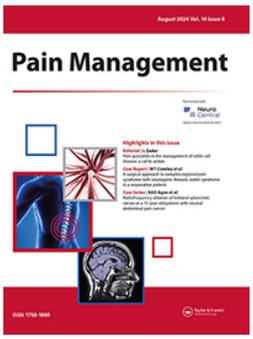

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META-ANALYSIS

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Efficacy of transdermal anti-inflammatory patches for musculoskeletal pain: a systematic review and meta-analysis

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ABSTRACT

Aim: To determine the efficacy of transdermal anti-inflammatory patches in the treatment of acute and chronic musculoskeletal pain.

Methods: A comprehensive search of: Cochrane Central register of controlled trials, EMBASE, MEDLINE, CINAHL and PubMed, for studies using transdermal anti-inflammatory patches vs placebo for management of musculoskeletal pain, e.g. soft tissue injuries or tendonitis (last search January 2024). Cochrane Risk of Bias Tools v1 was used for quality assessment and GRADE determined certainty of evidence. Meta-analysis was performed.

Results: Twenty-three randomized placebo-controlled trials (n = 4729) were included. There was low-certainty evidence that transdermal patches provided statistically and clinically significant pain relief on movement at long-term follow-up for chronic musculoskeletal pain (effect size -2-69 (95% CI: -4.14, -1.24) and at short-term follow-up which was non-clinically significant, (-1.24: 95% CI: -1.78, -0.69).

Conclusion: Several types of transdermal anti-inflammatory patches may offer short-term and long-term pain relief for acute and chronic musculoskeletal conditions. However, the clinical significance of this effect for the long-term pain relief was based on low-certainty evidence of transdermal anti-inflammatory patches versus placebo; for short-term pain there was an overall non-clinically significant improvement. Performing a meta-analysis for all outcomes was not possible due to insufficiency in the evidence-base.

Protocol registration: www.crd.york.ac.uk/prospero identifier is CRD42020185944.

PLAIN LANGUAGE SUMMARY

Do medication Patches Really Help with Muscle & Joint Pain? A Review of the evidence.

What We Did: We wanted to see if patches containing certain medicines that you stick on your skin can help with muscle and joint pain. We wanted to see if they did this in both in the short term and long term.

How We Did It: We searched through medical databases to find research that compared these patches to fake treatments (placebos). We wanted to see if they work for muscle and joint pain. We checked the quality of these studies and combined their results when possible.

What We Found: We found 23 studies that included a total of 4729 people. We found that these patches might help with long-term muscle and joint pain, but the evidence wasn't very strong. For short-term pain, the patches showed some improvement, but it wasn't enough to be considered important.

Conclusion: Medication patches might help reduce muscle and joint pain in both the short and long term. However, the evidence for long-term pain relief isn't very strong, and the short-term benefits are not that large.

ARTICLE HISTORY
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KEYWORDS
anti-inflammatory; meta-analysis; musculoskeletal; pain management; placebo; systematic review; transdermal patch

1. Introduction

Musculoskeletal pain is the leading cause of disability worldwide [1]. Since 1990, the incidence rate of musculoskeletal conditions has increased globally by 58% from 211.80 million to 334.74 million, with a decreasing age-standardized incidence rate of 0.18% annually [2]. There are several medication modalities to treat these conditions. These include non-steroidal anti-inflammatory drugs (NSAIDs) [3,4], corticosteroids [5] and glyceral trinitrate and nitric oxide [6]. They are usually delivered in tablet or injection preparations [7]. However, these approaches have several associated problems such as

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first pass hepatic metabolism, enzymatic digestion, drug hydrolysis, gastrointestinal irritation, drug fluctuations, adverse events and disease transmission [8]. There may be significant adverse reactions, particularly of the GI tract and cardiovascular system, as a result of the high plasma concentrations attained [9]. This can limit which patients receive these medications. Transdermal medication, whereby drugs are delivered via an adhesive patch applied to the skin, is an attractive alternative delivery mechanism of drug administration. The drug contained in the transdermal patch enters the body through the skin and diffuses into capillaries for systemic delivery [10]. They thus avoid the various problems associated with the other more common routes of delivery. Transdermal patches have become a common medical practice with over 20 commercially available transdermal drugs approved by the Food and Drug Administration (FDA) [11]. Transdermal patches can deliver a more precise dose of the active ingredient, as they prevent variability in the application process and can deliver a specific drug dose [10]. Patches allow more consistent serum drug levels, often a goal of therapy and improved local dermal penetration along with an extended drug release profile due to their smaller size and high surface area [10]. They are easy to apply and may be more convenient and more acceptable for patients [12]. However, they are used less frequently in routine clinical practice largely due to being twice as costly [13].

Systematic reviews have been undertaken to assess the efficacy of opioid and other analgesic medications with transdermal patch delivery for people with cancer and non-cancer pain [14]. To the authors' knowledge, no systematic reviews have been undertaken to determine the efficacy of transdermal patches for people with musculoskeletal pain. Given the potential benefit this may have to individuals for whom anti-inflammatory medication in tablet or injection form is contraindicated or who prefer an alternative method of delivery, determining the efficacy of this drug delivery approach is valuable. Furthermore, for this mode of delivery to be acceptable to practitioners in a variety of clinical settings, there should be evidence of its efficacy for acute and chronic musculoskeletal pain.

Therefore, the aim of the present systematic review is to determine the efficacy of transdermal anti-inflammatory patches in the treatment of acute and chronic musculoskeletal pain.

2. Methods

This systematic review was registered prior to commencing the search strategy through the International Prospective Register of Systematic Reviews database (Protocol registration: www.crd.york.ac.uk/prospero identifier is CRD42020185944). The review has been reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines [15].

2.1. Search strategy

The electronic search was undertaken in April 2020 and updated on January 2024. The following published and unpublished literature databases were searched: Cochrane Central register of controlled trials (CENTRAL), EMBASE, MEDLINE (Ovid), CINAHL and PubMed. We accessed clinical trial registries for unpublished or ongoing clinical trials including the WHO International Clinical Trial Registry and ClinicalTrials.gov registry. The search strategy for MEDLINE is presented in Supplementary Table S1 and modified for each database. The reference lists of all potentially eligible studies were screened for any additional eligible studies.

2.2. Eligibility criteria

Inclusion:

- Participants had acute or chronic pain from any musculoskeletal condition, including but not limited to soft tissue injuries or trauma, tendonitis and myofascial pain.
- Randomized placebo-controlled trials (RCTs) investigating the effects on pain relief of a transdermal delivery of an anti-inflammatory patch compared with a placebo.

Exclusion:

- RCTs comparing transdermal anti-inflammatory patch to another delivery method.
- RCTs comparing anti-inflammatory patches to another therapy.
- Studies where participants had musculoskeletal pain that resulted from a surgical intervention.
- Studies focused on dentistry conditions and interventions.
- Studies in animals.

2.3. Study identification

The titles and abstracts of all search results were independently reviewed by two authors (MBS, MJC). The full texts of all those deemed potentially eligible were gathered and reviewed against the criteria by the same two authors. Full texts which met the eligibility criteria and were agreed by two authors (MBS, MJC) were included. Any disagreement on study eligibility

was resolved through discussion until a consensus was reached.

2.4. Data extraction

All data were independently extracted by two authors (MBS, MJC). This was performed using a pre-defined data extraction template. Data extracted included: number of participants; population characteristics, participant characteristics including age and sex; the musculoskeletal pathology/condition; active intervention (dose, delivery, frequency); sham description; length of intervention (active and sham).

2.5. Outcome measures

The primary outcome was pain on movement in the long term (for 3 months or longer) resulting from the application of a transdermal patch. We assessed pain recorded by a visual analogue scale (VAS), a numerical rating scale (NRS), by the knee injury and osteoarthritis outcome score (KOOS), or the Western Ontario and McMasters (WOMAC) score.

Secondary outcomes included: pain on rest, a change in pain score, patient evaluation of function/pain, functional disability and capability, the use of rescue medication (and amount), patient and investigator global assessment of tolerability and patient and investigator global assessment of efficacy, and adverse events. Data were analyzed in the short-term (0–6 weeks), and medium term (6 weeks to 3 months).

Statistical significance is not equivalent to clinical significance, therefore we agreed a threshold of the measures that would signify an important improvement in a patient's symptoms. We based the decision on a reduction of approximately two points or a reduction of approximately 30% in the pain intensity NRS or the VAS (0–100 mm) which represented a clinically important difference [16].

2.6. Quality assessment

Two authors (MBS, MJC) independently assessment the quality of the evidence using the Cochrane Risk of Bias Tools v1 [17]. Where disagreements occurred in appraisal, these were resolved through discussion between the two authors.

2.7. Data analysis

Participant characteristics, study design and intervention (active patch or placebo) were assessed using the data extraction table. Where study heterogeneity was evident for one or more of those aspects, a narrative analysis was undertaken. When study homogeneity was evident, a random-effects meta-analysis was adopted for all continuous data outcomes. Standardized mean differences (SMD) were presented for each outcome at each time-point with 95% confidence intervals (CI). All analyses were conducted on Review Manager Web (RevMan Web, Version 1.22.0). The Cochrane Collaboration, (2020) (www.revman.cochrane.org). *A priori* subgroup analyses assessed the impact of specific transdermal patch medication and dosages. We grouped diclofenac epolamine 180 mg/1.3%w/w with diclofenac sodium 140 mg/1%w/w as these patches provide equivalent doses of diclofenac. Diclofenac sodium 60 mg and 75 mg were analyzed separately. The certainty of evidence was assessed for each outcome using the GRADE approach [18]. We planned to assess small sample size publication bias all outcomes where there were 10 datasets or more through the construction of a funnel plot which assessed symmetry. The 10-dataset threshold was only met for the primary outcome.

3. Results

3.1. Search results

The PRISMA flowchart (Figure 1) shows the search results. The combined search from all of the databases and manual searches produced 358 articles. Following removal of duplicates, conference abstracts, 133 were assessed for eligibility. Twenty-three RCTs with a placebo comparator were included in the review (Supplementary Table S2).

3.2. Characteristics of included studies

The total number of participants in the active treatment groups was 2604 and in the placebo groups was 2125. The duration of transdermal patch treatment varied considerably between the 23 trials. The longest treatment period was 24 weeks [19–21]. The shortest duration of treatment was 5 days (120 h) [22]. Assessment time points and the number of assessments also varied. One trial had two assessments (baseline and end of treatment at 14 days) [23]. The trial by Higashi [24] had 14 assessment points over a 12-h period. Of the 23 included trials, 13 applied the patch to acute musculoskeletal soft tissue injuries conditions described as a sprain, strain, or contusion (n = 10) [22–31], or specifically an ankle sprain (n = 3) [32–34]. One study recruited participants with knee osteoarthritis [35], one myofascial pain in the trapezius muscle but did not state its chronicity [36], and a third study recruited people with low back pain [37]. All other trials (n = 6) included participants with chronic tendinopathy of the upper [19,21,38–41] or lower limbs [20].

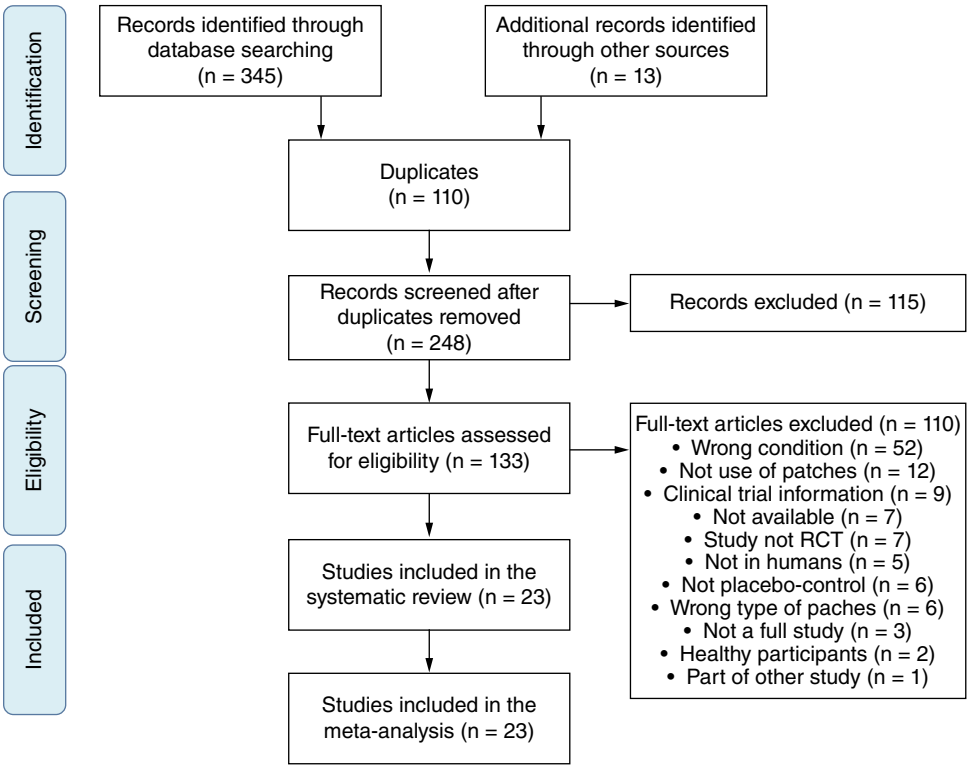

Figure 1. PRISMA flow-chart.

3.3. Quality assessment

The results of the quality assessment can be found in Table 1 and Figure 2. At least 70% of the studies included in this review had low risk of bias for most of the domains. The most common risk of bias related to the allocation concealment (64%, high risk and unclear risk combined) either because the allocation process was controlled by the same person distributing the patches to the patients [19–21], or because the information was not enough to understand if there had been a concealment process [22–25,27,28,30,31,34–36,38]. The second most common risk of bias was due to other sources of bias (60%, high risk and unclear risk combined); these included not having a clear disclaimer about conflict of interest of the sponsor or the authors working for the sponsor [20–25,28,29,34,35,40–42], or having groups different at baseline regarding important prognostic indicators [39].

3.4. Publication bias

There were sufficient data to perform a funnel plot for the primary outcome. There were moderate to high evidence of publication bias with evidence of bias for small sample size studies with positive and negative effect estimates (Figure 3).

3.5. Meta-Analysis

A summary of the meta-analysis for a transdermal patch versus placebo patch is shown in Table 2. This analysis included, betamethasone, diclofenac, ibuprofen, ketoprofen and nitic oxide patches.

3.5.1. Primary outcome

There was low-certainty evidence that transdermal anti-inflammatory patches provided greater pain relief on movement in the long-term for chronic musculoskeletal pain (SMD -2.69; 95% CI: -4.14 to -1.24; $p < 0.01$; N = 139) (Figure 4). This was above the threshold set of a reduction of approximately two points or a reduction of approximately 30% in the pain intensity NRS or the VAS and was deemed clinically significant.

3.5.2. Secondary outcomes

There was low-certainty evidence of short-term pain relief of transdermal anti-inflammatory patches over placebo for a variety of painful chronic musculoskeletal conditions (SMD: -1.12; 95% CI: -1.68 to -0.56; $p < 0.01$; N = 2434) (Figure 4). This was not clinically significant. There was low-certainty evidence of no benefit in medium-term pain relief of transdermal anti-inflammatory patches over placebo (SMD: -0.26; 95% CI: -4.01 to 3.48; $p = 0.89$; N = 144) (Figure 4). There was no benefit of transdermal

Table 1. Summary of the risk of bias/quality assessment evaluation.

Study	Random sequence generation	Allocation concealment	Selective Reporting	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Other Bias	Ref.
Bernasconi et al. (2019)	!	!	✓	!	✓	✓	✓	[38]
Brühlmann & Michel (2003)	✓	!	✓	✓	✓	✓	!	[35]
Costantino et al. (2011)	✓	✓	✓	✓	✓	✓	✓	[32]
Coudreuse et al. (2010)	✓	✓	✓	✓	✓	✓	✓	[33]
Frizziero et al. (2016)	✓	✓	✓	✓	✓	✓	✗	[39]
Galer et al. (2000)	!	!	✗	✗	!	✓	!	[25]
Higashi et al. (2010)	✓	!	✓	✓	✓	✓	!	[24]
Hoffmann et al. (2012)	!	✓	✓	✓	✓	✓	✓	[26]
Hsieh et al. (2010)	!	!	✓	✓	✓	✓	!	[36]
Klainguti et al. (2010)	✓	!	✓	✓	✓	✓	✓	[27]
Kuehl et al. (2011)	✓	!	✓	✓	✓	✗	!	[23]
Li et al. (2013)	✓	✓	✓	✓	✓	✓	✓	[28]
Mazières et al. (2005a)	✓	✓	✓	✓	✓	✓	!	[40]
Mazières et al. (2005b)	✓	!	✓	✓	✓	✓	!	[34]
Paoloni et al. (2003)	✓	✗	✗	✓	✓	✓	✓	[19]
Paoloni et al. (2004)	!	✗	✓	✓	✓	✓	!	[20]
Paoloni et al. (2005)	✓	✗	✓	✓	✓	✓	!	[21]
Paoloni et al. (2009)	✓	✓	✓	✓	✓	✓	!	[41]
Predel et al. (2004)	✓	✓	✓	✓	✓	✓	!	[29]
Predel et al. (2016)	!	!	✓	!	✓	✓	!	[22]
Predel et al. (2017)	✓	!	✓	✓	✓	✓	✓	[30]
Predel et al. (2018)	✓	!	✓	✓	✓	✓	✓	[31]
Taguchi et al. (2023)	✓	✓	✓	✓	✓	✓	!	[37]

Low risk (green ✓), high risk (red ✗), unclear risk (yellow !).

anti-inflammatory patches over placebo when assessed by adverse events in the short ($p = 0.09$) or long-term ($p = 0.36$) or for investigator global assessment in tolerability ($p = 0.09$). There was moderate-certainty evidence for greater change in pain score for anti-inflammatory patches compared with placebo within the first 6 weeks of treatment (SMD: -0.68; 95% CI: -1.30 to -0.06; $p = 0.03$; N = 2229) (Table 2) although the confidence intervals are wide and near crossing 1. There was high-certainty evidence that investigator global assessment was greater for anti-inflammatory patches compared with placebo when assessed for tolerability (SMD: 1.38; 95% CI: 0.96 to 1.98; $p = 0.09$; N = 1594) (Table 2). There was moderate-certainty evidence that global assessment of treatment efficacy was greater in the short-term for anti-inflammatory patches compared with placebo when assessed by the patient (SMD: 0.47; 95% CI: 0.37 to 0.60; $p < 0.01$; N = 1656) and investigator (SMD: 0.25; 95% CI: 0.18 to 0.35; $p < 0.01$; N = 2361) and long-term for patient global assessment (SMD: 0.31; 95% CI: 0.16 to 0.61; $p < 0.01$; N = 196) (Table 2). There was moderate-certainty evidence to suggest people who receive anti-inflammatory patches had significantly reduced pain at rest in the short-term (SMD: -1.04 95% CI: -1.99 to -0.10; $p = 0.03$; N = 1274) and low-certainty evidence in the medium-term (SMD: 2.24; 95% CI: 1.67 to 2.81; $p < 0.01$; N = 79) (Table 2), the latter being statistically and clinically significant. While there was no benefit of anti-inflammatory patches compared with placebo for use of rescue medication in the first 6 weeks (p = 0.71), those randomized to the anti-inflammatory groups took significantly less rescue medication than the placebo group (SMD: -0.59; 95% CI: -1.20 to -0.02; $p < 0.01$; N = 654). While there was low-certainty evidence of superior patient evaluation of function and pain in the long-term (SMD: 1.59; 95% CI: 1.06 to 2.12; $p < 0.01$; N = 74) there was no benefit in the short-term ($p = 0.49$) (Table 2).

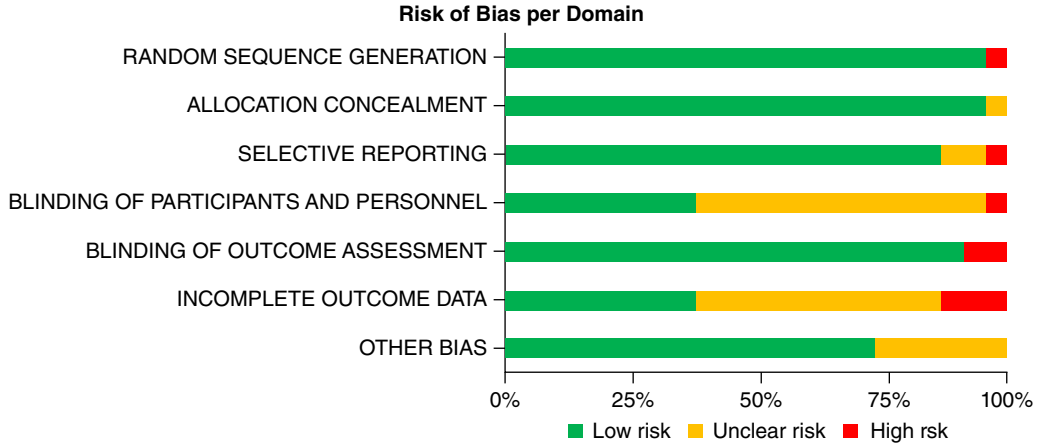

Figure 2. Risk of bias graph.

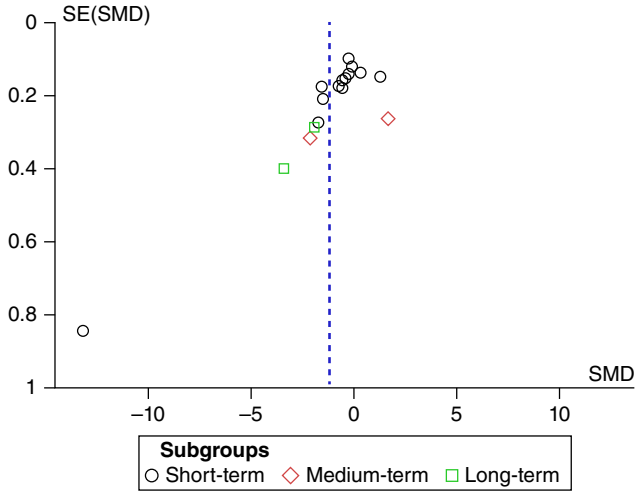

Figure 3. Funnel plot to assess small sample size publication bias for the primary outcome (pain on movement).

3.5.3. Subgroup analysis: by medication

3.5.3.1. Betamethasone: 2.25 mg. Figure 5 & Supplementary Table S3 illustrate the results of the meta-analysis when betamethasone patch (2.25 mg) was compared with placebo in the short-term. There were low-certainty evidence of no benefit of betamethasone patches over placebo in respect to short-term assessment of: pain on movement ($p = 0.06$), change in pain score ($p = 0.81$), patient evaluation of function and pain ($p = 0.55$), use of rescue medication ($p = 0.886$), amount of rescue medication taken ($p = 0.49$), assessment of patient ($p = 0.11$) and investigator ($p = 0.43$) global assessment of tolerability, assessment of patient efficacy ($p = 0.10$) and moderate-certainty evidence of no benefit for short-term adverse events ($p = 0.75$).

3.5.3.2. Diclofenac – 140 mg to 180 mg. Figure 5 & Supplementary Table S4 describe and illustrate the results of the meta-analysis when diclofenac 140–180 mg was compared with placebo in the short-term. There was low-certainty evidence of no benefit of patches over placebo for short-term outcomes of pain on movement ($p = 0.31$), change of pain score ($p = 0.20$), or adverse events ($p = 0.21$). There was moderate-certainty evidence of no benefit of diclofenac 140 mg to 180 mg patches compared with placebo in the short-term assessments of pain at rest ($p = 0.07$) patient ($p = 0.63$) or investigator ($p = 0.11$) global assessment of tolerability. While there was no difference between diclofenac 140 mg to 180 mg patches to placebo for the use of rescue medication in the short-term ($p = 0.5$), those randomized to the diclofenac patch required less rescue medication in the short-term compared with placebo (SMD: -1.72; 95% CI: -2.14 to -1.30; $p < 0.01$; $N = 120$). Furthermore, there was low-certainty evidence for a that diclofenac 140–180 mg was significantly beneficial compared with placebo on patient- (SMD: 0.37; 95% CI: 0.23 to 0.61; $p < 0.01$; $N = 510$) and investigator- (SMD: 0.20; 95% CI: 0.12 to 0.33; $p < 0.01$; $N = 1894$) global assessment of treatment efficacy.

3.5.3.3. Ibuprofen: 200 mg. Supplementary Table S5 describes the results of the meta-analysis when ibuprofen 200 mg was used for the ibuprofen patch compared with placebo patch in the short-term. There was very low-certainty evidence of no benefit in ibuprofen patches compared with placebo on pain on movement in the short-term ($p = 0.28$), or on adverse events ($p = 0.29$). There was a significant benefit of ibuprofen patches compared with placebo in the short-term on patient global assessment of tolerability (SMD: 9.57; 95% CI: 1.16 to 78.86; $p = 0.04$; $N = 132$) and efficacy (SMD: 0.14; 95% CI: 0.05 to 0.35; $p < 0.01$ $N = 152$). While there was no benefit between the interventions when assessed by investigator global assessment of tolerability ($p = 0.53$),

Table 2. Summary of the meta-analysis (total analysis).

Outcome	Time assessed	N[a]		Effect estimate			I2 value (%)	GRADE assessment
		Patch	Control	SMD	95% CI	*p*-value		
Pain on movement	Short	1237	1197	-1.12	-1.68 to -0.56	<0.01	98	Low[c]
	Medium	76	68	-0.26	-4.01 to 3.48	0.89	99	Low[c]
	Long	67	72	-2.69	-4.14 to -1.24	<0.01	89	Low[c]
Change pain score	Short	1053	1176	-0.68	-1.30 to -0.06	0.03	98%	Moderate[e]
Pain at rest	Short	639	635	-1.04	-1.99 to -0.10	0.03	98	Moderate[e]
	Medium	44	35	2.24	1.67 to 2.81	<0.01	99	Low[d]
Patient evaluation of function and pain	Short	284	245	0.27	-0.51 to 1.05	0.49	94	Moderate[e]
	Long	35	39	1.59	1.06 to 2.12	<0.01	NE[b]	NE[b]
Use of rescue medication	Short	216	216	0.94	0.67 to 1.32	0.71	0	High
Amount of rescue medication	Short	330	324	-0.59	-1.20 to -0.02	<0.01	93	Moderate[e]
Patient Global Assessment (tolerability)	Short	528	483	1.60	1.08 to 2.35	0.02	53	Moderate[e]
Investigator global assessment (tolerability)	Short	800	796	1.38	0.96 to 1.98	0.09	0	High
Patient Global Assessment (efficacy)	Short	845	811	0.47	0.37 to 0.60	<0.01	72	Moderate[e]
	Long	95	101	0.31	0.16 to 0.61	<0.01	0	Moderate[f]
Investigator global assessment (efficacy)	Short	887	1474	0.25	0.18 to 0.35	<0.01	56	Moderate[e]
Adverse events	Short	1650	1595	0.77	0.57 to 1.04	0.09	59	Moderate[e]
	Long	93	97	1.18	0.83 to 1.68	0.36	55	Low[d]

[a]N = number of participants in outcome analysis.
[b]NE = Not Evaluated.
[c]Downgraded one-level due to inconsistency and one-level for publication bias.
[d]Downgraded one-level due to inconsistency and one-level due to imprecision.
[e]Downgraded one-level due to imprecision.
[f]Downgraded one-level due to imprecision.

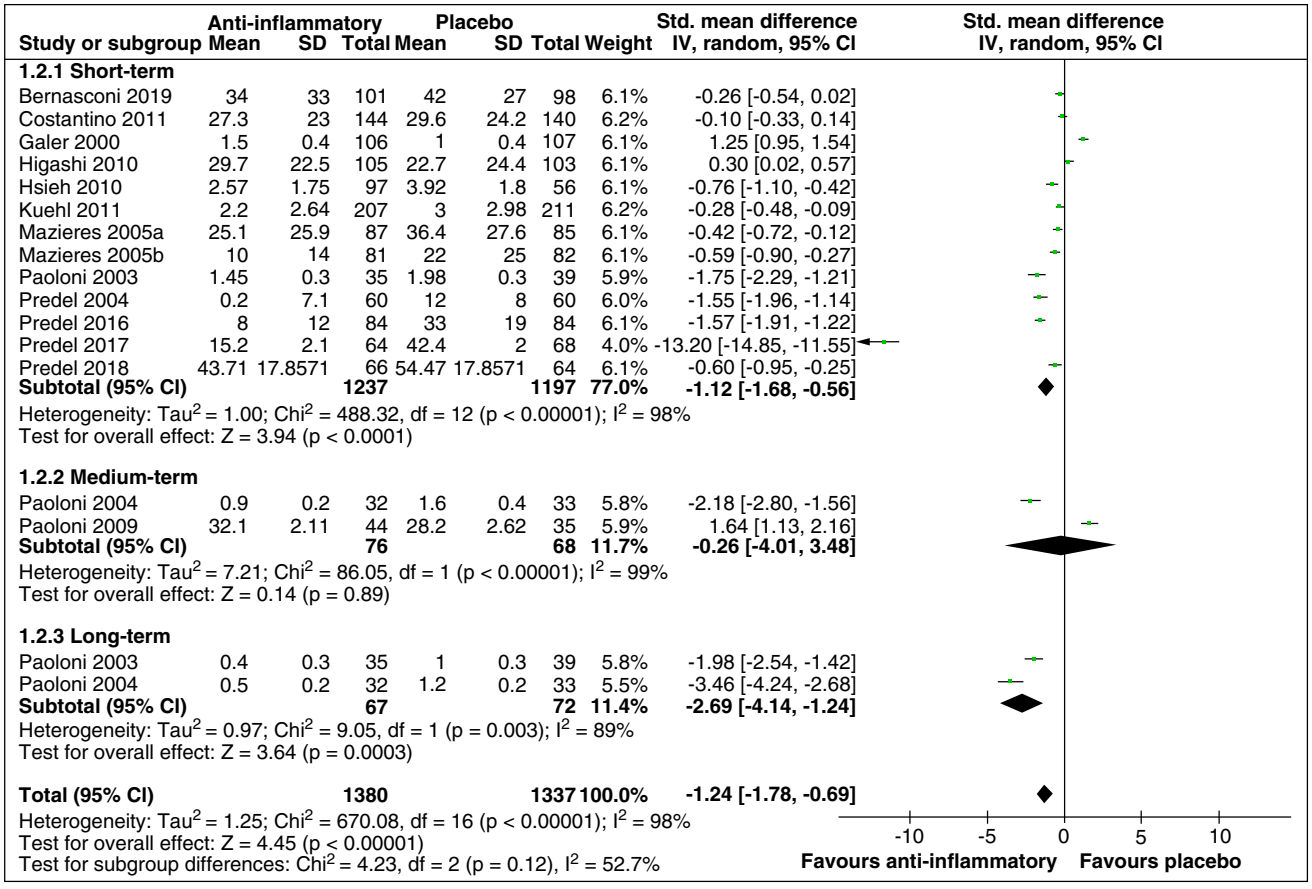

Figure 4. Forest-plot to illustrate the analysis of the primary outcome (pain on movement) at short-term, medium-term and long-term follow-up for anti-inflammatory patches compared with placebo for musculoskeletal pain.

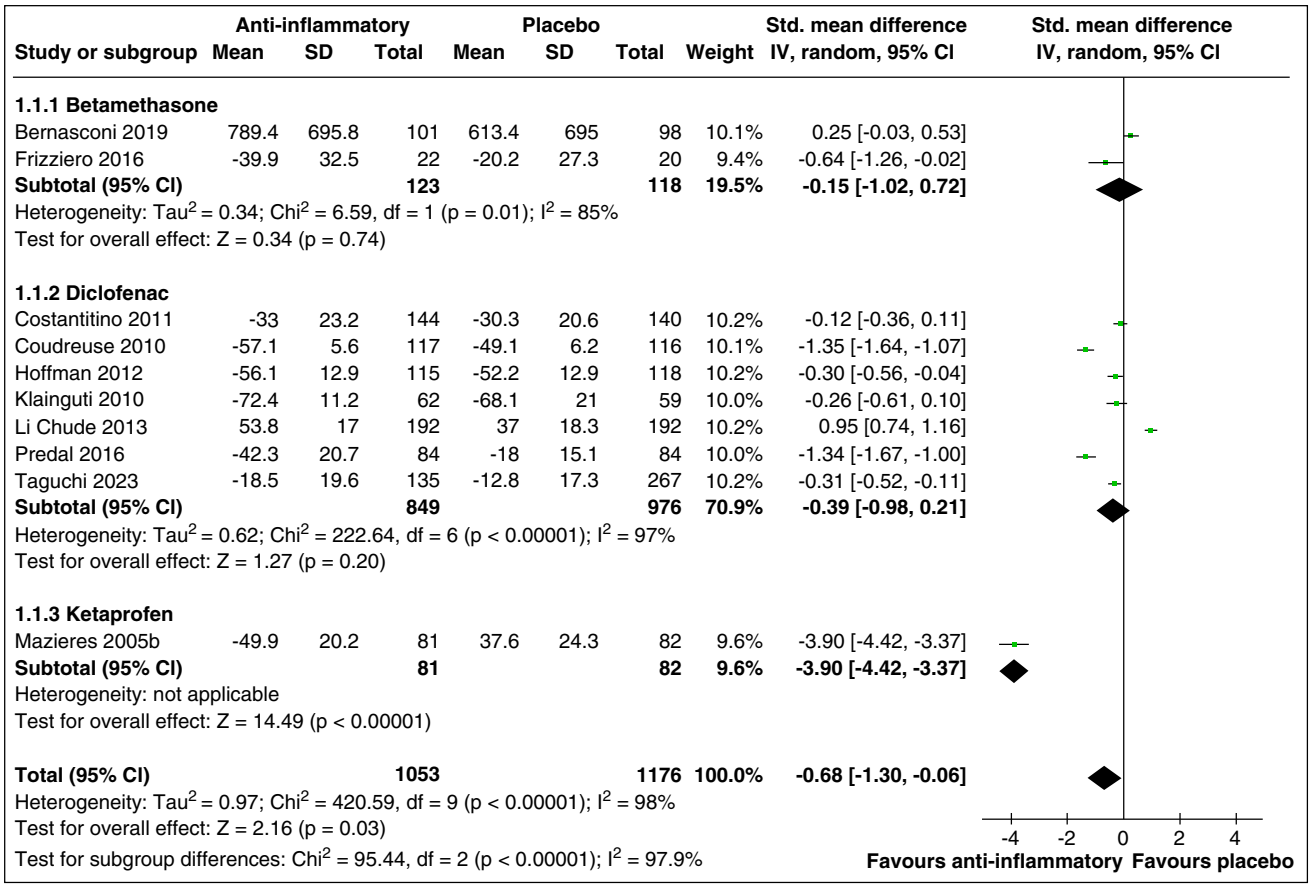

Figure 5. Forest-plot to illustrate the change of pain by the active drug (short term).

people randomized to the ibuprofen patch had greater investigator global assessment for intervention efficacy compared with the placebo (SMD: 0.05; 95% CI: 0.00 to 0.30; $p < 0.01$; N = 132).

3.5.3.4. Ketoprofen: 100 mg. Supplementary Table S6 describes the results of the meta-analysis when ketoprofen 100 mg patch was used compared with placebo patch in the short-term. People randomized to the ketoprofen 100 mg patch demonstrated significant benefit in the short-term when assessed by change of pain (SMD: -3.90; 95% CI: -4.42 to -3.37; $p < 0.01$; N = 163). There was moderate-certainty evidence that ketoprofen 100 mg patch offered significant benefit over placebo patch in the short-term when assessed by pain on movement (SMD: -0.50; 95% CI: -0.72 to -0.28; $p < 0.01$; N = 335), pain at rest (SMD: -0.45; 95% CI: -0.67 to -0.24; $p < 0.01$; N = 335) and amount of rescue medication (SMD: -0.30; 95% CI: -0.52 to -0.09; $p < 0.01$; N = 335). While there was no significant difference between the groups when assessed by investigator global assessment of tolerability, there was low-certainty evidence for greater patient assessed efficacy (SMD: 0.54; 95% CI: 0.33 to 0.88; $p = 0.01$; N = 335) and investigator efficacy (SMD: 0.42; 95% CI: 0.25 to 0.70; $p < 0.01$; N = 335) compared with placebo.

3.5.3.5. Nitric oxide: 1.25 mg. Supplementary Table S7 describes the results of the meta-analysis when a nitric oxide (1.25 mg) patch was used compared with placebo patch in the short-term. There was low-certainty evidence of a benefit for nitric oxide over a placebo patch when assessed by pain on movement in the short-term (SMD: -1.75; 95% CI: -2.29 to -1.21; $p < 0.01$; N = 74), medium-term (SMD: -2.18; 95% CI: -2.80 to -1.56; $p < 0.01$; N = 65). Similarly, those who received a nitric oxide patch demonstrated greater patient evaluated function and pain scores compared with the placebo group in the short (SMD: 1.87; 95% CI: 1.32 to 2.42; $p < 0.01$; N = 74) and long-term (SMD: 1.59; 95% CI: 1.06 to 2.12; $p < 0.01$; N = 74). There was low-certainty evidence that patient assessed efficacy was greater in those randomized to the nitric oxide patch compared with placebo in the long-term (SMD: 0.31; 95% CI: 0.16 to 0.61; $p < 0.01$; N = 196).

3.5.3.6. Not analyzed in meta-analysis. Four other medications were not pooled in a meta-analysis due to insufficient data reported. The results of patches of diclofenac

(60 and 75 mg) [36,37], glyceryl trinitrate [41] and methyl salicylate [24] are presented in Supplementary Table S8. All four interventions demonstrated improved pain scores ($p \leq 0.03$) and lower adverse events for those randomized to the diclofenac (60 mg) and glyceryl trinitrate groups compared with placebo groups ($p \leq 0.03$). While there was no benefit of the active intervention when assessed using diclofenac 60 mg for patient evaluation of function and pain ($p = 0.30$) or patient assessed efficacy ($p = 0.24$), those randomized to diclofenac 60 mg demonstrated a significant benefit in patient assessment of tolerability compared with the placebo group (SMD: 3.38; 95% CI: 1.09 to 10.45; $p = 0.03$; N = 153).

3.5.4. Subgroup analysis: by musculoskeletal condition

There were insufficient data to perform subgroup analyses by musculoskeletal condition.

3.5.5. Safety monitoring of adverse events

All trials reported the number of adverse events from the active treatment and the placebo groups. One trial [43] recorded the total number of adverse events in their trial without reporting the active and placebo groups separately. The number of adverse events reported which were, in the trial investigators' opinions related to the patch treatment, was 371 in the active groups and 358 in the placebo groups. No trial reported significant differences between active and placebo patches. The total number of adverse events including the numbers from Hoffmann et al. [43]. was 781 out of a total of 4729 participants (16.5%). Local skin irritation, skin atrophy, edema and pruritis, were the most frequent events. More serious events such as gastrointestinal irritation, tachycardia, headache and palpitations were rare. The trial with the smallest number of adverse events was Klainguti et al. [27]. with three events reported; only one event in the placebo group (n = 59) was treatment related and no events in the active group (n = 126) were related to the intervention.

4. Discussion

To our knowledge this is the first systematic review with meta-analysis to assess if transdermal patches which deliver an anti-inflammatory drug are efficacious in relieving pain in acute and chronic musculoskeletal conditions. It is based on 23 double blinded, randomized, placebo-controlled trials. In the long-term, there was low-certainty evidence based on two pooled trials, that a nitric oxide patch had a clinically significant effect on movement pain (-2.69; 95% CI -4.14 to -1.24; $p < 0.01$). Performing meta-analysis on different medications was difficult due to the variety of transdermal patches used and the variety of musculoskeletal conditions treated. Consequently, we were only able to meta-analyse the effect of seven trials using diclofenac and two with betamethasone on pain on several acute soft-tissue injuries (Figure 5). The results indicate there was low-certainty evidence that in the short-term (up to six weeks post treatment) a variety of transdermal patches on several musculoskeletal conditions improved the pain on movement outcome compared with placebo. However, the overall effect size of -1.12 (95% CI -1.68 to -0.56, $p < 0.01$) is below the clinically important difference for musculoskeletal pain [16]. Our analyses indicated low-quality evidence of no efficacy of the active patch over placebo in the medium-term (Figure 4).

The mixed pattern of results between the short, medium and long-term may have been due partly to poor treatment adherence. This key fidelity measure in clinical trial designs was not recorded in 15 of the 23 trials and was insufficiently reported in six out of the seven remaining trials. Only one study (a high-certainty evidence trial [32]) calculated a treatment compliance percentage of 100% in all three groups; others used patients' diaries. Despite reporting that their trial had perfect adherence, Costantino et al. [32]. found no significant treatment effect favoring an active patch over placebo, indicating that any differences between outcomes were not due to an imbalance of patch usage. The considerable variation in follow-up time may also have affected adherence. Some trials had follow-up at 24 weeks [19–21], while one followed up at only 5 days (120 h) [30]. Adherence to new medication is known to reduce over time [44] and can result in up to 50% of medicines not being taken as prescribed [45], so those trials with longer follow ups may have been susceptible to worsening adherence. Interestingly, Predel et al.'s [30] trial using an ibuprofen patch on soft tissue contusions had the shortest follow-up (5 days), but assessed pain on movement after only 72 h, and had the largest treatment effect of any trial. But as no treatment adherence data were reported, it was not possible to ascertain the impact on treatment effect of this on the trial's outcomes. The small number of trials which could be pooled in the medium- and long-term, compared with the 14 pooled trials in the short-term indicate the need for further research to assess if the use of transdermal patches is as susceptible to lack of adherence as other forms of drug delivery.

One consideration for a clinician considering transdermal patches to treat those with musculoskeletal pain is the reduction of adverse events associated with oral anti-inflammatory medication. Those typically associated with oral medications are gastrointestinal (perforation, ulcers,

bleeding), cardiovascular (myocardial infarction, heart failure, hypertension) and renal adverse events [46]. Every study in our review recorded adverse events for active and placebo arms which probably resulted from patch use. In the 23 trials, the total number of adverse events was 371 in the active group and 358 in the placebo group (14.2 and 12.1%, respectively). In comparison, a Cochrane review of topical NSAIDs for chronic musculoskeletal pain [47], found the proportion of local adverse events from using diclofenac gel was 14%, compared with 7.8% for the placebo gel. For topical ketoprofen the proportion was 15% for active gel versus 13% placebo [47].

The strengths of this review included its reporting in accordance with the PRISMA [15] reporting checklist and systematic approach to obtaining all potentially relevant studies robustly analyzed against GRADE [18]. All trials controlled for the placebo effect and in all studies were double blinded which reduced the risk of bias. This systematic review has three key limitations. First, it was not possible to perform meta-analysis to compare anti-inflammatory transdermal patches by musculoskeletal condition due to the variety of conditions, and the mixture of active ingredient in the patch used. As the evidence-base develops, it is anticipated that this limitation will resolve. Second, the results are only generalizable to individuals with moderate pain levels, and in good health. Further research is recommended to understand whether this modality may be beneficial for people with higher musculoskeletal pain levels. Finally, we included trials which assessed medications contained within transdermal patches which were not just anti-inflammatory medications. The transdermal delivery of nitric oxide was used based on the hypothesis that nitric oxide stimulates collagen synthesis by wound fibroblasts and is important for local blood flow. This hypothesis is a proposed mechanism for nitric oxide modulation of healing in tendons, which rely on fibroblastic production of collagen for repair [48].

5. Conclusion

This systematic review found low-certainty evidence that transdermal anti-inflammatory patches provided greater pain relief on movement at long-term follow-up for chronic musculoskeletal pain which was clinically significant compared with placebo. There was low-certainty evidence of an overall non-clinically significant improvement in pain at short-term follow-up on a variety of acute and chronic conditions. There is also low-certainty evidence of no effect in the medium-term and insufficient evidence of the superiority of one type of patch over another. Based on these results, transdermal anti-inflammatory patches using various medications may be used in the long-term management for those with pain caused from a musculoskeletal condition. The findings should be re-examined as the evidence-base develops in both quality and quantity.

Article highlights

- This systematic review is the first to compare patches with placebo in musculoskeletal conditions.
- This systematic review assessed if transdermal patches delivering anti-inflammatory drugs are efficacious in relieving pain in acute and chronic musculoskeletal conditions.
- The results indicate low-certainty evidence that a variety of transdermal patches on several musculoskeletal conditions improved the pain on movement outcome at long term follow-up compared with placebo.
- There is low-certainty evidence of no benefit of pain on movement reduction in the medium-term of anti-inflammatory patches compared with placebo.
- A clinician may opt for anti-inflammatory transdermal patches to treat those with chronic musculoskeletal pain due to the reduction of adverse events associated with anti-inflammatory oral medication.
- This systematic review included a variety of transdermal patches used and of musculoskeletal conditions treated.

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Author contributions

MJ Callaghan and J Selfe conceived the work, with the additional contribution of K Crossley. MB Sánchez retrieved the studies. MB Sánchez and MJ Callaghan screened all the studies against the inclusion and exclusion criteria; and performed the quality assessment. MB Sánchez extracted the data. T Smith performed the data analysis; MJ Callaghan, T Smith and M Twigg performed the data interpretation. MJ Callaghan, MB Sánchez, T Smith and M Twigg contributed to the drafting of the article. J Selfe critically revised the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

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Competing interests disclosure

The authors have no conflict of interest to declare.

Data availability statement

Data are available from the corresponding author on reasonable request.

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