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ORIGINAL RESEARCH ARTICLE

Satisfaction, Adherence and Health-Related Quality of Life with Transdermal Buprenorphine Compared with Oral Opioid Medications in the Usual Care of Osteoarthritis Pain

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Abstract

Background Osteoarthritis (OA) causes substantial pain and reduced health-related quality of life (HRQL). Although opioid analgesics are commonly used, the relative benefits of different opioids are poorly studied. Transdermal buprenorphine (TDB) offers an alternative to oral opioids for the treatment of moderate-to-severe chronic pain. This observational study of people with OA pain assessed satisfaction, HRQL and medication adherence.

Methods Patients in the UK with self-reported knee and/or hip OA who had been receiving one or more of TDB, co-codamol (an oral paracetamol/codeine combination) and tramadol for at least 1 month completed an online or telephone questionnaire. Medication satisfaction scores, HRQL scores (Short-Form 36 [SF-36]), medication adherence (Morisky Medication Adherence Scale [MMAS^{TM}]), adverse events and treatment discontinuations were recorded. Linear and logistic regression models were used to compare the treatment effect of TDB with co-codamol or tramadol.

Results Overall, 966 patients met the inclusion criteria; 701 were taking only one of the target medications (TDB: 85; co-codamol: 373; tramadol: 243). The largest age group was 50–59 years and 76.0 % of patients were female. The TDB group was younger, with more male patients, therefore the statistical models were adjusted for age and sex. Medication satisfaction scores were significantly higher in the TDB group than the other two groups (TDB vs. co-codamol: 3.56, 95 % confidence interval [CI] 1.90–6.68, $p < 0.0001$; TDB vs. tramadol: 3.22, 95 % CI 1.67–6.20, $p = 0.0005$). Physical Component Summary scores for HRQL and mean adherence were also higher in the TDB group, while Mental Component Summary HRQL scores were similar across the three groups.

Conclusions Patients with knee and/or hip OA pain treated with TDB were more satisfied and more adherent with their medication, and reported higher Physical Component Summary HRQL scores than those treated with co-codamol or tramadol, although demographic differences were observed between groups.

Electronic supplementary material The online version of this article (doi:10.1007/s40271-016-0181-0) contains supplementary material, which is available to authorized users.

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Key Points for Decision Makers

Low-dose transdermal buprenorphine (TDB) is an effective alternative to oral opioids such as co-codamol and tramadol for the treatment of moderate-to-severe osteoarthritis (OA) pain.

This prospective, observational study showed that patients with OA whose pain was treated with TDB reported increased satisfaction with their medication, better adherence, and improved Physical Component Summary health-related quality of life scores compared with patients treated with co-codamol or tramadol.

Physicians should consider patient satisfaction and quality of life when prescribing analgesics for chronic pain.

1 Introduction

Osteoarthritis (OA) is a debilitating condition, characterised by pain, joint inflammation and joint stiffness, which causes a substantial degree of physical disability. OA commonly affects the knee or the hip, and in England it is estimated that 4.11 million people have knee OA (approximately 18 % of the population aged 45 years and over) and 2.46 million have hip OA (approximately 11 % of the population aged 45 years and over) [1]. Figures from the US suggest approximately 13 % of women and 10 % of men over 60 years of age have knee OA [2].

The pain caused by OA can have a substantial impact on patients' quality of life. In a 2012 online survey of OA patients in the UK [3], 52 % of the 2001 respondents reported that OA had a large impact on their life, 71 % had persistent pain even after taking their prescribed pain medication, and 12 % said their pain was often unbearable.

Opioid analgesics are commonly used to treat chronic musculoskeletal pain, including OA pain. The National Institute for Health and Care Excellence (NICE) OA guidelines [4] recommend using opioids after other analgesics such as paracetamol and oral non-steroidal anti-inflammatory drugs (NSAIDs) have failed or are contraindicated. Similarly, the American College of Rheumatology guidelines [5] recommend opioids for the treatment of knee or hip OA pain in patients who have not responded to initial non-opioid treatment. Tramadol is considered separately to other opioids and is suggested as a first-line treatment. In their guidelines for the treatment of knee OA, The American Academy of Orthopaedic Surgeons [6] recommended the use of tramadol but were unable to recommend other opioids or pain patches due to a lack of published evidence that met their inclusion criteria.

At clinically prescribed doses, buprenorphine acts as a full μ-opioid agonist, and has a long duration of action [7–9]. It has been shown to have no analgesic ceiling effect, immunosuppressive activity or effect on gonadal hormones [7, 8, 10, 11]. In addition, the dose of buprenorphine does not need to be adjusted in elderly patients [12–15] or those with renal impairment [16].

Buprenorphine is available in the UK as transdermal patches (TDB), sublingual tablets, and as a solution for injection. This study focused on low-dose 7-day TDB, containing buprenorphine 5–20 mg with a nominal release rate of 5–20 μg/h. These patches are indicated for moderate chronic non-cancer pain, and have been shown to have comparable efficacy to oral opioids for the treatment of OA pain [17]. Two randomised controlled trials (RCTs) have demonstrated that 7-day TDB is non-inferior to co-codamol (an oral paracetamol/codeine combination) and tramadol for the treatment of OA pain [18, 19]. In addition, a retrospective database study into the use of 7-day TDB in primary care [20] found that significantly more patients persisted with their treatment after 6 and 12 months compared with codeine, dihydrocodeine and tramadol.

Tramadol has a dual mode of action as a μ-opioid agonist and as a weak serotonin and noradrenaline reuptake inhibitor. It is available in the UK as immediate- or prolonged release oral tablets or capsules, as an oral solution, and as a solution for injection or infusion. The maximum recommended dose is 400 mg/day [21].

Co-codamol is a combination analgesic containing codeine and paracetamol, which is commonly used in the UK. Three different dose strengths are available: 8/500 (codeine 8 mg/paracetamol 500 mg), 15/500 and 30/500. Codeine is a μ-opioid agonist and co-codamol is available in the UK as oral tablets or capsules. The maximum recommended daily dose is codeine 240 mg and paracetamol 4 g [21]. Codeine is a prodrug that is metabolised to morphine via cytochrome P450 (CYP) 2D6 in the liver to exert its analgesic effect.

Clinical trial data are essential for robust comparisons of the efficacy of different treatments but rarely reflect the way medicines are used in practice. Real-world evidence, such as observational studies conducted without any healthcare professional involvement, can provide useful insights into how patients really use their medications, and may help to inform prescribing decisions.

Despite opioid analgesics being recommended for suitable patients with OA pain, few studies have compared the relative benefits of different opioids. Previous studies have compared TDB with co-codamol and tramadol in an RCT [18, 19] and general practice setting [20], but not from a patient perspective.

We conducted an observational study to assess TDB, co-codamol and tramadol in patients with OA pain in a real-world, non-interventional setting. Our primary objective was to establish whether there were any differences between the study medications in patient-reported outcomes, including medication satisfaction, health-related quality of life (HRQL) and adherence to treatment.

2 Method

2.1 Patients and Study Design

This was a UK-based observational study, conducted in people with OA of the knee and/or hip, without any intervention from a healthcare professional. Questionnaires were completed online by the participants or conducted by telephone interview. Recruitment was through social media, general practitioner (GP) surgeries and pharmacies, and advertisements in newspapers and on patient websites. Please refer to the electronic supplementary material (ESM) for further details of the questionnaire.

Participants were included in the study if they had a self-reported diagnosis of knee and/or hip OA, and had been prescribed one of the target analgesic medications (low-dose 7-day TDB, co-codamol or tramadol) for their OA pain for at least 1 month prior to study entry.

The study was conducted between September 2012 and March 2013. Responses were measured at baseline (the first questionnaire), and after 1, 2 and 3 months. Following completion of the baseline questionnaire, patients were sent reminders to complete the follow-up surveys. For each follow-up, participants had up to 14 days to complete the questionnaire after receiving a reminder, and each participant was contacted by email, SMS or telephone at least three times to complete each follow-up survey.

The study was performed in accordance with the regulations and guidelines governing medical practice and ethics in the UK. Study documents were reviewed and approved by the appointed Research Ethics Committee (East of Scotland Research Ethics Service [EoSRES]; ref: LR/12/ES/0093), and all patients were provided with information about the study and asked to consent either by telephone or online before completing the baseline questionnaire.

2.2 Outcomes and Assessments

2.2.1 Patient Satisfaction

Satisfaction with current pain medication was assessed at baseline using a 6-point Likert scale comprising 'Very satisfied', 'Satisfied', 'Neither satisfied nor dissatisfied', 'Dissatisfied', 'Very dissatisfied' and 'No opinion'.

2.2.2 Health-Related Quality of Life (HRQL)

HRQL during the previous 4 weeks was assessed at baseline and in each follow-up questionnaire using the Short-Form 36, version 2 (SF-36v2; standard form) health survey, which measures eight different areas of patients' health: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Scores were recorded for each of these areas, and aggregate physical and mental scores (the Physical Component Summary and Mental Component Summary) were calculated. Scores range from 0–100, with 0 corresponding to low HRQL and 100 corresponding to high HRQL.

2.2.3 Adherence

Adherence was measured at baseline and in each follow-up questionnaire using the Morisky Medication Adherence Scale (MMAS^{TM}), a set of eight questions designed to identify medication use behaviour that can indicate non-adherence. Scores from 0 to 8 are possible, with a score of <6 indicating low adherence, 6–7 indicating medium adherence, and 8 indicating high adherence.

2.2.4 Adverse Events (AEs)

AEs related to treatment were recorded at baseline. Reasons for discontinuation were also recorded at baseline and in each follow-up questionnaire, which included discontinuations because of side effects.

2.3 Statistical Methods

Participants who met the inclusion criteria and had partially or fully completed at least the baseline questionnaire were included in the statistical analysis.

The full analysis population refers to all patients and their actual treatment groups at the time of follow-up. Due to the number of patients who changed treatment or dropped out of the study, analysis for the follow-up questionnaires was carried out on two study populations:

- *Intention-to-treat* (*ITT*) *population:* analysis of subjects as per their treatment groups at baseline, even if their treatment group later changed.
- *Per protocol* (*PP*) *population:* analysis of subjects who remained on the same treatment from baseline.

Follow-up data have been reported in this study using the PP population.

Data were analysed descriptively; for categorical variables, the number and percentage falling into each category were reported. Percentages were calculated from total

numbers excluding any missing observations. For continuous variables, the mean, standard deviation (SD), median, interquartile range (IQR) and range were reported.

Estimates for the treatment effect of single target medications (co-codamol and tramadol only) were obtained for continuous and binary outcomes (medication satisfaction, HRQL and treatment adherence) using linear and logistic regression models, respectively, compared with TDB. Each model included the treatment variable, with comparisons focusing on the treatment effect of TDB compared with the other two treatments. *p*-Values were provided for the differences across all three treatment groups and the comparisons between TDB and co-codamol, and TDB and tramadol. The estimates (or odds ratios where relevant) and a 95 % confidence interval for each treatment effect were also provided for the comparisons of TDB with co-codamol and with tramadol to show the likelihood of the outcome occurring in patients treated with TDB compared with patients treated with the other medication. Initial models were unadjusted, containing a covariate for treatment only. As subjects in the TDB group were more likely to be younger and/or male than those in the other groups, age- and sex-adjusted models were also investigated to remove potential bias in the results.

3 Results

3.1 Patient Characteristics

A total of 1011 patients completed the questionnaire, with 966 meeting the inclusion criteria (Fig. 1). Most of the patients (76.0 %) were female, and 91.3 % of the study population had been diagnosed with OA for 1 year or

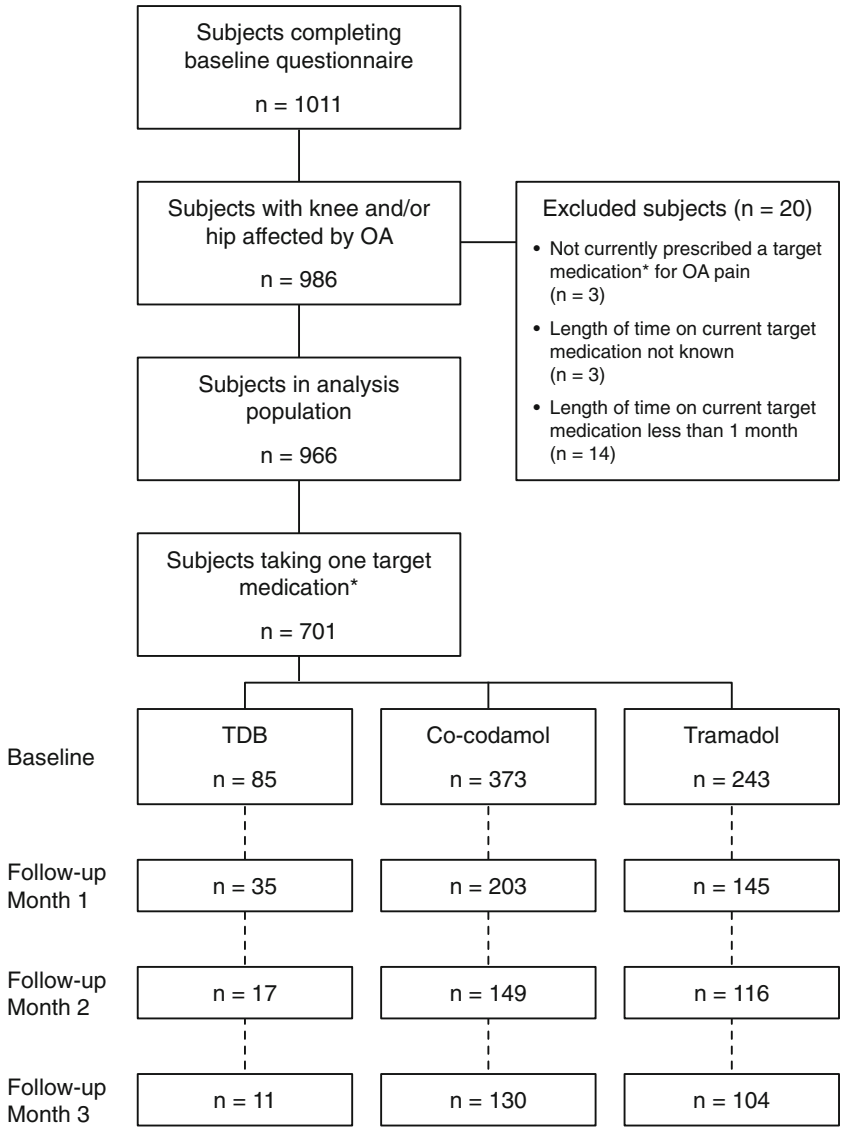

Fig. 1 Patient selection process. *Asterisk* target medications: 7-day TDB, co-codamol or tramadol. These figures are taken from the full analysis population. The follow-up numbers include participants taking one target medication at the time of each follow-up questionnaire, although participants may have moved from another medication group or may not have completed all follow-up questionnaires. *OA* osteoarthritis, *TDB* transdermal buprenorphine

more. Some of the patients were taking more than one of the target medications; therefore, to enable more accurate comparisons between the target medications, subjects taking a single target medication were analysed separately, with patients categorised into the TDB-only, co-codamol-only and tramadol-only groups.

3.1.1 Age and Sex Distribution

The study population included a range of ages, with the largest proportion aged between 50 and 59 years (Table 1), which was similar in all groups except the TDB group, in which most patients were under 40 years of age. Similarly, the sex distribution of the TDB group was different to the other groups. The total analysis population was 76.0 % female, with similar proportions in the co-codamol (75.3 %) and tramadol (81.1 %) groups. In the TDB group, 45.8 % were female. Age- and sex-adjusted analysis was performed to take into account differences in age and sex distribution between the groups (see the ESM for analysis results).

3.1.2 Comorbidities

Many of the patients had comorbidities alongside their OA, with a mean of 1.4 concomitant conditions across all groups. The most common condition was depression, seen in just over 1 in 10 patients in the TDB-only group, compared with approximately one-third in the co-codamol- and tramadol-only groups. High blood pressure, high cholesterol and type II diabetes were the next most commonly reported conditions.

Table 1 Patient demographics

	All	One target	TDB	Co-codamol	Tramadol
Age, years					
n (missing)	909 (57)	663 (38)	83 (2)	352 (21)	228 (15)
Under 40	126 (13.9)	107 (16.1)	41 (49.4)	49 (13.9)	17 (7.5)
40–49	179 (19.7)	127 (19.2)	15 (18.1)	66 (18.8)	46 (20.2)
50–59	367 (40.4)	259 (39.1)	13 (15.7)	131 (37.2)	115 (50.4)
60–69	186 (20.5)	133 (20.1)	6 (7.2)	85 (24.1)	42 (18.4)
70–79	40 (4.4)	29 (4.4)	5 (6.0)	17 (4.8)	7 (3.1)
80–89	9 (1.0)	6 (0.9)	2 (2.4)	3 (0.9)	1 (0.4)
≥90	2 (0.2)	2 (0.3)	1 (1.2)	1 (0.3)	0 (0.0)
Sex					
n (missing)	909 (57)	663 (38)	83 (2)	352 (21)	228 (15)
Male	218 (24.0)	175 (26.4)	45 (54.2)	87 (24.7)	43 (18.9)
Female	691 (76.0)	488 (73.6)	38 (45.8)	265 (75.3)	185 (81.1)
Years diagnosed with OA					
n (missing)	966 (0)	701 (0)	85 (0)	373 (0)	243 (0)
<1	84 (8.7)	61 (8.7)	5 (5.9)	40 (10.7)	16 (6.6)
1–4	278 (28.8)	226 (32.2)	46 (54.1)	115 (30.8)	65 (26.7)
5–9	235 (24.3)	164 (23.4)	15 (17.6)	93 (24.9)	56 (23.0)
10–14	164 (17.0)	109 (15.5)	5 (5.9)	56 (15.0)	48 (19.8)
≥15	205 (21.2)	141 (20.1)	14 (16.5)	69 (18.5)	58 (23.9)
Concomitant conditions					
n (missing)	966 (0)	701 (0)	85 (0)	373 (0)	243 (0)
Depression	330 (34.2)	214 (30.5)	10 (11.8)	120 (32.2)	84 (34.6)
High blood pressure	317 (32.8)	217 (31.0)	17 (20.0)	115 (30.8)	85 (35.0)
High cholesterol	223 (23.1)	153 (21.8)	12 (14.1)	85 (22.8)	56 (23.0)
Diabetes type II	115 (11.9)	87 (12.4)	15 (17.6)	39 (10.5)	33 (13.6)
Angina	42 (4.3)	28 (4.0)	3 (3.5)	15 (4.0)	10 (4.1)
Heart attack	42 (4.3)	19 (2.7)	0 (0.0)	10 (2.7)	9 (3.7)
Renal/kidney disease	28 (2.9)	16 (2.3)	4 (4.7)	8 (2.1)	4 (1.6)
Other condition	394 (40.8)	269 (38.4)	18 (21.2)	142 (38.1)	109 (44.9)

Data are expressed as *n* (%) unless otherwise stated

TDB transdermal buprenorphine, *OA* osteoarthritis

3.1.3 Target Medication Dose

In all groups, most patients had been taking their target medication for 6 months or more (89.4 % in the TDB group, 89.3 % in the co-codamol group and 91.8 % in the tramadol group).

The median strength of TDB used was 15 μg/h over 7 days. This strength was used by 32.9 % of patients in the TDB group. The lowest TDB strength was 5 μg/h, taken by 14.1 % of patients, and the highest strength was 30 μg/h (8.2 % of patients).

In the co-codamol group, the median dose was 180/3000 mg/day (six 30/500 mg tablets, taken by 55.8 % of patients). This was also the highest dose taken. The lowest dose was 48/3000 mg/day (six 8/500 mg tablets, taken by 23.6 % of patients).

The median dose in the tramadol group was 300 mg/day (taken by 58.4 % of patients), the lowest dose was 200 mg/day (6.6 % of patients), and the highest dose was 400 mg/day (35 % of patients).

3.1.4 Concomitant Medications

Many of the patients were taking concomitant non-target pain medications, either prescribed, purchased over-the-counter (OTC), or both prescribed and OTC. The use of these other pain medications was broadly similar across the three target medication groups (Table 2).

Nearly 30 % of patients taking one target medication also took prescribed paracetamol. Nearly one-fifth took OTC paracetamol, and 8.4 % took both prescribed and OTC paracetamol. Although co-codamol contains paracetamol, 21.4 % of patients in the co-codamol group were prescribed additional paracetamol, and 17.7 % bought paracetamol OTC. Nearly 1 in 12 patients taking co-codamol were taking prescribed and OTC paracetamol in addition to their co-codamol.

The total number of oral medications taken (for pain and other conditions), in addition to the target medication, are shown in Table A of the ESM. The proportions of patients were fairly similar across the groups, except the '10 or more' oral medications category, which accounted for a considerably higher percentage of the tramadol group than the TDB or co-codamol groups.

3.2 Patient Satisfaction

At baseline, nearly 80 % of patients in the TDB group reported being either 'very satisfied' or 'satisfied' with their medication, compared with fewer than 40 % of patients in both the co-codamol and tramadol groups (Fig. 2); this difference was statistically significant. When adjusted for age and sex, the estimated treatment effect for TDB vs. co-codamol was 3.56 (95 % CI 1.90–6.68; $p < 0.0001$). For TDB vs. tramadol, the estimated treatment effect was 3.22 (95 % CI 1.67–6.20; $p = 0.0005$).

3.3 HRQL

The SF-36 Physical Component Summary and Mental Component Summary scores for each group at baseline are shown in Table 3. The mean Physical Component

Table 2 Other pain medications taken by patients

	All [$N = 966$]	One target [$N = 701$]	TDB [$N = 85$]	Co-codamol [$N = 373$]	Tramadol [$N = 243$]
Other medications (prescribed)					
Paracetamol	279 (28.9)	205 (29.2)	19 (22.4)	80 (21.4)	106 (43.6)
Codeine-containing	124 (12.8)	93 (13.3)	24 (28.2)	47 (12.6)	22 (9.1)
Oral NSAID	401 (41.5)	296 (42.2)	46 (54.1)	160 (42.9)	90 (37.0)
Any topical	350 (36.2)	241 (34.4)	39 (45.9)	121 (32.4)	81 (33.3)
Other medications (OTC)					
Paracetamol	160 (16.6)	131 (18.7)	18 (21.2)	66 (17.7)	47 (19.3)
Codeine-containing	96 (9.9)	77 (11.0)	22 (25.9)	41 (11.0)	14 (5.8)
Oral NSAID	217 (22.5)	170 (24.3)	39 (45.9)	97 (26.0)	34 (14.0)
Any topical	351 (36.3)	264 (37.7)	37 (43.5)	149 (39.9)	78 (32.1)
Other medications (prescribed and OTC)					
Paracetamol	74 (7.7)	59 (8.4)	6 (7.1)	29 (7.8)	24 (9.9)
Codeine-containing	22 (2.3)	16 (2.3)	4 (4.7)	7 (1.9)	5 (2.1)
Oral NSAID	142 (14.7)	117 (16.7)	32 (37.6)	62 (16.6)	23 (9.5)
Any topical	127 (13.1)	86 (12.3)	20 (23.5)	41 (11.0)	25 (10.3)

Data are expressed as *n* (%)

TDB transdermal buprenorphine, *NSAID* non-steroidal anti-inflammatory drug, *OTC* over-the-counter

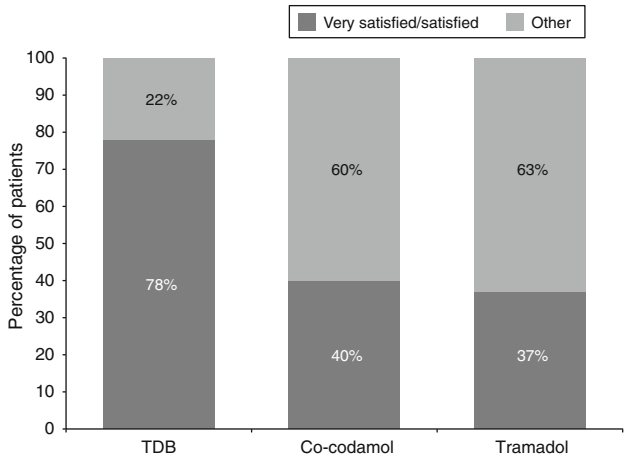

Fig. 2 Patient satisfaction with their current pain medication. Measured at baseline in patients taking one target medication (TDB, $n = 85$; co-codamol, $n = 373$; tramadol, $n = 243$). 'Other' includes 'Neither satisfied nor dissatisfied', 'Dissatisfied', 'Very dissatisfied' and 'No opinion'. *TDB* transdermal buprenorphine

Summary score was higher in the TDB group (38.39) than in both the co-codamol (30.99) and tramadol (27.83) groups. In the age- and sex-adjusted analysis, this difference was statistically significant for the TDB group when compared with the tramadol group ($p < 0.0001$), but not when compared with the co-codamol group ($p = 0.0910$). No significant differences in the Mental Component Summary scores were observed between the groups. The scores from the follow-up questionnaires from months 1, 2 and 3 are shown in Table 4. The Physical Component Summary results were broadly similar to baseline after 1 month, but after 2 and 3 months the treatment differences were smaller. For the Mental Component Summary scores, all of the follow-up results showed that mean scores were numerically higher in patients taking co-codamol and tramadol than those taking TDB, but that these differences were not significant.

3.4 Adherence

The mean MMAS score in the TDB group at baseline was 6.01, which corresponds to 'medium adherence'. Mean results for the co-codamol and tramadol groups were 5.24 and 5.73, respectively, putting both groups in the 'low adherence' category. The mean MMAS score in the TDB group was significantly higher than the mean scores for both the co-codamol and tramadol groups. The adjusted analysis showed that the estimated treatment effect for TDB vs. co-codamol was 1.07 (95 % CI 0.57–1.56; $p < 0.0001$), and 0.54 (95 % CI 0.02–1.07; $p = 0.0435$) for TDB vs. tramadol.

Looking at the trends in individual scores at baseline, there were more patients in the TDB group with high and medium adherence, and fewer patients with low adherence, compared with the co-codamol and tramadol groups (Fig. 3). Results for each question are shown in Table B of the ESM.

Table 3 SF-36 Physical Component and Mental Component Scores at baseline

	Analysis population	One target	TDB	Co-codamol	Tramadol
SF-36 Physical Component Summary					
n (missing)	965 (1)	701 (0)	85 (0)	373 (0)	243 (0)
Mean (SD)	29.40 (9.85)	30.79 (10.08)	38.39 (11.52)	30.99 (9.73)	27.83 (8.54)
Median (IQR)	27.37 (22.35–36.25)	28.65 (23.30–38.34)	44.68 (27.13–47.34)	28.90 (23.91–37.77)	26.83 (22.24–32.42)
Min, max	5.42, 55.37	5.48, 55.37	14.41, 51.33	11.20, 55.37	5.48, 51.82
Adjusted analysis					
p-Value for difference across all three treatment groups					$p < 0.0001$
Buprenorphine vs. co-codamol treatment difference				1.75 (95 % CI −0.28 to 3.78)	$p = 0.0910$
Buprenorphine vs. tramadol treatment difference				4.29 (95 % CI 2.12–6.46)	$p < 0.0001$
SF-36 Mental Component Summary					
n (missing)	965 (1)	701 (0)	85 (0)	373 (0)	243 (0)
Mean (SD)	33.94 (12.78)	35.63 (12.51)	36.99 (8.73)	35.19 (12.67)	35.84 (13.36)
Median (IQR)	34.35 (25.77–42.24)	35.03 (27.04–42.35)	36.18 (33.38–38.67)	34.36 (26.07–42.39)	35.41 (26.42–44.84)
Min, max	0.88, 72.58	8.42, 67.78	12.83, 59.68	8.42, 67.78	8.95, 66.41
Adjusted analysis					
p-Value for difference across all three treatment groups					$p = 0.4204$
Buprenorphine vs. co-codamol treatment difference				1.68 (95 % CI −1.46 to 4.82)	$p = 0.2945$
Buprenorphine vs. tramadol treatment difference				0.62 (95 % CI −2.75 to 3.98)	$p = 0.7193$

SF-36 Short-Form 36, *TDB* transdermal buprenorphine, *SD* standard deviation, *IQR* interquartile range, *min* minimum, *max* maximum, *CI* confidence interval

Table 4 SF-36 Physical Component Score and Mental Component Score recorded at 1, 2 and 3 months

	TDB	Co-codamol	Tramadol	Adjusted analysis	
SF-36 Physical Component Summary					
Month 1					
n	29	190	136	*p*-Value for difference across all three treatment groups	0.035
				Buprenorphine vs. co-codamol treatment difference	0.82 (95 % CI −2.44, 4.09), $p = 0.620$
Mean (SD)	32.91 (10.99)	30.00 (8.88)	27.15 (8.07)	Buprenorphine vs. tramadol treatment difference	3.03 (95 % CI −0.36, 6.43), $p = 0.080$
Month 2					
n	14	138	102	*p*-Value for difference across all three treatment groups	0.151
				Buprenorphine vs. co-codamol treatment difference	−0.64 (95 % CI −5.06, 3.77), $p = 0.775$
Mean (SD)	28.34 (5.73)	29.47 (8.47)	27.22 (8.10)	Buprenorphine vs. tramadol treatment difference	1.43 (95 % CI −3.09, 5.95), $p = 0.534$
Month 3					
n	9	114	87	*p*-Value for difference across all three treatment groups	0.267
				Buprenorphine vs. co-codamol treatment difference	−0.25 (95 % CI −5.67, 5.17), $p = 0.928$
Mean (SD)	28.34 (4.37)	29.90 (9.26)	27.62 (7.35)	Buprenorphine vs. tramadol treatment difference	1.63 (95 % CI −3.87, 7.14), $p = 0.559$
SF-36 Mental Component Summary					
Month 1					
n	29	190	136	*p*-Value for difference across all three treatment groups	0.341
				Buprenorphine vs. co-codamol treatment difference	−3.39 (95 % CI −8.42, 1.63), $p = 0.185$
Mean (SD)	34.34 (10.39)	37.28 (12.83)	34.53 (13.71)	Buprenorphine vs. tramadol treatment difference	−3.88 (95 % CI −9.10, 1.35), $p = 0.145$
Month 2					
n	14	138	102	*p*-Value for difference across all three treatment groups	0.139
				Buprenorphine vs. co-codamol treatment difference	−3.94 (95 % CI −11.2, 3.32), $p = 0.286$
Mean (SD)	33.92 (9.20)	36.98 (13.69)	38.40 (12.86)	Buprenorphine vs. tramadol treatment difference	−6.49 (95 % CI −13.9, 0.95), $p = 0.087$
Month 3					
n	9	114	87	*p*-Value for difference across all three treatment groups	0.247
				Buprenorphine vs. co-codamol treatment difference	−2.77 (95 % CI −11.4, 5.90), $p = 0.530$
Mean (SD)	33.19 (10.75)	35.94 (12.49)	36.93 (13.45)	Buprenorphine vs. tramadol treatment difference	−5.42 (95 % CI −14.2, 3.39), $p = 0.227$

SF36 Short-Form 36, *TDB* transdermal buprenorphine, *SD* standard deviation

After 1 month, adherence results were broadly similar to those recorded at baseline, with mean MMAS total scores of 6.33 for TDB, 5.45 for co-codamol, and 5.61 for tramadol. More patients in the TDB group were classed as having high and medium adherence, and fewer patients had low adherence, than in the co-codamol and tramadol groups. However, at months 2 and 3, there were very few differences between the groups.

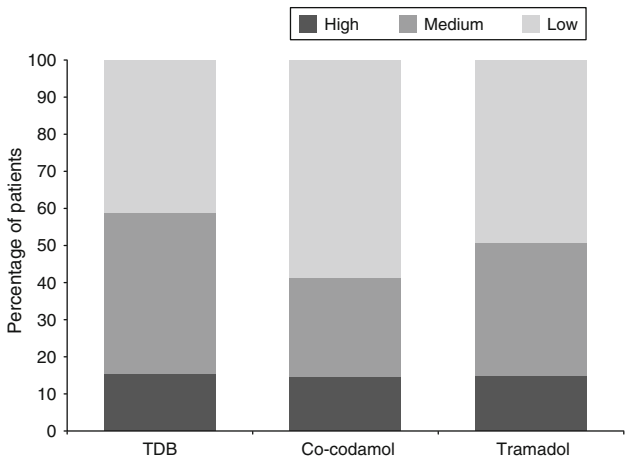

Fig. 3 Patient adherence with their pain medication. Percentages of patients in each target medication group with high, medium and low adherence, according to the Morisky Medication Adherence Scale. $N = 701$ patients taking one target medication: TDB, $n = 85$; co-codamol, $n = 373$; tramadol, $n = 243$. *TDB* transdermal buprenorphine

3.5 Reasons for Discontinuation

Reasons for discontinuation at months 1, 2 and 3 for the full analysis population are shown in Table C of the ESM. Although the numbers of patients who recorded reasons for discontinuation were small, discontinuations due to side effects were more common in the co-codamol and tramadol groups than in the TDB group.

3.6 Adverse Events

AEs were reported by 30.6 % of patients in the TDB group, compared with 53.4 % in the co-codamol group and 55.1 % in the tramadol group (Table D of the ESM). The incidence of constipation was much higher in the co-codamol group (23.9 %) than in the TDB group (9.4 %) or tramadol group (10.3 %); dizziness occurred in more patients in the tramadol group (10.7 %) than the TDB group (5.9 %) or co-codamol group (6.7 %); somnolence was reported in only 1.2 % of patients in the TDB group compared with 11.3 % in the co-codamol group and 14.8 % in the tramadol group; and psychiatric disorders were reported in more patients in the tramadol group (11.1 %) than the TDB group (1.2 %) or the co-codamol group (4.6 %).

4 Discussion

We believe this is the first study comparing patient-reported outcomes for medication satisfaction, HRQL and treatment adherence between different opioid analgesics in the treatment of OA pain. Previous studies have demonstrated comparable analgesia between TDB and co-codamol and tramadol [18, 19]. The intention was to highlight the other potential benefits of using a patch besides pain relief that may be important to patients, such as satisfaction with their medication or improvements in HRQL. TDB has the convenience of once-weekly administration and reduces the overall pill burden [18], which may be particularly important for patients with concomitant conditions who are taking multiple medications. Patients in the current study with additional medical conditions may have already been taking a number of non-analgesic medicines every day. The additional conditions most commonly reported in this study were depression, high blood pressure, high cholesterol and type II diabetes, which are all likely to require long-term medication use. Analgesic patches provide continuous pain relief without the risk of peaks and troughs of dosing that might be seen when taking regular oral analgesics. The patches may be useful for patients who are unable to take oral medications or have difficulty swallowing.

This study indicates that patients prescribed TDB for self-reported OA pain are more satisfied with their medication compared with patients taking co-codamol or tramadol. It would seem logical that increased patient satisfaction with pain medication might improve treatment adherence, and consequently patient outcomes, but there have been few studies looking at this for pain. Hirsh et al. [22] suggested a link between patient satisfaction and compliance with treatment in patients with chronic pain. However, a recent study showed that adherence and treatment satisfaction were not linked to quality-of-life outcomes in patients with chronic pain [23]. In our study, patients in the TDB group reported both greater treatment satisfaction and higher Physical Component Summary SF-36 scores compared with the co-codamol and tramadol groups. At baseline, the difference in Physical Component Summary SF-36 scores in the TDB group was statistically significant compared with tramadol, and scores were numerically higher compared with co-codamol.

Quality of life is an important consideration in the treatment of chronic pain patients. All aspects of quality of life are compromised when pain is inadequately treated, and effective pain relief has been shown to improve HRQL [24]. When patients with chronic pain were asked to rank aspects of quality of life impacted by their condition, they highlighted enjoyment of life, fatigue, emotional wellbeing and physical activities as the most important areas they would consider when evaluating the success of their pain treatment [25]. Our study indicates that SF-36 Physical Component Summary HRQL scores are higher for patients prescribed TDB compared with co-codamol or tramadol. After adjusting for age and sex, the treatment difference in

SF-36 Physical Component Summary score between the TDB and co-codamol groups was 1.75, which was not statistically significant (p .0910); however, the difference between the TDB and tramadol groups was 4.29. As well as being statistically significant ($p < 0.0001$), this is also likely to be clinically relevant. For patients with OA of the lower extremities, the minimal clinically important difference (MCID) for SF-36 scores has been reported as ranging from 2.0 to 7.8 depending on the subscale used; for the Physical Component Summary, 2.0 was suggested as the MCID to show improvement [26]. In the current study, after 1 month the SF-36 Physical Component Summary scores were broadly similar to baseline, with smaller treatment differences after 2 and 3 months. However, the number of patients in the TDB group completing questionnaires at months 2 and 3 was too low for any conclusions to be drawn from these data. In all three of the follow-up questionnaires, SF-36 Mental Component Summary scores were better for patients taking co-codamol or tramadol than for patients taking TDB; however, these differences were not significant. Over one-third of patients in the study reported depression as a comorbidity. This was not unexpected as depression is very common in people with chronic pain, and it is therefore important for pain to be treated using a biopsychosocial model [27]. It is possible that the high level of depression reported in the study population affected the SF-36 Mental Component Summary scores and may have contributed to the lack of differences seen in these scores between the groups.

Adherence is difficult to measure in clinical studies because of increased monitoring, and possibly increased awareness, by patients that their adherence is being measured. Real-world studies may be more useful for measuring adherence but often (as in this study) rely on patients accurately recalling and reporting their medication use behaviour. The results of this study suggest that patients in the TDB group show medium adherence to their medicine compared with low adherence in the co-codamol and tramadol groups. To qualify for high adherence, a patient would need a perfect score on the MMAS questionnaire. For example, this means they must never forget a dose or forget to take their medicine with them when travelling. When considering patch medications, some of the questions may be misleading; for example, asking if there were any days in the last week when the medication was not taken, or if the medication was taken yesterday. Patients could misinterpret these questions as asking whether they had applied a patch on the days in question, when in reality they would be 'taking' their medication on any of the 7 days after patch application. Many patients with OA are likely to be prescribed a number of different medications, both for pain and other comorbid conditions; however, increasing numbers of concomitant medications have been linked with a decrease in medication adherence [28]. This is an increasing problem, particularly in older people. A recent review of Scottish medical records found that in 2010, 17.2 % of people over 65 years of age were prescribed 10 medications in an 84-day period [29]. In our study, most of the patients (just over one-third) were taking between three and five additional oral medications, with 8.7 % of the overall study population and 21.0 % of patients in the tramadol group taking over 10 additional oral medications. Once-weekly transdermal patches are likely to be easier for patients to remember to use than oral medications, which could help to explain the improved adherence seen with TDB compared with co-codamol and tramadol in this study. Importantly, patients in the TDB group were younger than those in the co-codamol and tramadol groups, which may also have contributed to the improved compliance. The convenience of a medicine is likely to be important for people who are working, and oral medication may be less convenient than a transdermal patch. For example, a patient who has been prescribed tablets may forget to take their medicine to work with them, it could be inconvenient to stop work to administer their dose, or the patient might forget to take their tablets at the right time while working. In this study, the patient population in the TDB group was predominantly of working age, and the potential convenience benefits of a patch formulation could account for the increased adherence seen in the TDB group. Although the follow-up results were similar after 1 month, there were few differences between the groups after 2 and 3 months. Again, the number of TDB patients completing questionnaires at months 2 and 3 was too low for any conclusions to be drawn.

People with OA pain often take a combination of different analgesic medications [4]. In the current study, patients were divided into groups depending on the target medication they were taking (TDB, co-codamol or tramadol), but 265 patients were taking two or more of the target medications and were removed from the medication-specific analyses. Many patients were also taking concomitant non-target pain medications. However, use of these other pain medications was broadly similar across the three target medication groups, allowing comparisons to be made between the groups. A substantial proportion of patients were taking prescribed and/or OTC paracetamol in addition to the target medication, even for patients already receiving paracetamol from co-codamol. It is important to consider the risk of toxicity in these patients taking high doses of paracetamol. A recent review has suggested that paracetamol may be linked to cardiovascular, gastrointestinal and renal side effects, even at standard therapeutic doses [30]. In addition, high use of paracetamol may indicate that the intensity of patients' pain and recommended treatment guidelines are not being taken into

account in the management of OA pain [31]. Higher proportions of patients in the TDB group were using concomitant analgesics (including prescribed, OTC, and prescribed/OTC) compared with the co-codamol and tramadol groups. It is possible this could have contributed to the improved satisfaction, SF-36 Physical Component Summary HRQL, and adherence scores in the TDB group. It is likely that many patients in this study were self-administering their OTC pain medications without notifying their GP. Physicians should consider this and ask about OTC medication use at each consultation to ensure prescribed analgesia is suitable for the patient's level of pain, and to reduce the need for the patient to make unnecessary pharmacy visits. Regular pain assessments would also be beneficial, ensuring pain is being treated appropriately in each patient.

AEs reported in this study were typical of those seen with opioid medications. The proportion of patients experiencing AEs was smaller in the TDB group than in the co-codamol or tramadol groups. Constipation was more common in the co-codamol group than the TDB and tramadol groups, and is a well-known side effect of codeine, which has been described as "too constipating for long-term use" [21]. Constipation can have a large impact on patients' quality of life. In a survey of patients taking opioids and laxatives, it was shown that constipation was the 'most bothersome' gastrointestinal side effect of opioids [32] and does not decrease over time as with other opioid side effects. Nervous system disorders and psychiatric disorders occurred more often in the tramadol group than the TDB or co-codamol groups. This included dizziness, which can be a particular problem in the elderly, and is present in some form in 30 % of people over 65 years of age, and 50 % of people aged 85 years and over. Almost 60 % of older primary care patients with dizziness experience a moderate or severe impact on their daily life as a result [33]. Dizziness has been linked to anxiety and avoidance behaviour, such as avoiding crowds and being away from home, and can also cause occupational problems in people of working age [34].

The high dropout rate over the study period was mostly due to patients not completing the follow-up questionnaires, rather than discontinuation of treatment. This highlights the difficulties in carrying out this type of research in patients without healthcare professional input. Because of the drop in patient numbers, the main statistics in this study have been taken from the baseline population. However, the results are still a valid measure of patients' opinions and treatment outcomes as most of the patients had been stabilised on their medication for 6 months or more, and were not new patients. We did not expect so many long-term patients when we designed the study, and thought that the follow-up questionnaires would show differences, for example as patients changed treatments due to side effects or lack of efficacy. In reality, even if patient numbers had been higher at follow-up, we would have been unlikely to see much difference from baseline in a population largely well-established on their target medication.

As this study had no healthcare professional involvement, some of the information collected may not be as accurate as in a controlled clinical trial, where source data are verified. For example, the self-reported diagnosis of OA was not medically confirmed. However, self-reported OA has recently been shown to have high specificity when compared with a radiographic diagnosis of OA [35]. Patients' recall of information such as current and recent medications and concomitant conditions may be unreliable. In addition, as this was a non-randomised, non-blinded study, factors that may have influenced the type of analgesic each patient was prescribed may have had an effect on their responses to questions. The treatment groups in the study were unequal, with the co-codamol group over four times larger than the TDB group, although this may reflect the proportion of OA patients taking each medication in the wider population. The TDB group was noticeably younger than the other groups analysed in this study, and younger than the average ages in most OA studies. This could be due to the use of social media and online advertising for patient recruitment, which may have led to selection bias, favouring younger and more IT-literate patients; however, this would have affected all groups equally. It is also possible that healthcare professionals prefer to prescribe TDB for younger patients of working age because it is less intrusive on their daily schedule as it does not require regular administration throughout the day. The TDB group was quite different to the other groups in terms of gender balance, with a much higher proportion of male subjects. It is not clear why there was this gender recruitment difference, as, for example, IT literacy would not be expected to be different by gender. It is possible that GPs were more cautious about using oral opioids in younger males [36], although we have no supporting data. Although an age- and sex-adjusted analysis was performed, the differences in patient numbers and demographics between the groups should be taken into account when interpreting the results of this study. In addition, due to the drop in patient numbers after the baseline questionnaire, it is difficult to interpret the significance of any trends seen in the follow-up results.

5 Conclusions

Although there were between-group differences in patient demographics, this observational study showed that patients prescribed TDB for their hip and/or knee OA pain

had higher scores for medication satisfaction, SF-36 Physical Component Summary HRQL measures, and medication adherence than those taking co-codamol or tramadol, two commonly-used oral opioids.

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Author contributions Philip G. Conaghan, Michael Serpell, Rod Junor and Sara Dickerson were involved in study design, analysis and interpretation of data; Paula McSkimming provided statistical analysis and interpretation of data. All authors provided critical revision of the manuscript for important intellectual content, and approved the submitted manuscript and subsequent revisions. As corresponding author, Sara Dickerson acts as the overall guarantor of the manuscript.

Compliance with Ethical Standards

Ethical approval Study documents were reviewed and approved by the EoSRES, and all patients participating in the study were asked to provide informed consent by telephone or online. All procedures performed in studies involving human participants were in accordance with the ethical standards of the appointed Research Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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