan. 2015;53:71–6.
20. Napp Pharmaceuticals Limited. Transtec: summary of product characteristics. Cambridge: Napp Pharmaceuticals Limited; 2014.
21. Napp Pharmaceuticals Limited. BuTrans: summary of product characteristics. Cambridge: Napp Pharmaceuticals Limited; 2014.
22. De Barutell C, Gonzalez-Escalada JR. Efficacy and safety of buprenorphine TDS in conjunction with oral tramadol or morphine as rescue medication in the treatment of 390 patients with chronic pain: a summary of two retrospective Spanish multicenter studies. J Appl Ther Res. 2007;5:14–24.
23. Zarth R. Comparison of buprenorphine, morphine sulphate and fentanyl citrate as rescue medication for breakthrough pain in cancer patients. J Appl Ther Res. 2008;6:15–9.
24. Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. Eur J Pain. 2014;18:1343–51.
25. Breivik H, Marte Ljossa T, Stengaard-Pedersen K, et al. A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patient naive to potent opioids. Scand J Pain. 2010;1:122–41.
26. Gordon A, Callaghan D, Spink D, et al. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. Clin Ther. 2010;32:844–60.
27. Landau CJ, Carr WD, Razzetti AJ, et al. Buprenorphine transdermal delivery system in adults with persistent noncancer-related pain syndromes who require opioid therapy: a multicenter, 5-week run-in and randomized, double-blind maintenance-of-analgesia study. Clin Ther. 2007;29:2179–93.
28. Steiner DJ, Sitar S, Wen W, et al. Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naive patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study. J Pain Symptom Manage. 2011;42:903–17.
29. Poulain P, Denier W, Douma J, et al. Efficacy and safety of transdermal buprenorphine: a randomized, placebo-controlled trial in 289 patients with severe cancer pain. J Pain Symptom Manage. 2008;36:117–25.
30. James IG, O'Brien CM, McDonald CJ. A randomized, double-blind, double-dummy comparison of the efficacy and tolerability of low-dose transdermal buprenorphine (BuTrans seven-day patches) with buprenorphine sublingual tablets (Temgesic) in patients with osteoarthritis pain. J Pain Symptom Manage. 2010;40:266–78.
31. Karlsson M, Berggren AC. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 μg/h) versus prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: a 12-week, randomized, open-label, controlled, parallel-group noninferiority study. Clin Ther. 2009;31:503–13.
32. Conaghan PG, O'Brien CM, Wilson M, et al. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomised trial. Osteoarthritis Cartilage. 2011;19:930–8.
33. Vander HK, Parera AE, Jacobs C, et al. Allergic contact dermatitis from transdermal buprenorphine. Contact Dermatitis. 2008;59:366–9.
34. Graziottin A, Gardner-Nix J, Stumpf M, et al. Opioids: how to improve compliance and adherence. Pain Pract. 2011;11:574–81.
35. Elliott AM, Smith BH, Penny KI, et al. The epidemiology of chronic pain in the community. Lancet. 1999;354:1248–52.
36. Muller-Lissner S. Opioid-induced constipation—mechanisms, relevance and management. Eur Gastroenterol Hepatol Rev. 2010;6:54–7.
37. Holzer P, Ahmedzai SH, Niederle N, et al. Opioid-induced bowel dysfunction in cancer-related pain: causes, consequences, and a novel approach for its management. J Opioid Manag. 2009;5:145–51.
38. Marks DM, Park MH, Ham BJ, et al. Paroxetine: safety and tolerability issues. Expert Opin Drug Saf. 2008;7:783–94.
39. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010;(1):CD006605.
40. Gallagher AM, Leighton-Scott J, van Staa TP. Utilization characteristics and treatment persistence in patients prescribed low-dose buprenorphine patches in primary care in the United Kingdom: a retrospective cohort study. Clin Ther. 2009;31:1707–15.
41. Alhewiti A. Adherence to long-term therapies and beliefs about medications. Int J Family Med. 2014;2014:479596.
42. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;(11):CD000011.
43. World Health Organization (WHO). Adherence to long-term therapies: evidence for action. Geneva: WHO; 2015.