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Salicylate-containing rubefacients for acute and chronic musculoskeletal pain in adults (Review)

Derry S, Matthews PRL, Wiffen PJ, Moore RA

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[Intervention Review]

Salicylate-containing rubefacients for acute and chronic musculoskeletal pain in adults

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ABSTRACT

Background

Rubefacients containing salicylates cause irritation of the skin and are believed to relieve various musculoskeletal pains. They are available on prescription, and are common components in over-the-counter remedies. This is an update of a review of rubefacients for acute and chronic pain, originally published in 2009, which found limited evidence for efficacy.

Objectives

To assess the efficacy and safety of topically applied salicylates in acute and chronic musculoskeletal pain in adults.

Search methods

We searched CENTRAL, MEDLINE, and EMBASE, from inception to 22 August 2014, together with the Oxford Pain Relief Database, two clinical trial registries, and the reference lists of included studies and relevant reviews.

Selection criteria

Randomised, double-blind, placebo- or active-controlled clinical trials of topical rubefacients containing salicylates to treat musculoskeletal pain in adults, with at least 10 participants per treatment arm, and reporting outcomes at close to 7 (minimum 3, maximum 10) days for acute conditions and 14 (minimum 7) days or longer for chronic conditions.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, and extracted data. We calculated risk ratio (RR) and number needed to treat to benefit or harm (NNT or NNH) with 95% confidence intervals (CI) using a fixed-effect model. We analysed acute and chronic conditions separately.

Main results

New searches for this update identified one new study that satisfied our inclusion criteria, although it contributed information only for withdrawals. Six placebo- and one active-controlled studies (560 and 137 participants, respectively) in acute pain, and seven placebo- and three active-controlled studies (489 and 182 participants, respectively) in chronic pain were included in the review. All studies were potentially at risk of bias, and there were substantial differences between studies in terms of the participants (for example the level of baseline pain), the treatments (different salicylates combined with various other potentially active ingredients), and the methods (for example the outcomes reported). Not all of the studies contributed usable information for all of the outcomes sought.

For the primary outcome of clinical success at seven days in acute conditions (mostly sprains, strains, and acute low back pain), the RR was 1.9 (95% CI 1.5 to 2.5) and the NNT was 3.2 (2.4 to 4.9) for salicylates compared with placebo, but this result was not robust (very low quality

evidence). Using a random-effects model for analysis the RR was 2.7 (1.05 to 7.0). For the same outcome in chronic conditions (mostly osteoarthritis, bursitis, and chronic back pain), the RR was 1.6 (1.2 to 2.0) and the NNT was 6.2 (4.0 to 13) (very low quality evidence). This result was not substantially changed using a random-effects model for analysis. In both categories there were a number of factors might have influenced the results but sensitivity analysis was limited because of the small number of studies and participants.

For both acute and chronic painful conditions any evidence of efficacy came from the older, smaller studies, while the larger, more recent studies showed no effect.

Adverse events were more common with salicylate than with placebo but most of the events occurred in only two studies. There was no difference when these studies were removed from the analysis (very low quality evidence). Local adverse events (at the application site) were again more common with salicylate but were nearly all in one study (in which salicylate was combined with another irritant). There was no difference when this study was removed (very low quality evidence).

There were insufficient data to draw conclusions against active controls.

Authors' conclusions

The evidence does not support the use of topical rubefacients containing salicylates for acute injuries or chronic conditions. They seem to be relatively well tolerated in the short-term, based on limited data. The amount and quality of the available data mean that uncertainty remains about the effects of salicylate-containing rubefacients.

PLAIN LANGUAGE SUMMARY

Topical rubefacients for acute and chronic musculoskeletal pain in adults

This is an update of a review of rubefacients for acute and chronic pain, originally published in 2009, that includes one new study.

A topical medication is a one that is applied to body surfaces such as the skin to treat ailments. Topical products might be creams, foams, gels, lotions, and ointments. Topical products can include a large range of medicines.

Rubefacients are drugs that cause irritation and reddening of the skin due to increased blood flow. They are believed to relieve pain in various musculoskeletal conditions and are available on prescription and in over-the-counter remedies. Salicylate is a commonly used rubefacient.

This review looked for evidence about the usefulness of topical rubefacients containing salicylate from randomised and double-blind studies. These studies were in people with acute painful conditions like strains and sprains, or chronic painful conditions like osteoarthritis. We wanted to know whether topical salicylate-containing rubefacients helped with the pain.

Evidence for topical salicylate–containing rubefacients is limited by the quality, validity, and size of the available studies. For both acute and chronic painful conditions any evidence of efficacy came from the older, smaller studies, while the larger, more recent studies showed no effect. There is no good evidence that topical salicylate-containing rubefacients give useful pain relief.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Salicylate-containing topical rubefacients compared with topical placebo for acute and chronic painful conditions

Patient or population: adults with strains or sprains (acute) or osteoarthritis or low back pain (chronic)

Settings: community

Intervention: salicylate-containing topical rubefacient

Comparison: topical placebo

Outcomes	Probable outcome with intervention	Probable outcome with comparator	RR NNT, NNTp, or NNH (95% CI)	No of studies, participants	Quality of the evidence (GRADE)	Comments
Clinical success (eg 50% reduction in pain) **Acute conditions**	**640 in 1000**	**335 in 1000**	**RR 1.9 (1.5 to 2.5)** **NNT 3.2 (2.4 to 4.9)**	4 studies 324 participants	⊕⊖⊖⊖ **very low**	Most recent, largest study showed no effect Note NNT cannot be trusted because of low numbers and poor quality studies
Clinical success (eg 50% reduction in pain) **Chronic conditions**	**447 in 1000**	**284 in 1000**	**RR 1.6 (1.2 to 2.0)** **NNT 6.2 (4.0 to 13)**	6 studies 455 participants	⊕⊖⊖⊖ **very low**	Most recent, largest studies showed no effect Note NNT cannot be trusted because of low numbers and poor quality studies
Adverse events - any adverse events **Acute and chronic conditions combined**	**152 in 1000**	**94 in 1000**	**RR 1.6 (1.2 to 2.0)** **NNH 17 (9.9 to 58)**	11 studies 984 participants	⊕⊕⊖⊖ **low**	Inadequate reporting of adverse events is common Acute and chronic conditions combined
Adverse events - local adverse events **Acute and chronic conditions combined**	**56 in 1000**	**24 in 1000**	**RR 2.2 (1.1 to 4.1)** **NNH 31 (16 to 300)**	10 studies 869 participants	⊕⊖⊖⊖ **very low**	Small numbers of events Acute and chronic conditions combined

Withdrawals - lack of efficacy **Acute and chronic conditions combined**	**24 in 1000**	**72 in 1000**	**RR 0.4 (0.2 to 0.9**) **NNTp 21 (12 to 120)**	5 studies 501 participants	⊕⊖⊖⊖ **very low**	Small numbers of events Acute and chronic conditions combined
Withdrawals - adverse events **Acute and chronic conditions combined**	**49 in 1000**	**11 in 1000**	**RR 4.2 (1.5 to 12)** **NNH 26 (15 to 85)**	7 studies 737 participants	⊕⊖⊖⊖ **very low**	Small numbers of events Acute and chronic conditions combined

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

CI: confidence interval; RR: risk ratio; NNT: number needed to treat; NNTp: number needed to prevent an event happening; NNH: number needed to harm

BACKGROUND

This review is an update of a previously published review on topical rubefacients for acute and chronic pain in adults (Matthews 2009). We made the decision to change the title from "rubefacients" to "salicylate-containing rubefacients" because all the included studies used salicylates, either alone or in combination with other compounds. We have also specified musculoskeletal pain because topical salicylates are not normally used to treat visceral pain, neuropathic pain, or cancer pain. We felt that the new title better reflected the content of the review.

Rubefacients have been used for many years to treat musculoskeletal pains, but earlier reviews have found little evidence to support their use (Mason 2004; Matthews 2009). There has been confusion about which compounds should be classified as rubefacients. Some, such as salicylates, are related pharmacologically to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), but as topical products their primary action is as skin irritants. Capsaicin applied topically can produce a burning sensation at the application site and has been grouped with rubefacients, although the mechanism of pain relief is different. This review included salicylates, but not capsaicin as this is covered in other reviews (Derry 2012a; Derry 2013).

This review is one of a series on topical analgesics, including topical capsaicin at low and high doses (Derry 2012a; Derry 2013), and topical NSAIDs in acute (Massey 2010), and chronic (Derry 2012b), pain conditions.

Description of the condition

This review looked at the use of salicylate-containing rubefacients to relieve musculoskeletal pain (pain in muscles, joints, and tendons). We considered acute conditions such as sprains, strains, and bruises (typical of sports injuries) separately from chronic conditions such as osteoarthritis. Acute pain typically lasts for hours, days, or a few weeks, while an injury is healing. Chronic pain lasts beyond the normal time of healing, in situations where healing does not occur (rheumatoid arthritis, for example), or where changes occur in the nervous system that maintain pain. Non-malignant chronic pain is typically considered to be pain that has been present for at least three, or six, months (Merskey 2002; Turk 2001).

Description of the intervention

The earlier review considered all rubefacients, but searches identified only formulations containing salicylates (Matthews 2009). We have changed the review title to better reflect the content.

Salicylates are derivatives of salicylic acid, and those used in topical preparations are often amine derivatives. They are most often formulated as creams or gels, but sometimes as sprays, which are applied directly onto the affected area two to four times daily. In 2013 there were almost 1.4 million prescriptions for topical salicylates in primary care in England (PCA 2014). Many products that are on sale directly to the public contain salicylates. The quality and cost of these are unknown, but the latter is likely to be substantial.

While topical salicylates are considered relatively safe, particularly in relation to oral NSAIDs, overuse or ingestion can lead to salicylate toxicity, and even death (Davis 2007; O'Malley 2008).

How the intervention might work

Salicylate-containing rubefacients cause irritation of the skin, and are believed to relieve pain in muscles, joints, and tendons, and other musculoskeletal pains in the extremities, by counter-irritation (BNF 2008). The term 'counter-irritant' derives from the fact that they cause a reddening of the skin by dilating the blood vessels of the skin, which gives a soothing feeling of warmth. Irritation of the sensory nerve endings is thought to alter or offset pain in the underlying muscle or joints that are served by the same nerves (Morton 2002).

Salicylates are related pharmacologically to aspirin and NSAIDs, but when used in topical products (often as amine derivatives) their principal action is as skin irritants. By contrast, topical NSAIDs penetrate the skin and underlying tissues where they inhibit cyclo-oxygenase enzymes responsible for prostaglandin biosynthesis and the development of inflammation.

Why it is important to do this review

The original Cochrane review was published five years ago, and its conclusions were limited by the small number of studies (Matthews 2009). New studies may have been published subsequently. In addition, the standards by which we assess and interpret evidence are now more rigorous (Moore 2010).

Topical salicylates are widely available and are often perceived to be effective and safe. It is important to establish whether new data are available, or whether this will remain an intervention for which there is little evidence.

OBJECTIVES

To assess the efficacy and safety of topically applied salicylates in acute and chronic musculoskeletal pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double-blind studies comparing salicylate-containing rubefacients with placebo or other active treatment for acute (strains, sprains, and bruises) or chronic (arthritis) musculoskeletal pain, with at least 10 participants per treatment arm. Study duration had to be a minimum of three days for acute conditions and seven days for chronic conditions. We excluded studies published only as short abstracts (usually meeting abstracts) because they do not provide sufficient information to adequately assess the study, and those studying experimentally induced pain because it does not correlate well with clinical pain.

Types of participants

Adult participants (16 years or more) with acute or chronic musculoskeletal pain of at least moderate intensity resulting from any cause.

Types of interventions

Included studies had at least one treatment arm using a topical salicylate preparation, and a comparator arm using placebo or other active treatment, with treatment applied at least once daily.

Types of outcome measures

We sought information on participant characteristics (age, sex, and condition treated) and outcomes at close to 7 days (minimum 3 days, maximum 10 days) for acute conditions, and 14 days (minimum 7 days) for chronic conditions.

Primary outcomes

The primary outcome was 'clinical success', defined as a 50% reduction in pain, measured on a visual analogue scale (VAS) or numerical rating scale (NRS), or an equivalent measure such as a "very good" or "excellent" global assessment of treatment, or "none" or "slight" pain on rest or movement, measured on a categorical scale (or similar wording) (Moore 1998). We used the following hierarchy of outcomes, in order of preference, to extract data for the primary outcome.

- Participant-reported reduction in pain of at least 50%.
- Participant-reported global assessment of treatment.
- Pain on movement.
- Pain on rest, or spontaneous pain.
- Undefined "improvement".

Only participant-reported outcomes were used. Physician- or investigator-reported outcomes of efficacy were not used.

Secondary outcomes

- Numbers of participants with adverse events: local and systemic.
- Numbers of withdrawals: all cause, lack of efficacy, adverse events.

Outcomes were reported after different durations of treatment, so care was taken to extract data reported as close to specified times as possible, and not less than the minimum. We additionally extracted longer-duration outcomes where available. We took care to determine whether adverse events were comprehensively reported, and the methods of ascertainment.

Search methods for identification of studies

Electronic searches

We searched the following databases.

- Cochrane Central Register of Controlled Trials via CRSO (to 22 August 2014).
- MEDLINE via Ovid (from 1948 to December 2008 for the earlier review, and from 2008 to 22 August 2014 for this update).
- EMBASE via Ovid (from 1976 to December 2008 for the earlier review, and from 2008 to 22 August 2014 for this update).
- Oxford Pain Relief Database for the original review (Jadad 1996a).

See Appendix 1 for the CENTRAL search strategy, Appendix 2 for the MEDLINE search strategy, and Appendix 3 for the EMBASE search strategy used for this update of the review.

We did not apply any language restrictions.

Searching other resources

We reviewed the bibliographies of all randomised trials identified and of review articles, and searched clinical trial databases (ClinicalTrials.gov (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/)) to identify additional published or unpublished data.

Manufacturers have previously been asked for details of unpublished studies (Mason 2004), and new manufacturers or UK distributors were sought to ask them about unpublished studies in the earlier review (Matthews 2009). No further attempt was made to contact manufacturers for this update.

Data collection and analysis

Two review authors independently searched for and selected the studies for inclusion, assessed methodological quality, and extracted data. Disagreements were resolved through discussion with a third author.

Selection of studies

We reviewed on screen the titles and abstracts of studies identified by the searches to eliminate those that clearly did not satisfy inclusion criteria and obtained full reports of the remaining studies to determine inclusion in the review. We considered cross-over studies only if data from the first treatment period were reported separately. We did not include studies in oral, ocular, or buccal diseases.

Data extraction and management

We extracted information on participants, interventions, and outcomes from the original reports using a standard data extraction form. We did not contact study authors for further information.

Assessment of risk of bias in included studies

We used the Oxford Quality Score as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum (Jadad 1996b).

Two authors independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, for example, random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (for example, odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or

changed after assignment. We assessed the methods as: low risk of bias (for example, telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (for example, open list).

3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, for example, identical tablets; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how blinding was achieved). We excluded studies that were not double-blind.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study or used 'baseline observation carried forward' (BOCF) analysis, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); high risk of bias (used 'completer' analysis).
5. Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

Measures of treatment effect

We used risk ratio (or 'relative risk', RR) to establish statistical difference. We used numbers needed to treat (NNT) and pooled percentages as absolute measures of benefit or harm.

We used the following terms to describe adverse outcomes in terms of harm or prevention of harm:

- when significantly fewer adverse outcomes occurred with salicylate than with control (placebo or active) we used the term the number needed to treat to prevent one event (NNTp);
- when significantly more adverse outcomes occurred with salicylate compared with control (placebo or active) we used the term the number needed to harm or cause one event (NNH).

Unit of analysis issues

We accepted randomisation by individual patient only.

Dealing with missing data

The most likely source of missing data was expected to be from participants dropping out from the studies. We looked specifically for evidence of LOCF and used a dichotomous responder analysis, where a responder was defined as a participant who experienced the predefined outcome and remained in the study (for example, did not withdraw due to adverse events). LOCF is a potential source of major bias in chronic pain studies (Moore 2012a).

For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat (ITT) basis, including all participants who were randomised and received an intervention. Where sufficient information was reported, we added back missing data in the analyses we undertook.

Assessment of heterogeneity

We assessed heterogeneity of studies visually (L'Abbé 1987). Where data could be pooled, we reported the I^2 statistic.

Data synthesis

We undertook meta-analysis using a fixed-effect model. A random-effects model was also used for meta-analysis if there was significant clinical heterogeneity and it was considered appropriate to combine studies.

We calculated RR estimates with 95% confidence intervals (CI) (Morris 1995). Where appropriate we calculated NNT and NNH, with 95% CIs, using the pooled number of events (Cook 1995). We assumed a statistically significant difference from control when the 95% CI of the RR did not include the number one.

Subgroup analysis and investigation of heterogeneity

We analysed data for acute and chronic conditions separately. The evidence base was known to be small, making analysis of different salicylates impossible, so for each category we combined data for all rubefacients versus placebo for analysis of the primary outcome of clinical success. For secondary outcomes relating to adverse events and withdrawals, data for all rubefacients versus placebo, in acute and chronic conditions, were combined.

Studies comparing rubefacients with an active comparator were also examined.

At least 200 patients were required in any of these different contexts before information was pooled (Moore 1998b).

Sensitivity analysis

We planned sensitivity analyses of the primary outcome only, for:

- baseline pain intensity (including mild pain versus moderate to severe pain);
- outcome (undefined "improvement" versus defined outcomes);
- time of assessment of primary outcome (6 days or less versus 7 days or more for acute conditions, and 13 days or less versus 14 days or more for chronic conditions).

RESULTS

Description of studies

Results of the search

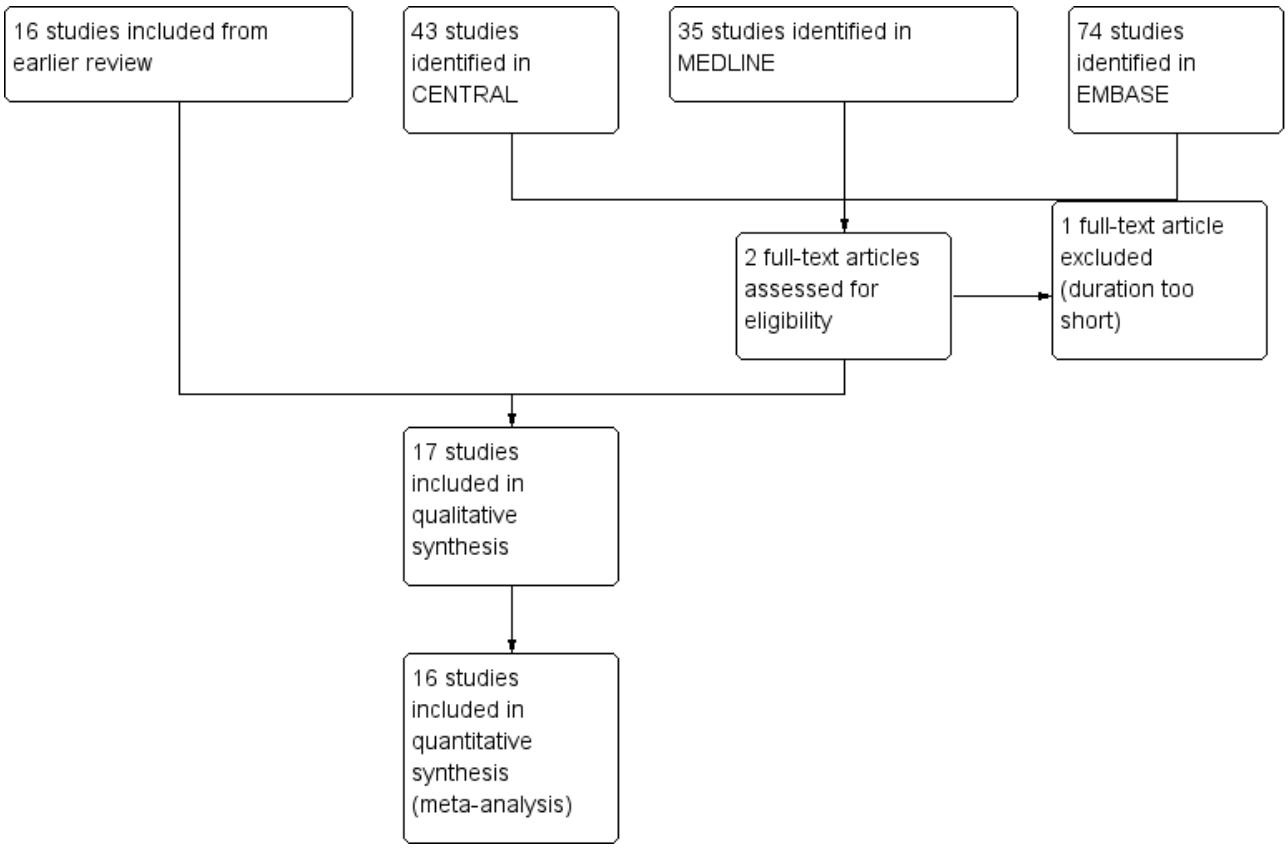
Searches for this update identified 43 potential studies in CENTRAL, 35 in MEDLINE, and 74 in EMBASE. Two studies were read in full, one of which satisfied the inclusion criteria (92 participants) (Zahmatkash 2011). The other did not because its duration was too short (Higashi 2010). No additional studies were identified through the reference lists of included studies or searching clinical trial registries.

Searches for the earlier review identified 28 potentially relevant studies. Twelve were excluded after reading the full publication (Crielaard 1986; Dettoni 1982; He 2006; Heindl 1977; Howell 1955; Jolley 1972; Kantor 1990; Kleinschmidt 1975; Pasila 1980; Shamszad 1986; von Batky 1971; Weisinger 1970) and 16 were included (Algozzine 1982; Camus 1975; Diebschlag 1987; Frahm 1993; Geller 1980; Ginsberg 1987; Golden 1978; Ibanez 1988; Lester

1981; Lobo 2004; Rothhaar 1982; Rutner 1995; Shackel 1997; Stam 2001; von Bach 1979; Wanet 1979).

See Figure 1.

Figure 1. Study flow diagram.



Included studies

Six placebo-controlled studies of acute injuries were included (Diebschlag 1987; Frahm 1993; Ginsberg 1987; Lester 1981; Rothhaar 1982; Stam 2001), with 560 participants in total, of whom 236 were in two studies that did not have usable information for efficacy and provided data for withdrawals and adverse events only (Diebschlag 1987; Frahm 1993). One acute study with an active comparator was included, involving 137 participants (Ibanez 1988).

Seven placebo-controlled studies in chronic pain conditions were included, involving 489 participants (including 26 receiving both treatment and placebo in a cross-over trial) (Algozzine 1982; Camus 1975; Lobo 2004; Rutner 1995; Shackel 1997; von Bach 1979; Wanet 1979). Three studies with active comparators in chronic pain conditions, involving 182 participants, were also included (Geller 1980; Golden 1978; Zahmatkash 2011). Two studies included a minority (20% to 30%) of participants with acute musculoskeletal conditions (Geller 1980; Wanet 1979); we analysed these as chronic studies, subject to a planned sensitivity analysis. Lobo 2004 (52 participants) provided data only for adverse events, and Zahmatkash 2011 (92 participants) provided usable data only for all cause withdrawals.

Acute conditions studied were sprains (Diebschlag 1987; Frahm 1993; Lester 1981), other sports injuries (Ibanez 1988; Rothhaar 1982), or acute lower back pain (Ginsberg 1987; Stam 2001). Chronic conditions included articular musculoskeletal pain (Algozzine 1982; Geller 1980; Golden 1978; Shackel 1997; von Bach 1979; Wanet 1979; Zahmatkash 2011), extra-articular pain (Camus 1975; Geller 1980; Golden 1978; von Bach 1979), back pain (Geller 1980; Rutner 1995; von Bach 1979; Wanet 1979), and temporomandibular disorders (Lobo 2004).

Our intention was to include only studies of participants with at least moderate pain intensity at baseline. Not all of the studies clearly stated baseline pain intensity and, where stated, the range of pain sometimes included mild pain. We included all levels of pain, with the intention to carry out a sensitivity analysis for this characteristic.

Participants were instructed to apply the study medication directly onto the skin over the painful site, except in one study (Shackel 1997), where the medication was applied distally to the skin of the inner forearm. This site was chosen because the skin is thin and should allow rapid absorption. The aim of this study was to assess the systemic effect of the gel on distant targets, which was fundamentally different from the other studies in the review.

All studies used salicylates as the rubefacient: trolamine salicylate (Algozzine 1982; Golden 1978), diethylamine salicylate (Camus 1975; Geller 1980; Rothhaar 1982; Wanet 1979), salicylic acid (Diebschlag 1987; Frahm 1993; Lester 1981), benzydamine salicylate (Ibanez 1988), methyl salicylate (Lobo 2004), glycol salicylate (Rutner 1995; Stam 2001), copper salicylate (Shackel

1997), ethylene glycol monosalicylate ester (von Bach 1979), a mixture of salicylates (Ginsberg 1987), or unspecified salicylate (Zahmatkash 2011). Formulations varied widely. A variety of additional components were added to the principal ingredient, such as the local anaesthetic myrtecaine (Camus 1975; Wanet 1979), capsicum oleoresin (Ginsberg 1987; Stam 2001), nonivamide (a capsaicinoid) (von Bach 1979), or adrenal extract (Diebschlag 1987; Lester 1981).

The active comparators used were oral aspirin (Golden 1978), the topical NSAIDs etofenamate (Geller 1980) and fepradinol (Ibanez 1988), and a herbal mixture containing cinnamon, ginger, mastic, and sesame oil (Zahmatkash 2011). In some studies participants received additional oral analgesics or physical therapy.

In two studies it was unclear whether the comparator was a placebo or active control, with one study in acute low back pain using a "homeopathic" control (containing appreciable concentrations of herbal ingredients with no known analgesic effects) (Stam 2001), and one study in chronic musculoskeletal conditions using a lower concentration of salicylate, without additional ingredients (von Bach 1979). We analysed these studies as placebo-controlled trials, but subject to sensitivity analysis.

Of the studies in acute conditions, two were of 7 days duration (Lester 1981; Stam 2001), three between 7 and 14 days (Frahm 1993; Ibanez 1988; Rothhaar 1982), and two of 14 days or more (Diebschlag 1987; Ginsberg 1987). Three studies in chronic conditions lasted for 7 days (Algozzine 1982; Geller 1980; Golden 1978), one for 10 days (Camus 1975), and six for 14 days or more (Lobo 2004; Rutner 1995; Shackel 1997; von Bach 1979; Wanet 1979; Zahmatkash 2011).

Two studies used a cross-over design (Algozzine 1982; Geller 1980), and the remainder used a parallel-group design. One of the cross-over studies did not report outcome data for the first treatment period only (Algozzine 1982).

The dose of rubefacient applied was poorly reported. Even if the application schedule was specified, most studies did not provide details of the volume applied, and some did not provide details of the concentration of the active ingredients. Although outcomes were usually defined, a variety of scales were used to assess efficacy. Adverse events and withdrawals were generally poorly reported with little detail provided.

Details of individual studies are provided in the Characteristics of included studies table.

Excluded studies

Thirteen studies were excluded after reading the full publications (Crielaard 1986; Dettoni 1982; He 2006; Heindl 1977; Higashi 2010; Howell 1955; Jolley 1972; Kantor 1990; Kleinschmidt 1975; Pasila 1980; Shamszad 1986; von Batky 1971; Weisinger 1970). Reasons for exclusion are provided in the Characteristics of excluded studies table.

Risk of bias in included studies

All studies were randomised and double-blind. Of those in acute conditions, two had a quality score of two (Ibanez 1988; Lester 1981), two of three (Frahm 1993; Ginsberg 1987), two of four (Rothhaar 1982; Stam 2001), and one of five (Diebschlag 1987). One study had a validity score of seven (Ibanez 1988), one of eight (Rothhaar 1982), one of nine (Ginsberg 1987), one of 10 (Frahm 1993), one of 11 (Lester 1981), and two of 12 (Diebschlag 1987; Frahm 1993).

In chronic conditions there were six studies with a quality score of three (Camus 1975; Geller 1980; Lobo 2004; Rutner 1995; Wanet 1979; Zahmatkash 2011), two of four (Algozzine 1982; Golden 1978), and two of five (Shackel 1997; von Bach 1979). Two studies had validity scores of seven (Geller 1980; Lobo 2004), two of nine (Golden 1978; Wanet 1979); three of 10 (Algozzine 1982; Camus 1975; von Bach 1979), one of 11 (Shackel 1997), and one of 12 (Rutner 1995).

Comments on potential biases in individual studies are reported in the Risk of bias section of the Characteristics of included studies table. The findings are displayed in Figure 2 and Figure 3 The greatest risk of bias came from small study size.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

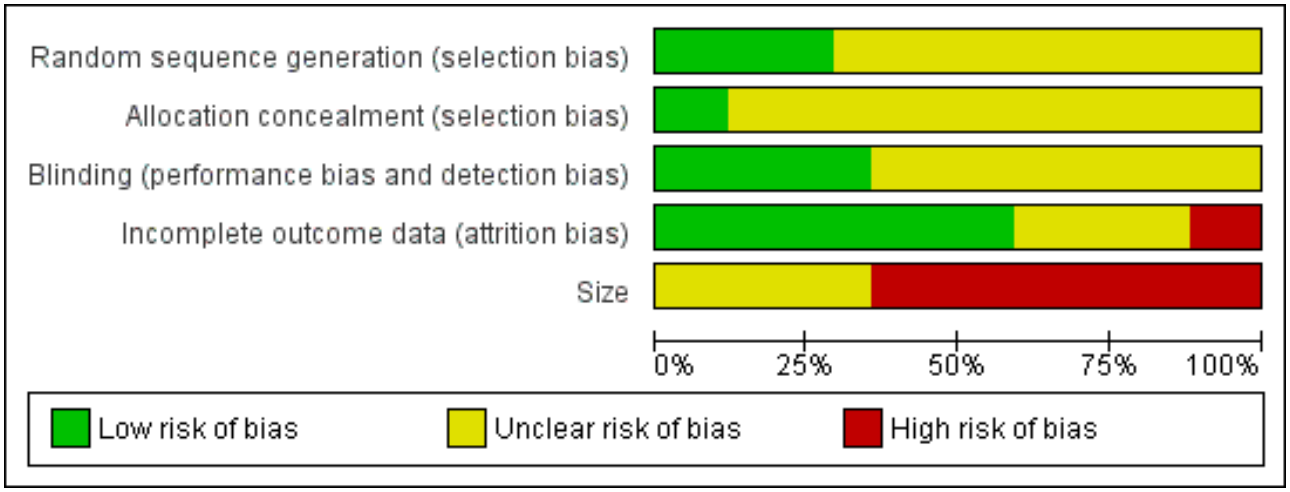
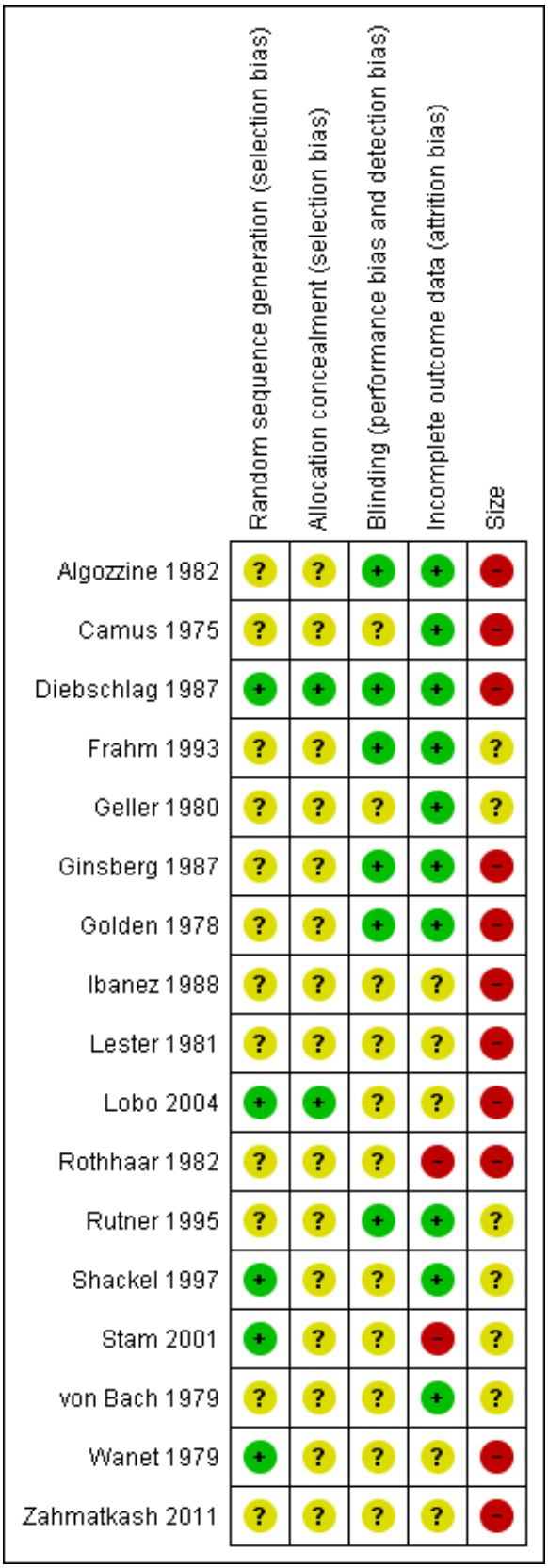


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies stated that they were randomised but only five reported the method used to generate the random sequence, and only two adequately described the method used to conceal the allocation sequence.

Blinding

All studies stated that they were double-blind, but only seven adequately described the method used to conceal the treatment identity from the participants and study personnel.

Incomplete outcome data

Ten studies appeared to account for all participants in a true responder analysis. We judged two studies to be at high risk of bias because of high (> 10%) levels of attrition, poor compliance, and lack of information about any imputation methods used (Rothhaar 1982; Stam 2001). We judged the remaining six studies to be at unclear risk of bias due to a lack of information about withdrawals and participants lost to follow-up (Ibanez 1988; Lester 1981; Lobo 2004; von Bach 1979; Wanet 1979; Zahmatkash 2011).

Other potential sources of bias

We judged 11 studies to be at high risk of bias because they randomised fewer than 50 participants to each treatment arm (Algozzine 1982; Camus 1975; Diebschlag 1987; Ginsberg 1987; Golden 1978; Ibanez 1988; Lester 1981; Lobo 2004; Rothhaar 1982; Wanet 1979; Zahmatkash 2011), and the remaining six to be at unclear risk because they included between 50 and 90 participants per treatment arm.

Effects of interventions

See: **Summary of findings for the main comparison**

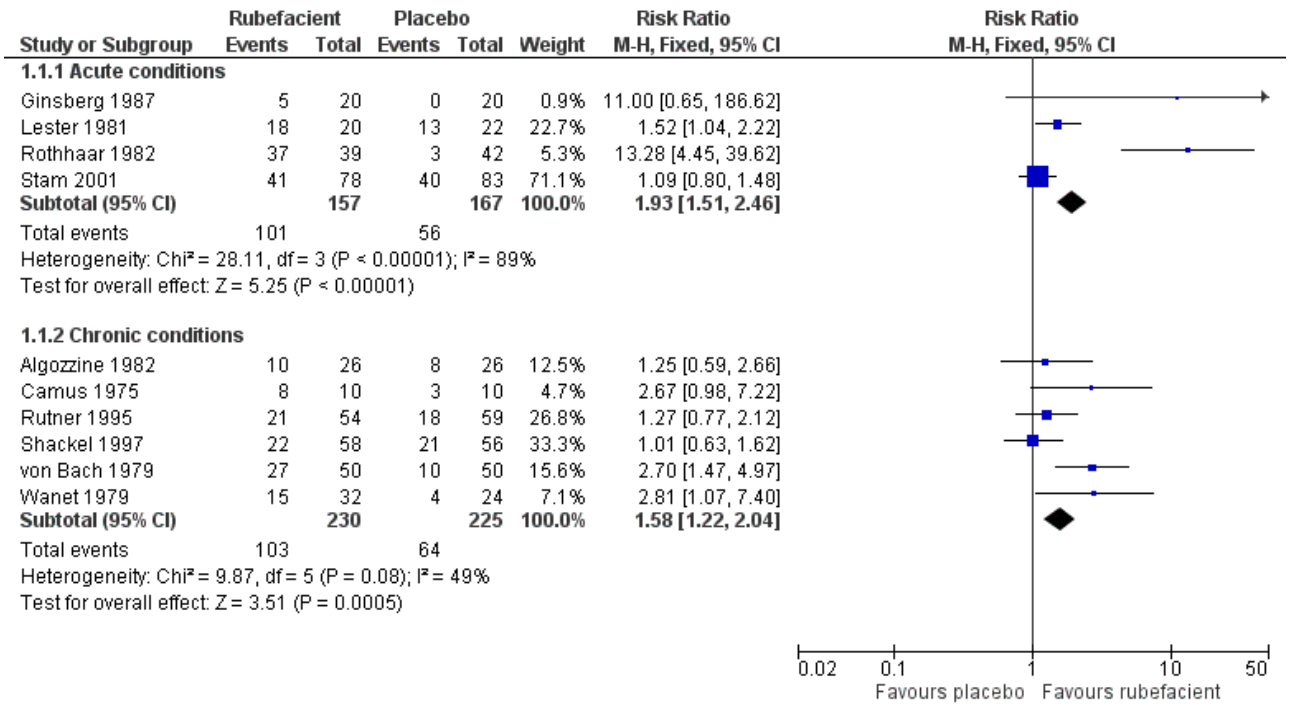
Summaries of the efficacy outcomes are provided in Appendix 4 and of adverse events and withdrawals in Appendix 5. Because there were a small number of studies with a wide variety of formulations and inadequate reporting of dosage, it was not possible to assess dose-response relationships. Due to insufficient data it was not possible to perform additional post hoc sensitivity analyses of particular salicylate formulations, most additional active ingredients, and different musculoskeletal conditions.

Number of participants achieving clinical success (at least 50% pain relief or equivalent)

Acute conditions

Four placebo-controlled studies with 324 participants provided data for efficacy analysis (Ginsberg 1987; Lester 1981; Rothhaar 1982; Stam 2001). The proportion of participants achieving 50% pain relief or equivalent at seven days was 64% (range 25% to 95%; 101/157) for the rubefacient group, and 34% (0% to 59%; 56/167) for the placebo group, giving a RR of 1.9 (95% CI 1.5 to 2.5) and a NNT of 3.2 (2.4 to 4.9) (Figure 4).

Figure 4. Forest plot of comparison: 1 Rubefacient versus placebo, outcome: 1.1 Clinical success (eg 50% reduction in pain).



Because studies were small, and with high variability between them (I^2 = 89%), we also checked this result using the random-effects model; the RR increased, remaining significant, with wide confidence intervals (RR 2.7 (1.05 to 7.0)). The largest and most recent study showed no difference between topical salicylate and a homeopathic gel, regarded as placebo (Stam 2001).

Only one active-controlled study was identified (Ibanez 1988). At 12 days, 23/35 participants were reported to be "cured" with salicylate

spray, and 85/102 with fepradinol spray. There were insufficient data for statistical analysis.

Sensitivity analyses

The studies differed from one another in a number of factors that might affect the estimate of efficacy. While we planned to carry out sensitivity analyses, for the most part there were too few studies and participants, and too many different factors, to make any such analyses feasible. Instead, we listed the most obvious factors that should be considered when interpreting the results of this analysis.

Baseline pain

Of the four studies contributing data to this outcome, only one clearly stated that the participants had at least moderate baseline pain (Stam 2001). Two stated that the participants had mild to severe pain (Lester 1981; Rothhaar 1982), and the other did not state the level of baseline pain (Ginsberg 1987). Low levels of baseline pain would make the study insensitive to changes in pain intensity associated with the study medication.

Time of assessment

One study had the efficacy outcome measured at < 7 days (Ginsberg 1987), although using additional data from this study measured at 14 days did not appreciably change the result.

Post hoc

The acute study of Stam 2001 used a control treatment containing herbal ingredients that could potentially have represented an active control and underestimated the effect of the rubefacient treatment in acute conditions.

None of the studies used salicylate alone. Lester 1981 included adrenal extracts and mucopolysaccharide; Rothhaar 1982 included escin, an extract of horse chestnut; and Ginsberg 1987 and Stam 2001 included low levels of capsicum oleoresin. The effects of the additional ingredients were unknown.

Chronic conditions

Six placebo-controlled studies with 455 participants provided data for efficacy analysis (Algozzine 1982; Camus 1975; Rutner 1995; Shackel 1997; von Bach 1979; Wanet 1979). The proportion of participants achieving 50% pain relief or equivalent at 14 days was 45% (range 38% to 80%; 103/230) for the rubefacient group, and 28% (17% to 38%; 64/225) for the placebo group, giving a RR of 1.6 (1.2 to 2.0) and a NNT of 6.2 (4.0 to 13) (Figure 4). The I^2 statistic for this analysis was 49%. Using a random-effects model did not change the result (RR 1.6 (1.1 to 2.4)). The two largest and most recent studies showed no difference from placebo (Rutner 1995; Shackel 1997).

Two active-controlled studies reported outcomes at seven days. The first found a benefit of rubefacient compared with the topical NSAID etofenamate (50 participants) (Geller 1980), although this topical NSAID has no evidence of efficacy (Massey 2010). The second found no benefit compared with oral aspirin (40 participants; (Analysis 2.1) (Golden 1978). A third active-controlled study reported outcomes at two, four, and six weeks (92 participants) (Zahmatkash 2011). The mean pain intensity fell in both treatment groups at two weeks, with further, smaller reductions up to six weeks, but there was no difference between the groups. Studies were too small for any of these results to be robust.

Sensitivity analyses

For the most part there were too few studies and participants and too many different factors to make formal sensitivity analyses feasible. We have listed the most obvious factors that should be considered when interpreting the results of this analysis, together with the results of any statistical analysis where it was felt appropriate.

Baseline pain

Of the six studies contributing data to this outcome, only one clearly stated that participants had at least moderate baseline pain (Algozzine 1982). Three studies included participants with mild pain (Camus 1975; Shackel 1997; Wanet 1979), and two did not state the level of baseline pain (Rutner 1995; von Bach 1979). Low levels of baseline pain would make the study insensitive to changes in pain intensity associated with the study medication.

Study outcome

Two studies used undefined improvement as the measure of clinical success (Algozzine 1982; Camus 1975). Outcomes that are easy to achieve can inflate response rates, but excluding these studies did not substantially change the estimated benefit in this data set.

Time of assessment

Two studies had efficacy outcomes measured at < 14 days (Algozzine 1982; Camus 1975), but excluding these did not substantially affect the estimated benefit in this data set.

Post hoc

One study used a cross-over design and did not report the results for the first treatment period separately (Algozzine 1982). There was no reported assessment for a carry-over effect.

One study contributing to this analysis included a substantial minority (30%) of participants with acute conditions (Wanet 1979). Acute and chronic conditions may respond differently.

One study (von Bach 1979) used a control treatment containing lower doses of salicylate, which could be considered an active control and lead to underestimation of the beneficial effect of rubefacients.

In Shackel 1997 the rubefacient was applied distant to the site of pain, which could lead to underestimation of any benefit.

Three of the studies contributing to this analysis included additional components, which may have contributed to any observed effect. Two included the local anaesthetic myrtecaine (Camus 1975; Wanet 1979), and one included nonivamide (related to capsaicin) (von Bach 1979). Omitting von Bach 1979 reduced the RR to a barely statistically significant finding (RR 1.4 (1.03 to 1.8)), and omitting all three studies made the result not significant (RR 1.2 (0.84 to 1.6)).

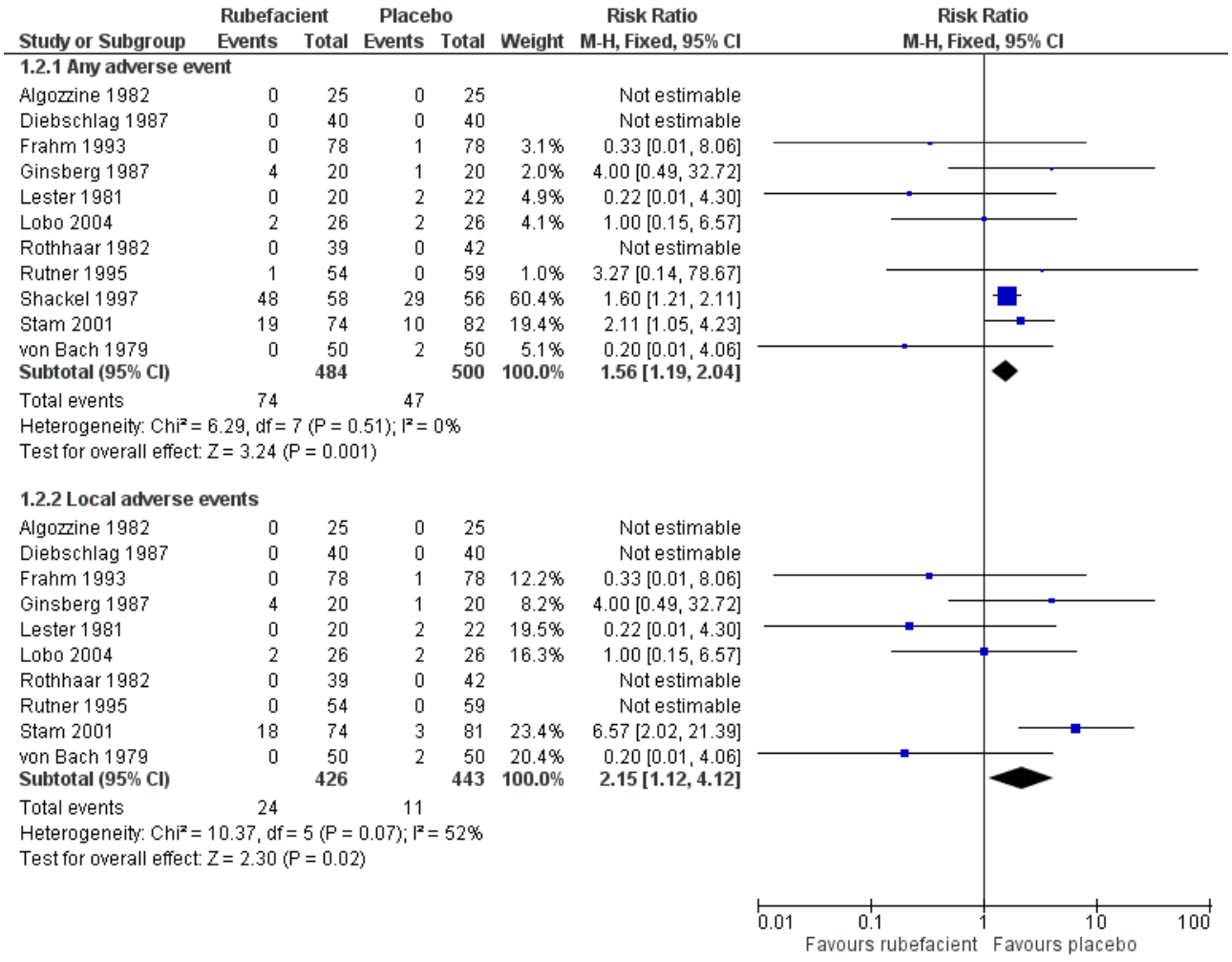
Adverse events

Three studies (Camus 1975; Wanet 1979; Zahmatkash 2011) did not provide any information about adverse events. In the remaining studies, data were collected over periods of 7 to 15 days, except in Shackel 1997 where data were collected over four weeks.

All adverse events

Eleven studies provided data on adverse events with salicylates compared to placebo, six in acute conditions (Diebschlag 1987; Frahm 1993; Ginsberg 1987; Lester 1981; Rothhaar 1982; Stam 2001), and five in chronic conditions (Algozzine 1982; Lobo 2004; Rutner 1995; Shackel 1997; von Bach 1979). Three had no events in either study arm (Algozzine 1982; Diebschlag 1987; Rothhaar 1982). In all studies combined, adverse events were relatively uncommon, with 15% (74/484, range 0% to 83%) of participants in the rubefacient group experiencing an adverse event and 9% (47/500, range 0% to 52%) in the placebo group. The RR with rubefacient compared to placebo was 1.6 (1.2 to 2.0), and the NNH was 17 (9.9 to 58) (Figure 5).

Figure 5. Forest plot of comparison: 1 Rubefacient versus placebo, outcome: 1.4 Adverse events.



In two studies it was not clear that the control was truly a placebo (Stam 2001; von Bach 1979) and this could over estimate the rate of adverse events in the placebo group. Excluding these studies made little difference, with event rates of 15% and 10% for rubefacient and placebo respectively, and RR of 1.5 (1.1 to 2.0). Most of the events were in the single study lasting four weeks (Shackel 1997), which had high rates in both treatment arms, and excluding this study gave event rates of 6% and 4% for rubefacient and placebo respectively, and no significant difference between groups.

Local adverse events

Ten studies provided data on local adverse events, six in acute conditions (Diebschlag 1987; Frahm 1993; Ginsberg 1987; Lester 1981; Rothhaar 1982; Stam 2001), and four in chronic conditions (Algozzine 1982; Lobo 2004; Rutner 1995; von Bach 1979), with four having no events in either study arm (Algozzine 1982; Diebschlag 1987; Rothhaar 1982; Rutner 1995). The local adverse event rates were 6% (24/426, range 0% to 24%) and 2% (11/443, range 0% to 9%) for rubefacient and placebo groups respectively, with a significant RR of 2.2 (1.1 to 4.1) and an NNH of 31 (16 to 300) (Figure 5). The I^2 for this analysis was 52%; using a random-effects model the comparison of the treatment groups was no longer significantly different (RR 1.3 (0.35 to 4.7)).

Excluding Stam 2001 and von Bach 1979 (control not a true placebo) gave an event rate of 2% for both treatment arms.

Post hoc sensitivity analyses

Omitting the three studies that contained the potent irritant capsicum oleoresin or nonivamide (Ginsberg 1987; Stam 2001; von Bach 1979) somewhat reduced the estimated RR for any adverse

event (RR 1.4 (1.1 to 1.9)). Local adverse events were reduced to 2/282 and 5/292 in the rubefacient and placebo groups respectively, with too few events for analysis.

The two active-controlled studies using topical NSAIDs (Geller 1980; Ibanez 1988) found no difference in adverse event rates between the study arms, and the aspirin-controlled chronic study (Golden 1978) reported high rates of adverse events in the aspirin arm (Analysis 2.2).

Withdrawals

Six studies did not provide information on all cause withdrawals (Camus 1975; Diebschlag 1987; Ginsberg 1987; Ibanez 1988; Lobo 2004; Wanet 1979). In the remaining studies data were collected over periods of 7 to 15 days, except for two studies in which data were collected over four and six weeks (Shackel 1997; Zahmatkash 2011).

Placebo-controlled studies

Five placebo-controlled studies had information on withdrawals due to lack of efficacy, two in acute conditions (Frahm 1993; Rothhaar 1982) and three in chronic conditions (Algozzine 1982; Shackel 1997; von Bach 1979), with two having no events in either group (Algozzine 1982; Frahm 1993). The withdrawal rate due to lack of efficacy for all studies combined was 2% (6/250, range 0% to 5%) and 7% (18/251, 0% to 38%) for rubefacient and placebo respectively, giving a RR of 0.36 (0.15 to 0.87) and an NNTp of 21 (12 to 120). (Analysis 1.3)

Seven placebo-controlled studies provided data on withdrawals due to adverse events, four in acute conditions (Diebschlag 1987; Frahm 1993; Rothhaar 1982; Stam 2001) and three in chronic conditions (Algozzine 1982; Shackel 1997; von Bach 1979), and four of these had no events in either treatment arm (Algozzine 1982; Diebschlag 1987; Frahm 1993; Rothhaar 1982). The withdrawal rate due to adverse events was 5% (18/364, range 0% to 17%) and 1% (4/373, 0% to 4%) for rubefacient and placebo respectively, with a significant relative harm of 4.2 (1.5 to 12) and a NNH of 26 (15 to 85) (Analysis 1.3)

Post hoc sensitivity analyses

All 18 adverse event withdrawals with active treatment were in two studies (Stam 2001 (acute), Shackel 1997 (chronic)). Stam 2001 included the potent irritant capsicum oleoresin in the active treatment, and Shackel 1997 had data collected over four weeks. Although combining all studies gave a significantly greater risk of withdrawal due to adverse events with rubefacients than placebo, the result is not robust, since removing either of these studies resulted in no significant difference between treatment arms.

Active-controlled studies

The topical NSAID-controlled study in chronic conditions (Geller 1980) had no withdrawals from either treatment arm, but the aspirin-controlled study in chronic conditions (Golden 1978) reported one withdrawal due to lack of efficacy in the rubefacient arm, and two due to lack of efficacy and six due to adverse events in the aspirin arm (Analysis 2.3).

Withdrawals and exclusions for reasons other than lack of efficacy and adverse events were uncommon and generally due to protocol violations or loss to follow up.

DISCUSSION

Summary of main results

One new study (92 participants) was identified for this update but it contributed data only for all cause withdrawals and the conclusions of the previous review are unchanged, although the grading and interpretation of the results is now more cautious (Summary of findings for the main comparison).

Analysis of four studies involving 324 participants with acute musculoskeletal injuries showed a significant benefit of salicylate-containing rubefacients compared with placebo at 7 days, with an NNT for 50% pain relief of 3.2 (2.4 to 4.9), suggesting a useful therapeutic effect of rubefacients (very low quality evidence). In chronic conditions, six studies involving 455 participant with chronic conditions gave a significant benefit compared with placebo at 14 days, with a NNT for 50% pain relief of 6.2 (4.0 to 13) (very low quality evidence).

In 11 studies (984 participants), in both acute and chronic conditions, rubefacients showed a higher rate of adverse events than placebo with a risk of harm over 1.5-fold, giving an NNH of 17 over 7 to 14 days (low quality evidence), and a two-fold risk of local adverse events, giving an NNH of 31 over 7 to 14 days (very low quality evidence). Withdrawals due to adverse events were increased four-fold in the rubefacient group with a NNH of 26 (very low quality evidence). There were significantly fewer withdrawals due to lack of efficacy with rubefacient than with placebo, giving an NNTp of 21 over 7 to 14 days (very low quality evidence).

There was considerable heterogeneity amongst the trials, particularly for acute conditions, and the results were not robust. They were sensitive to the model used for analysis and the inclusion or exclusion of individual studies.

Overall completeness and applicability of evidence

The number of studies and participants identified for this review was small. Acute conditions that were studied were mainly sprains, strains, and acute low back pain, and are probably representative of the conditions suitable for topical treatment. The timing of enrolment and outcome assessment was generally appropriate for acute, self-limiting conditions. Chronic conditions studied were not always well described, but appeared to be mainly osteoarthritis, bursitis, and chronic back pain, which again are those potentially suitable for topical treatment. Most studies did not report the duration of the condition at enrolment, so 'chronicity' was taken as reported, and most studies assessed outcomes within two weeks, with only two studies reporting after one month or longer. Studies of longer duration are desirable in chronic conditions.

Not all of the included studies reported outcomes of interest and, when they did, they were not always reported in a form that was clinically useful and that we were able to use in our analyses. This further limited the strength and interpretation of any results.

Quality of the evidence

We identified relatively few studies in either acute or chronic conditions, and all were potentially subject to bias. A major potential source of bias was the size of the studies; there were no studies with over 90 participants in each treatment arm. In addition to random variation, small studies are known to be associated with

larger treatment effects (Dechatres 2013; Moore 2012b; Nüesch 2010), and for acute and chronic pain conditions, any statistical significance came from older, smaller studies, while more recent larger studies showed no effect.

Few of the studies adequately described the methods used to generate the random sequence, conceal its allocation, or maintain blinding of the treatments, but this may reflect more on the age of the studies than the conduct; older studies tended not to report such details.

Many of the studies did not report baseline pain intensity or included participants with mild pain, or a range of pain intensities from mild to severe. Measurement of a reduction in pain intensity is difficult when initial pain is mild. Additionally, some studies used poorly defined outcomes, such as 'any improvement'. These factors can make studies insensitive to demonstrating efficacy.

Almost half of the studies did not specifically report the number of participants in each treatment arm who withdrew from the studies, who were excluded from analyses for any reason, or who were lost to follow-up. Wherever possible we have carried out an ITT analysis, assuming that missing participants were non-responders, but some uncertainty still remains where studies were not explicit about withdrawals or imputation methods.

Potential biases in the review process

We have combined all acute conditions, and all chronic conditions, for efficacy analyses. Within each category there is heterogeneity in the condition, baseline pain intensity, duration of treatment, outcomes measured, and method of measurement, as well as the treatment applied (salicylate and additional ingredients). While there are too few studies, participants, and events for many sensitivity analyses to be carried out, we have investigated the effect of including individual studies where possible, and highlighted other factors that might influence the results. It is clear that the studies are heterogenous and the results are not robust.

Agreements and disagreements with other studies or reviews

The findings of this update did not change from those of the 2009 review (Matthews 2009), although our interpretation of the results is now more cautious. A systematic review of rubefacients in 2004 found 12 trials that were small and of only moderate quality and validity (Mason 2004). This review concluded that, at best, rubefacients containing salicylates had moderate to poor efficacy in chronic pain and good efficacy in acute pain. These results were judged not robust due to the very limited data. Other reviews have come to similar conclusions about topical rubefacients (Moore 2008).

Guidelines for the treatment of osteoarthritis in England say that rubefacients should not be offered (NICE 2014). In Scotland, guidelines for chronic pain say that "Topical rubefacients should be considered for the treatment of pain in patients with musculoskeletal conditions if other pharmacological therapies have been ineffective" (SIGN 2013).

AUTHORS' CONCLUSIONS

Implications for practice

Updated searches identified only one new study for inclusion in this review, and it contributed data only for withdrawals. The evidence is unchanged and does not support the use of topical rubefacients containing salicylates for either acute or chronic musculoskeletal pain. For both acute and chronic painful conditions any evidence of efficacy came from older, smaller studies, while larger, more recent studies showed no effect.

There are insufficient data of adequate quality to judge whether rubefacients are effective for acute injuries or chronic conditions. Topical salicylates do appear to be relatively well tolerated in the short-term, though this conclusion is severely limited by a relatively small number of participants.

Implications for research

Good quality randomised controlled trials of topical salicylates are needed to legitimise their clinical use. These trials need to be large to provide evidence about harm as well as efficacy, of long duration if the intention is to use topical salicylates in chronic painful conditions, enrol participants with baseline pain of sufficient intensity to reliably detect change, and should use outcomes with clinical utility, such as participants achieving at least 50% reduction in pain. These are now standard features of good quality trials in both acute and chronic pain. They need also to carefully control the content of the rubefacient (for example, additional active ingredients such as local anaesthetic or capsaicin), and the comparator treatment.

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Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS, or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Algozzine 1982

Methods	RCT, DB, cross-over groups Duration 7 days in each phase
Participants	Chronic osteoarthritis of the knee (mean 17 years duration, not secondary to other arthritis or acute trauma, confirmed by X-ray) All participants had at least moderate pain N = 26 (one excluded from analysis due to unrelated medical problem) M = 24, F = 1 Mean age 62 years (range 35-72)
Interventions	Triethanolamine salicylate (10%) cream (Myoflex), n = 25 Placebo cream, n = 25 3.5 g x 4 daily to affected knee
Outcomes	Preferred drug or placebo or neither based on: PI: 4-point scale PI: 11-point scale Patient assessed pain relief: 5-point scale Patient preference Continuous measures of swelling, stiffness, and activity Withdrawals Adverse events
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5 Ineligible for inclusion if salicylates within two days before test period Eligible if on other drug treatment, if taking NSAIDs included only if stable on stated dose for preceding month No change in dose of existing drugs or new analgesics started during the study period No intra-articular steroids within last 6 weeks No other treatment (heat, exercise, massage) during study period Adria Laboratories Inc, Columbus, Ohio, provided the study drug and general support

Risk of bias

Bias	Authors' judgement	Support for judgement

Algozzine 1982 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical, indistinguishable placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1/25 withdrew (unrelated to study intervention)
Size	High risk	< 50 participants per treatment arm

Camus 1975

Methods	RCT, DB, parallel groups Duration 10 days
Participants	Musculoskeletal pain (eg tendon, muscle, or ligament injury) Patients had moderate or mild pain N = 20 M = 8, F = 12 Age range 19 - 86 years
Interventions	Diethylamine salicylate (10%), myrtecaine (1%) cream (Algesal Suractive), n = 10 Placebo cream, n = 10 x 3 daily at the site of pain
Outcomes	PI at rest: 4-point scale Functional limitation: 5-point scale Presence of spontaneous pain, swelling, heat Composite score based on above (20 points) Improvement in: PI at rest, Composite score
Notes	Oxford Quality Score: R1, DB2, W0. Total = 3/5 Myrtecaine (Nopoxamine) is a local anaesthetic agent

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described

Camus 1975 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study
Size	High risk	< 50 participants per treatment arm

Diebschlag 1987

Methods	RCT, DB, parallel groups Duration 15 days Assessment on days 2, 3, 4, 8, 15, 29
Participants	Acute ankle sprain presenting within 48 h Injury severity rated moderate or severe N = 80 M = 63, F = 17 Mean age 27 years (range 18 - 50)
Interventions	Salicylic acid (2%), adrenal extract (1%), mucopolysaccharide polysulphate (0.2%) ointment (Mobilat), n = 40 Placebo ointment, n = 40 10 - 15 cm x 2 daily
Outcomes	Pressure distribution on walking Swelling Ankle joint movement PI at rest: 100 mm VAS PI on movement: 100 mm VAS Adverse events
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5 Suprarenal extract results in 0.02% corticosteroids

Risk of bias

Bias	Authors' judgement	Support for judgement

Diebschlag 1987 *(Continued)*

Random sequence generation (selection bias)	Low risk	"wurden mittels einer Zufallszahlentabelle mit fortlaufenden Behandlungnummern versehen" [sequence generated by means of a random numbers table]
Allocation concealment (selection bias)	Low risk	"Die Reihenfolge des Eintritts der Patienten in den Versuch bestimmte die Zuordnung zu der jeweils folgenden Behandlungnummern und damit die Zuordnung zu einem der Vergleichspräparte" [participants were allocated consecutive treatment numbers in order of enrolment into the study]
Blinding (performance bias and detection bias) All outcomes	Low risk	"Das Placebo enthielt die wirkstofffreie Salbengrundlage. Beide Zubereitungen unterscheiden sich nicht nach Aussehen, Geruch und physikalischen Eigenschaften" [The placebo contained the drug-free ointment base. The preparations were identical in appearance, odour and physical properties]
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study
Size	High risk	< 50 participants per treatment arm

Frahm 1993

Methods	RCT, DB, parallel groups Duration 11 days Assessment at on days 2, 4, 9, 11
Participants	Acute ankle or knee sprain within 24 h Patients had moderate or slight pain N = 156 (163 randomised, 7 protocol infringements) M = 98, F = 58 Mean age 32 years (range 18 - 65)
Interventions	Salicylic acid (2%), mucopolysaccharide polysulphate (0.2%) cream (Movelat), n = 78 Placebo cream, n = 78 10 cm x 2 daily
Outcomes	PI on movement: 100 mm VAS PI at rest: 100 mm VAS Swelling Withdrawals Adverse events
Notes	Oxford Quality Score: R1, DB2, W0. Total = 3/5 No concomitant treatment allowed except max 1 g paracetamol x3 daily

Risk of bias

Frahm 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described. Block randomisation used
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"There were no differences in the appearance, smell, or physical properties of the preparations"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions (protocol infringements) < 10% (7/163)
Size	Unclear risk	50 - 200 participants per treatment arm

Geller 1980

Methods	RCT, DB, active control, cross-over groups Duration 7 days in each phase 4-day washout between phases
Participants	Chronic musculoskeletal disorders (extra-articular, articular, and vertebral musculoskeletal illness, some sprains) N = 50 M = 25, F = 25 Mean age 49 years
Interventions	Diethylamine salicylate (10%), sodium heparin (50 IU/g), menthol (0.2%) gel (Dolo-Menthoneurin) Etofenamate (5%)
Outcomes	PI (spontaneous): 4-point scale Tenderness: 4-point scale Swelling: 4-point scale Movement restriction: 4-point scale Patient global assessment: 4-point scale (1st phase), 3-point scale (2nd phase) Withdrawals Adverse events
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3/5 Etofenamate is an NSAID Adverse events reported for both phases combined

Geller 1980 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Weder dem Arzt noch den Patienten war während der Prufung bekannt, mit welchem Präparat jeweils behandelt wurde" [Niether doctor nor patient knew which treatment was used - method of blinding not described]
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Size	Unclear risk	< 50 participants per treatment arm

Ginsberg 1987

Methods	RCT, DB, parallel groups Duration 14 days Assessment on days 3, 14
Participants	Acute mechanical low back pain N = 40
Interventions	Methylsalicylate (2.6%), ethylsalicylate (1.8%), glycol salicylate (0.9%), salicylic acid (0.9%), camphor (0.4%), menthol (5.5%), capsicum oleoresin (1.5%) ointment (Rado-Salil), n = 20 Placebo ointment, n = 20 Frequency of application not stated
Outcomes	PI: 100 mm VAS Duration of confinement to bed Muscular reflex contracture 5-point scale Spine mobility: Schober's index Finger-floor distance Lumbar extension Patient global assessment: 5-point scale Use of rescue medication (paracetamol 250 mg tablets) Amount of ointment used

Ginsberg 1987 *(Continued)*

	Adverse events
Notes	Oxford Quality Score: R1, DB2, W0. Total = 3/5 No analgesics, anti-inflammatories, or physical treatments allowed other than rescue medication (max 45 x 250 mg paracetamol)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Placebo was identical in appearance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Size	High risk	< 50 participants per treatment arm

Golden 1978

Methods	RCT, DB, double-dummy, active control, parallel groups Duration 7 days Daily assessment
Participants	Chronic musculoskeletal pain (articular, eg osteoarthritis, and non-articular, eg bursitis) for at least weeks (mean 3 years' duration, range weeks to 25 years) Baseline pain at least mild to moderate N = 40 M = 10, F = 30 Mean age 53 years (range 20 - 81)
Interventions	Triethanolamine salicylate (10%) cream (Aspercreme) + placebo tablets, n = 20 Aspirin (325 mg) tablets + placebo cream, n = 20 Cream applied to affected area and two tablets taken x 4 daily (mealtimes and bedtime)
Outcomes	PR: 4-point scale (excellent, good, fair, poor) Speed of pain relief PI: 4-point scale Patient global assessment of PR: 4-point scale

Golden 1978 *(Continued)*

	Withdrawals
	Adverse events
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5
	One week washout of aspirin before trial
	All other anti-inflammatories allowed during trial
	Excluded if pre-existing high dose aspirin therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically appearing materials"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Size	High risk	< 50 participants per treatment arm

Ibanez 1988

Methods	RCT, DB, active control, parallel group
	Duration 12 days
	Assessment on days 4, 8, 12
Participants	Slight articular and extra-articular sports injuries in last 24 h
	N = 137
	Average age 23 years (range 13 - 59)
Interventions	Benzydamine salicylate (6%) spray (Benzasal), n = 35
	Fepradinol (6%) spray (Dalgen), n = 102
	One spray x 4 daily
Outcomes	PI on passive movement: 5-point scale
	PI on active movement: 5-point scale
	Inflammation: 5-point scale
	Functional limitation: 5-point scale

Ibanez 1988 *(Continued)*

	Time to cure
	Adverse events
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2/5
	Baseline scores for inflammation differed between the two groups
	Fepradinol is an NSAID

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data on withdrawals or dropouts, or method of imputation
Size	High risk	< 50 participants per treatment arm

Lester 1981

Methods	RCT, DB, parallel groups
	Duration 7 days
	Assessment on days 3, 7
Participants	Sprained ankle
	Baseline pain slight to severe
	N = 42 (50 randomised: 4 ineligible, 4 lost to follow-up)
	M = 20, F = 22
	Age range 15 to 60+ years
Interventions	Salicylic acid (2%), adrenal extract (1%), mucopolysaccharide polysulphate (0.2%) gel (Movelat), n = 20
	Placebo gel, n = 22
Outcomes	Relief of pain
	Time to return to normal activity
	Adverse events
	Composite score based on above plus ankle range of movement, swelling

Lester 1981 *(Continued)*

	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2/5 Tubes of Movelat and placebo gel supplied by Luitpold-Werk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants lost to follow-up (did not state group)
Size	High risk	< 50 participants per treatment arm

Lobo 2004

Methods	RCT, DB, parallel groups Duration 15 days Assessment on days 10, 15, 20
Participants	Temporomandibular disorders N = 52 M = 5, F = 47
Interventions	Methylsalicylate, copper and zinc pyrocarboxylate, lysine-aspartic acid, herbal extracts cream (Theraflex-TMJ), n = 26 Placebo cream, n = 26 1/4 to 1/2 teaspoon cream onto affected area x 2 daily (morning, bedtime)
Outcomes	PI (spontaneous): 10 cm VAS Adverse events
Notes	Oxford Quality Score: R2, DB1, W0. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement

Lobo 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	"blind selection from a pool of 52 numbers (26 experimental, 26 control) in a box"
Allocation concealment (selection bias)	Low risk	"Numbers assigned to each subject were monitored by the employee [not involved in study] and not disclosed until study was completed"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Mean results only, with no mention of withdrawals or exclusions
Size	High risk	< 50 participants per treatment arm

Rothhaar 1982

Methods	RCT, DB, parallel groups Duration 9 days Assessment on days 3, 7, 9
Participants	Sports injuries Baseline pain mild to severe N = 100 M = 49, F = 32 Average age 30 years (range 14 to 58)
Interventions	Escin 1%, diethylamine salicylate 5% (Reparil-Gel), n = 50 Placebo gel, n = 50 Gel applied at least x 4 daily to affected area
Outcomes	PI (spontaneous): 4-point scale PI with load: 4-point scale PI on movement: 4-point scale PI with pressure: 4-point scale Tightness: 4-point scale Temperature: 4-point scale Haematoma: 4-point scale Swelling: 4-point scale Ratio of range of movement to unaffected limb Ratio of size to unaffected limb Patient global assessment: 5-point scale

Rothhaar 1982 *(Continued)*

	Improvement in spontaneous pain: 3-point scale
	Improvement in movement pain: 3-point scale
	Remission in spontaneous pain: 3-point scale
	Remission in movement pain: 3-point scale
	Withdrawals
	Adverse events
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4/5
	19 patients had no data and were not included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Geprüft wurde gegen ein vom Verum-Präparat hinsichtlich Verpakkung, Aussehen und Geruch nicht unterscheidbares Plazebo-Gel" [tested against a placebo gel which was indistinguishable in packaging, appearance and odour]
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% randomised participants provided no data
Size	High risk	< 50 participants per treatment arm provided data

Rutner 1995

Methods	RCT, DB, parallel groups
	Duration 14 days
	Assessment days 7, 14
Participants	Non-articular rheumatic back pain
	N = 113
	Mean age 56 years
Interventions	Glycol salicylate 10% gel (Phardol-Mono), n = 54
	Placebo gel, n = 59
	5 cm x 3 or x 4 on affected area
Outcomes	Dropout pain-free at day 14
	Dropout pain-free at day 7

Rutner 1995 *(Continued)*

	2-point reduction on 10 cm VAS at day 14
	Withdrawals
	Adverse events
Notes	Oxford Quality Score: R1, DB2, W0. Total = 3/5
	16 patients excluded due to high rheumatoid factor levels

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"einem Plazebo-Gel mit ansonsten identischer Zusammensetzung" [a placebo gel with otherwise identical composition]
Incomplete outcome data (attrition bias) All outcomes	Low risk	~ 5% lost to follow-up
Size	Unclear risk	50 to 200 participants per treatment arm

Shackel 1997

Methods	RCT, DB, parallel groups
	Duration 4 weeks
	Assessment weeks 2, 4
Participants	Osteoarthritis of the hip or knee
	N = 116
	M = 52, F = 64
	Mean age 61 years (range 19 to 86)
Interventions	Copper (0.4%) salicylate (4%) gel in vehicle (methanol 2%, camphor 1%, eucalyptus oil 1%), n = 58
	Placebo vehicle gel, n = 58
	1.5 g x 2 daily applied to inner forearm
Outcomes	PI at rest: 100 mm VAS
	PI on movement: 100 mm VAS
	Patient rated efficacy: 4-point scale
	Use of rescue medication

Shackel 1997 *(Continued)*

	Withdrawals
	Adverse events
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5
	Gel applied remote to site of injury
	500 mg paracetamol rescue medication provided
	Excluded if:
	NSAIDs in last 7 days
	Corticosteroids in last 28 days
	Alterations in arthritis treatment in last 28 days
	Study sponsored by FH Faulding & Co Pty Ltd, who monitored data collection, but had no direct input into analysis or interpretation of the data, or writing of the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random number table"
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"gels .... were equivalent in texture". No comment made about colour, smell etc.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Size	Unclear risk	50 to 200 participants per treatment arm

Stam 2001

Methods	RCT, DB, pseudo-active control (assumed to be placebo in this review), parallel groups
	Duration 7 days
	Daily assessment
	One day washout if NSAIDs or other analgesia taken in last 24 h
Participants	Acute low back pain in last 72 h
	Moderate to severe pain on movement
	N = 161
	M = 87, F = 74
	Mean age 41 years

Stam 2001 *(Continued)*

Interventions	Glycol salicylate (10%), methylnicotinate (1%), capsicum oleoresin (0.1%), histamine hydrochloride (0.1%) (Cremor Capsici Compositus FNA), n = 78 Comfrey (10%), poison ivy (5%), marsh Labrador tea (5%) gel (Spiroflor SRL), n = 83 3 g x 3 daily applied to affected area
Outcomes	80% reduction in pain: 100 mm VAS 100% reduction in pain: 100 mm VAS Nights of disturbed sleep Absence from work Use of rescue analgesia Patient global assessment: 6-point scale Withdrawals Adverse events
Notes	Oxford Quality Score: R2, DB1, W1. Total = 4/5 Spiroflor SRL, while officially classified as 'homeopathic' in some countries, would be better considered as a herbal remedy because the active ingredients are not diluted to homeopathic levels 500 mg paracetamol rescue medication (max 8 x 500 mg tablets daily) Treatments were not identical in smell, colour, or consistency Protocol compliance was poor (mainly due to under/over dosing) Concentration of capsaicin is only 0.008%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Medications differed in smell, colour, and consistency, so provided in identical white 80 g tubes, which were coded
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 21 participants met all per protocol criteria, mainly die to poor compliance. ITT analysis appears to use LOCF
Size	Unclear risk	50 to 200 participants per treatment arm

von Bach 1979

Methods	RCT, DB, pseudo-active control (assumed to be placebo in this review), parallel groups

von Bach 1979 *(Continued)*

	Duration 14 days Assessment at days 3, 6, 9, 14
Participants	Musculoskeletal (knee, spinal or shoulder) disease N = 100 M = 48, F = 52 Average age 51 years
Interventions	Ethylene glycol monosalicylate ester (10%), nonivamide (0.2%) in ointment base of sodium heparin (50 IU/g), methylsalicylate (0.1%) and essential oils (Enelbin-Rheuma), n = 50 Salicylic acid (2%) in above ointment base n = 50 8 to 10 cm of ointment on affected site x 3 or x 4 daily
Outcomes	Restriction of movement: 4-point scale Swelling: 4-point scale Muscle tension: 4-point scale PI (spontaneous): 4-point scale PI with pressure: 4-point scale PI on movement): 4-point scale Curative efficacy: 4-point scale Withdrawals Adverse events
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"im Random-Verfahren nach der Zufallszahlen-tabelle" [using a random number table]
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Die äußere Verpackung sowie Aussehen und Geruch der beiden Salbenpräparate waren nicht unterscheidbar" [The outer packaging and appearance and odor of the ointment preparations were indistinguishable]
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Size	Unclear risk	50 participants per treatment group

Wanet 1979

Methods	RCT, DB, parallel groups Duration 15 days
Participants	Musculoskeletal disease (eg osteoarthritis) and traumatic injury (eg sprains) Baseline pain none to intense N = 56 M = 20, F = 36 Mean age 54 years
Interventions	Diethylamine salicylate (10%), myrtecaine (1%) cream (Algesal Suractive), n = 32 Placebo cream, n = 24 Application x 3 daily
Outcomes	Improvement in global assessment: 4-point scale (global assessment based on 18 point scale of basic pain, paroxysmal pain, swelling, functional limitation) Improvement in PI at rest: 4-point scale Improvement in paroxysmal PI: 4-point scale Improvement in swelling: 4-point scale Improvement in functional limitation: 4-point scale
Notes	Oxford Quality Score: R2, DB1, W0. Total = 3/5 Myrtecaine (Nopoxamine) is a local anaesthetic agent Patients on anti-inflammatories or analgesics excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"de tables de permutation" [random number tables/permutation tables]
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"les tubes contenant les deux types de pommade étant strictement identiques" [the tubes contained strictly identical ointment]
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data on withdrawals or dropouts, or method of imputation
Size	High risk	< 50 participants per treatment arm

Zahmatkash 2011

Methods	RCT, DB, parallel groups Duration 6 weeks Assessment weekly
Participants	Osteoarthritis of the knee N = 92 M = 2, F = 90 Mean age 52 years (SD 12.4)
Interventions	Salicylate (unspecified), n = 46 Herbal (cinnamon, ginger, mastic, sesame oil) ointment, n = 46 2 g ("a knuckle") of ointment massaged over knee for 1 minute, x 3 daily, for 6 weeks
Outcomes	PI: 100 mm VAS Morning stiffness: 100 mm VAS Nightly pains: 100 mm VAS Walking pain in previous 24 h assessed each week Use of rescue medication (paracetamol, sedatives)
Notes	Oxford Quality Score: R1 DB1 W1. Total = 3/5 Participants had to have "stability in taking medication within last two weeks", but it is unclear whether this medication was continued during the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate random sequence not described. Used block randomisation.
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals < 10% (apparently lost to follow-up). No indication of compliance or tolerability
Size	High risk	< 50 participants per treatment arm

DB: double-blind; F: female; LOCF: last observation carried forward; M: male; N: total number in study; n: number in treatment arm; PI: pain intensity; PR: pain relief; R: randomised; RCT: randomised controlled trial; W: withdrawals

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Crielaard 1986	Not RCT
Dettoni 1982	Not RCT
He 2006	Not rubefacient, not blinded
Heindl 1977	Not RCT
Higashi 2010	Too short duration (12 hours)
Howell 1955	Not randomised
Jolley 1972	Oral condition
Kantor 1990	Too short duration
Kleinschmidt 1975	Quasi-randomised
Pasila 1980	Not stated to be double-blind. Short report, ?abstract
Shamszad 1986	Study I is a re-published version of Golden 1978 but no data could be extracted for either Study I or Study II
von Batky 1971	Not RCT
Weisinger 1970	Oral condition, not RCT

DATA AND ANALYSES

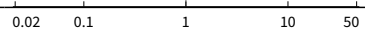
Comparison 1. Rubefacient versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical success (eg 50% reduction in pain)	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Acute conditions	4	324	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.51, 2.46]
1.2 Chronic conditions	6	455	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.22, 2.04]
2 Adverse events	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Any adverse event	11	984	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.19, 2.04]
2.2 Local adverse events	10	869	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.12, 4.12]
3 Withdrawals	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Lack of efficacy	5	501	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.15, 0.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Adverse events	7	737	Risk Ratio (M-H, Fixed, 95% CI)	4.19 [1.52, 11.56]

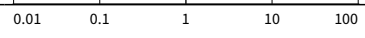
Analysis 1.1. Comparison 1 Rubefacient versus placebo, Outcome 1 Clinical success (eg 50% reduction in pain).

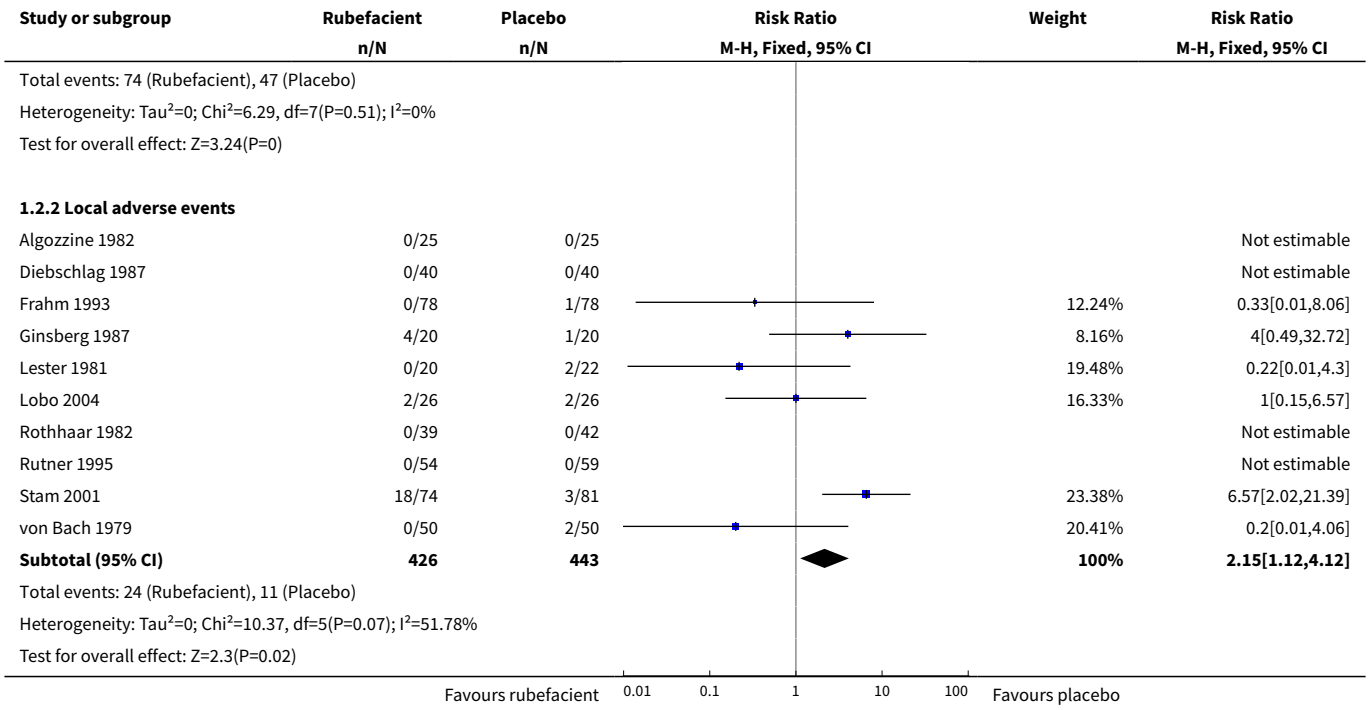
Study or subgroup	Rubefacient n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Acute conditions					
Ginsberg 1987	5/20	0/20		0.92%	11[0.65,186.62]
Lester 1981	18/20	13/22		22.71%	1.52[1.04,2.22]
Rothhaar 1982	37/39	3/42		5.3%	13.28[4.45,39.62]
Stam 2001	41/78	40/83		71.08%	1.09[0.8,1.48]
Subtotal (95% CI)	**157**	**167**		**100%**	**1.93[1.51,2.46]**
Total events: 101 (Rubefacient), 56 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=28.11, df=3(P<0.0001); I^2=89.33%					
Test for overall effect: Z=5.25(P<0.0001)					
1.1.2 Chronic conditions					
Algozzine 1982	10/26	8/26		12.47%	1.25[0.59,2.66]
Camus 1975	8/10	3/10		4.68%	2.67[0.98,7.22]
Rutner 1995	21/54	18/59		26.82%	1.27[0.77,2.12]
Shackel 1997	22/58	21/56		33.31%	1.01[0.63,1.62]
von Bach 1979	27/50	10/50		15.59%	2.7[1.47,4.97]
Wanet 1979	15/32	4/24		7.13%	2.81[1.07,7.4]
Subtotal (95% CI)	**230**	**225**		**100%**	**1.58[1.22,2.04]**
Total events: 103 (Rubefacient), 64 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.87, df=5(P=0.08); I^2=49.34%					
Test for overall effect: Z=3.51(P=0)					



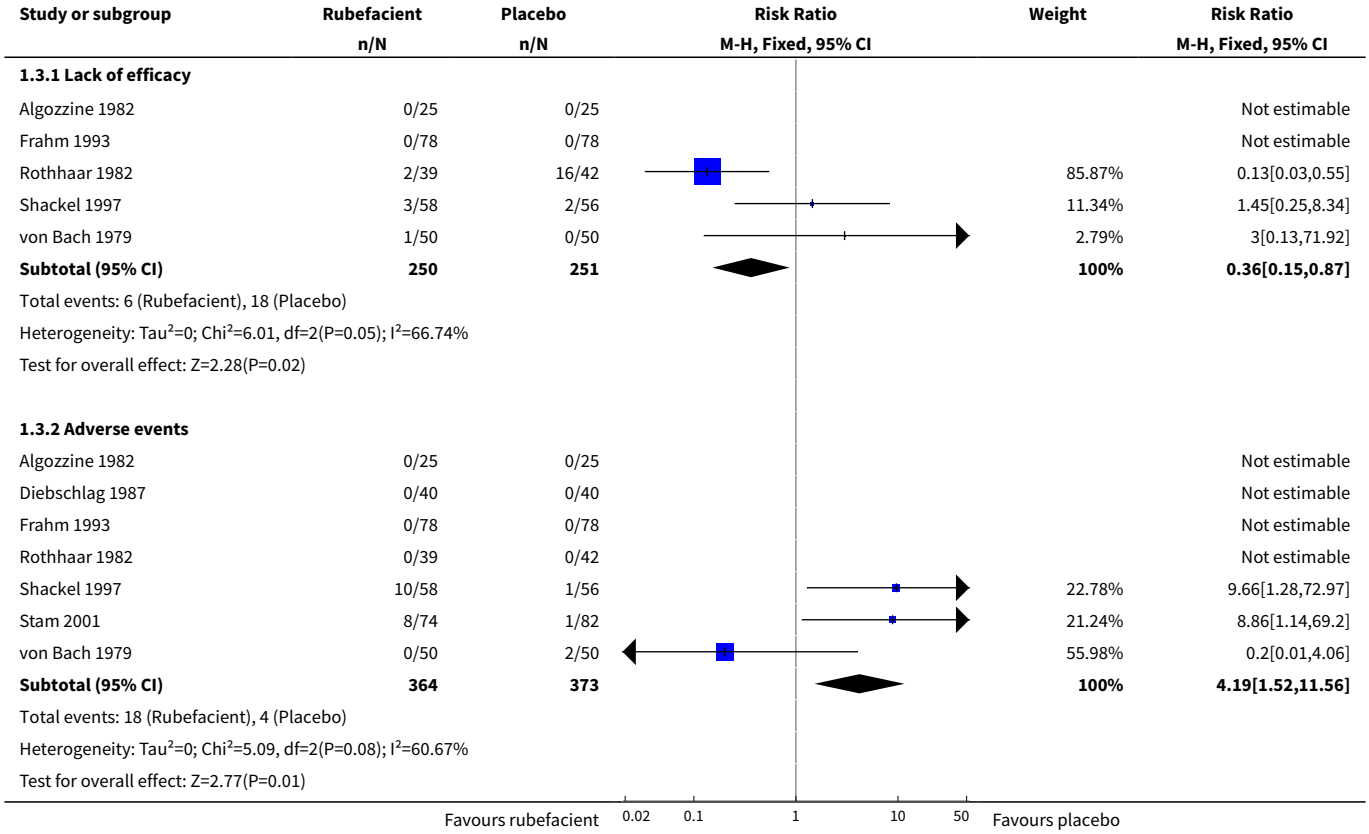
Analysis 1.2. Comparison 1 Rubefacient versus placebo, Outcome 2 Adverse events.

Study or subgroup	Rubefacient n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Any adverse event					
Algozzine 1982	0/25	0/25			Not estimable
Diebschlag 1987	0/40	0/40			Not estimable
Frahm 1993	0/78	1/78		3.07%	0.33[0.01,8.06]
Ginsberg 1987	4/20	1/20		2.05%	4[0.49,32.72]
Lester 1981	0/20	2/22		4.88%	0.22[0.01,4.3]
Lobo 2004	2/26	2/26		4.09%	1[0.15,6.57]
Rothhaar 1982	0/39	0/42			Not estimable
Rutner 1995	1/54	0/59		0.98%	3.27[0.14,78.67]
Shackel 1997	48/58	29/56		60.39%	1.6[1.21,2.11]
Stam 2001	19/74	10/82		19.42%	2.11[1.05,4.23]
von Bach 1979	0/50	2/50		5.12%	0.2[0.01,4.06]
Subtotal (95% CI)	**484**	**500**		**100%**	**1.56[1.19,2.04]**





Analysis 1.3. Comparison 1 Rubefacient versus placebo, Outcome 3 Withdrawals.



Comparison 2. Rubefacient versus active control

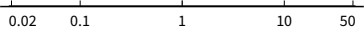
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical success (eg 50% reduction in pain)	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Acute	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Chronic	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Any adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Local adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawals	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Lack of efficacy	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

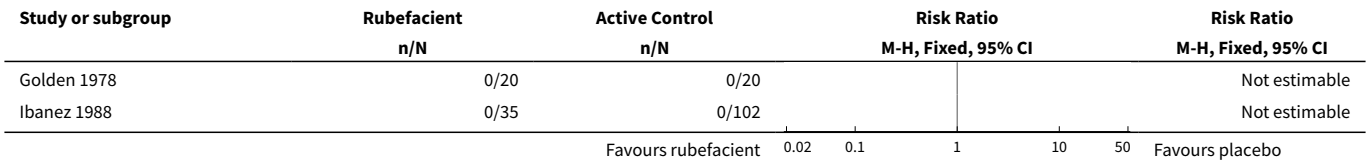
Analysis 2.1. Comparison 2 Rubefacient versus active control, Outcome 1 Clinical success (eg 50% reduction in pain).

Study or subgroup	Rubefacient n/N	Active Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Acute				
Ibanez 1988	23/35	85/102		0.79[0.61,1.02]
2.1.2 Chronic				
Geller 1980	24/25	8/25		3[1.68,5.34]
Golden 1978	13/20	10/20		1.3[0.75,2.24]

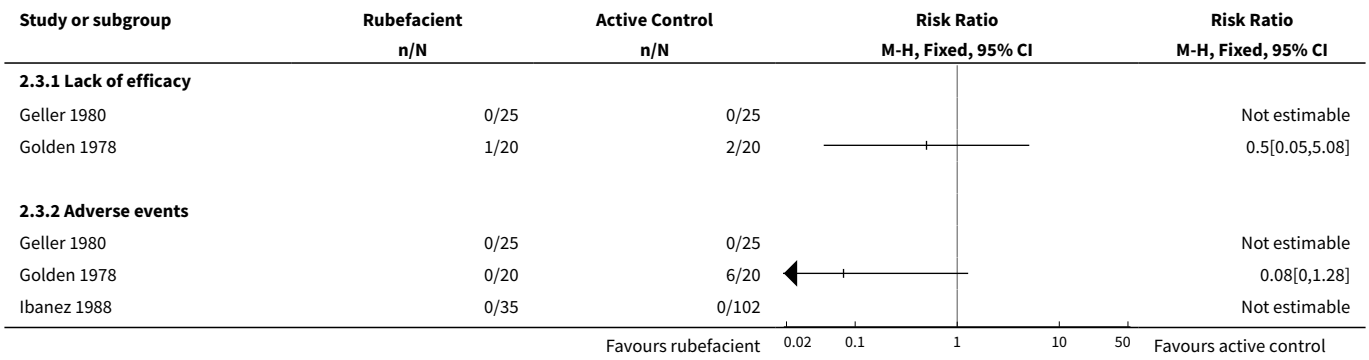
Analysis 2.2. Comparison 2 Rubefacient versus active control, Outcome 2 Adverse events.

Study or subgroup	Rubefacient n/N	Active Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Any adverse events				
Geller 1980	2/50	2/50		1[0.15,6.82]
Golden 1978	3/20	12/20		0.25[0.08,0.75]
Ibanez 1988	0/35	0/102		Not estimable
2.2.2 Local adverse events				
Geller 1980	2/50	2/50		1[0.15,6.82]





Analysis 2.3. Comparison 2 Rubefacient versus active control, Outcome 3 Withdrawals.



APPENDICES

Appendix 1. CENTRAL search strategy (2014 update)

1. MESH descriptor Irritants EXPLODE ALL TREES (187)
2. (rubefacient OR "counter-irritant" OR "ammonium salicylate" OR "radian B" OR "benzyl nicotinate" OR kausalpunkt OR pykaryl OR rubriment OR "bornyl salicylate" OR camphor OR "choline salicylate" OR "diethylamine salicylate" OR algesal OR algoderm OR algoflex OR artogota OR "Lloyd's cream" OR physiogesic OR rheumagel OR "transvasin heat spray" OR "diethyl salicylate" OR "ethyl nicotinate" OR mucotherm OR transvasin "PR heat spray" OR "ethyl salicylate" OR "glycol monosalicylate" OR ralgex OR salonpas OR intralgin OR "glycol salicylate" OR "algipan rub" OR menthol OR "methyl butetisalicylate" OR doloderm OR "methyl gentisate" OR "methyl nicotinate" OR "nella red oil" OR wintergreen OR "sweet birch oil" OR "methyl salicylate" OR aezodent OR argesic OR aspellin OR balmosa OR "bengue's balsam" OR "chymol emollient balm" OR " deep heat" OR dencorub OR dermacreme OR dubam OR eftab OR exocaine OR germolene OR "gone balm" OR gordogesic OR linsal OR salonpas OR intralgin OR mentholatum OR monophytol OR nasciodine OR phlogont rheuma OR "PR heat spray" OR ralgex OR rheumabad OR rheumax OR salonair OR thermo-rub OR nicoboxil OR finalgon OR ortholan OR nonivamide OR Warme-Pflaster OR picolamine OR salicylate OR algiospray OR reflex OR "propyl nicotinate" OR elacur OR nicodan OR salicylamide OR isosal OR salicylate OR salycilic OR movelat OR radian OR "thurfyl salicylate" OR "triethanolamine salicylate" OR "analgesia crme" OR antiphlogistine OR aspercreme OR Ben-Gay OR bexidermil OR dencorub OR exocaine OR metsal OR miosal OR mobisyl OR myoflex OR pro-gesic OR royflex OR sportscreme OR topicrem): TI,AB,KY (4095)
3. 1 OR 2 (4273)
4. MESH descriptor Administration, topical EXPLODE ALL TREES (12155)
5. (topical* OR cutaneous OR dermal OR transcutaneous OR transdermal OR percutaneous OR skin OR massage OR embrocation OR gel OR ointment OR aerosol OR cream OR creme OR lotion OR mousse OR foam OR liniment OR spray OR rub OR balm OR salve OR emulsion OR oil OR patch OR plaster): TI,AB,KY (65584)
6. 4 OR 5 (68135)
7. MESH descriptor Athletic injuries EXPLODE ALL TREES (411)
8. (strain OR sprain* OR "sports injury"): TI,AB,KY (3671)
9. MESH descriptor Musculoskeletal diseases EXPLODE ALL TREES (20514)
10. (arthrit* OR rhemat* or osteoarth* OR tend?nitis OR sciatica OR lumbago OR fibrositis): TI,AB,KY (12221)
11. 7 OR 8 OR 9 OR 10 (29202)
12. (pain OR painful OR analgesi*): TI,AB,KY (71595)
13. 3 AND 6 AND 11 AND 12 (43)

Appendix 2. MEDLINE search strategy (2014 update)

1. exp Irritants/ (12084)
2. (rubefacient OR "counter-irritant" OR "ammonium salicylate" OR "radian B" OR "benzyl nicotinate" OR kausalpunkt OR pykaryl OR rubriment OR "bornyl salicylate" OR camphor OR "choline salicylate" OR "diethylamine salicylate" OR algesal OR algoderm OR algoflex OR artogota OR "Lloyd's cream" OR physiogesic OR rheumagel OR "transvasin heat spray" OR "diethyl salicylate" OR "ethyl nicotinate" OR mucotherm OR transvasin "PR heat spray" OR "ethyl salicylate" OR "glycol monosalicylate" OR ralgex OR salonpas OR intralgin OR "glycol salicylate" OR "algipan rub" OR menthol OR "methyl butetisalicylate" OR doloderm OR "methyl gentisate" OR "methyl nicotinate" OR "nella red oil" OR wintergreen OR "sweet birch oil" OR "methyl salicylate" OR aezodent OR argesic OR aspellin OR balmosa OR "bengue's balsam" OR "chymol emollient balm" OR " deep heat" OR dencorub OR dermacreme OR dubam OR eftab OR exocaine OR germolene OR "gone balm" OR gordogesic OR linsal OR salonpas OR intralgin OR mentholatum OR monophytol OR nasciodine OR phlogont rheuma OR "PR heat spray" OR ralgex OR rheumabad OR rheumax OR salonair OR thermo-rub OR nicoboxil OR finalgon OR ortholan OR nonivamide OR Warme-Pflaster OR picolamine OR salicylate OR algiospray OR reflex OR "propyl nicotinate" OR elacur OR nicodan OR salicylamide OR isosal OR salicylate OR salycilic OR movelat OR radian OR "thurfyl salicylate" OR "triethanolamine salicylate" OR "analgesia crme" OR antiphlogistine OR aspercreme OR Ben-Gay OR bexidermil OR dencorub OR exocaine OR metsal OR miosal OR mobisyl OR myoflex OR pro-gesic OR royflex OR sportscreme OR topicrem).mp. (99561)
3. 1 OR 2 (111385)
4. exp Administration, topical/ (67911)
5. (topical* OR cutaneous OR dermal OR transcutaneous OR transdermal OR percutaneous OR skin OR massage OR embrocation OR gel OR ointment OR aerosol OR cream OR creme OR lotion OR mousse OR foam OR liniment OR spray OR rub OR balm OR salve OR emulsion OR oil OR patch OR plaster).mp. (1380924)
6. 4 OR 5 (1396722)
7. exp Athletic injuries/ (29773)
8. (strain OR sprain* OR "sports injury").mp. (296402)
9. exp Musculoskeletal diseases/ (842839)
10. (arthrit* OR rhemat$* or osteoarth* OR tend?nitis OR sciatica OR lumbago OR fibrositis).mp. (215793)
11. 7 OR 8 OR 9 OR 10 (1179700)
12. (pain OR painful OR analgesi*).mp. (537105)
13. randomized controlled trial.pt. (385551)
14. controlled clinical trial.pt. (89638)
15. randomized.ab. (282279)
16. placebo.ab. (149897)
17. drug therapy.fs. (1733690)
18. randomly.ab. (199106)
19. trial.ab. (292620)
20. groups.ab. (1274063)
21. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 (3262413)
22. 3 AND 6 AND 11 AND 12 AND 21 (106)
23. Limit 22 to yr="2008 - Current" (35)

Appendix 3. EMBASE search strategy (2014 update)

1. exp Irritants/ (2671)
2. (rubefacient OR "counter-irritant" OR "ammonium salicylate" OR "radian B" OR "benzyl nicotinate" OR kausalpunkt OR pykaryl OR rubriment OR "bornyl salicylate" OR camphor OR "choline salicylate" OR "diethylamine salicylate" OR algesal OR algoderm OR algoflex OR artogota OR "Lloyd's cream" OR physiogesic OR rheumagel OR "transvasin heat spray" OR "diethyl salicylate" OR "ethyl nicotinate" OR mucotherm OR transvasin "PR heat spray" OR "ethyl salicylate" OR "glycol monosalicylate" OR ralgex OR salonpas OR intralgin OR "glycol salicylate" OR "algipan rub" OR menthol OR "methyl butetisalicylate" OR doloderm OR "methyl gentisate" OR "methyl nicotinate" OR "nella red oil" OR wintergreen OR "sweet birch oil" OR "methyl salicylate" OR aezodent OR argesic OR aspellin OR balmosa OR "bengue's balsam" OR "chymol emollient balm" OR " deep heat" OR dencorub OR dermacreme OR dubam OR eftab OR exocaine OR germolene OR "gone balm" OR gordogesic OR linsal OR salonpas OR intralgin OR mentholatum OR monophytol OR nasciodine OR phlogont rheuma OR "PR heat spray" OR ralgex OR rheumabad OR rheumax OR salonair OR thermo-rub OR nicoboxil OR finalgon OR ortholan OR nonivamide OR Warme-Pflaster OR picolamine OR salicylate OR algiospray OR reflex OR "propyl nicotinate" OR elacur OR nicodan OR salicylamide OR isosal OR salicylate OR salycilic OR movelat OR radian OR "thurfyl salicylate" OR "triethanolamine salicylate" OR "analgesia crme" OR antiphlogistine OR aspercreme OR Ben-Gay OR bexidermil OR dencorub OR exocaine OR metsal OR miosal OR mobisyl OR myoflex OR pro-gesic OR royflex OR sportscreme OR topicrem).mp. (89247)
3. 1 OR 2 (91804)
4. exp Administration, topical/ (14446)

5. (topical* OR cutaneous OR dermal OR transcutaneous OR transdermal OR percutaneous OR skin OR massage OR embrocation OR gel OR ointment OR aerosol OR cream OR creme OR lotion OR mousse OR foam OR liniment OR spray OR rub OR balm OR salve OR emulsion OR oil OR patch OR plaster).mp. (1214203)
6. 4 OR 5 (1214204)
7. exp Athletic injuries/ (15192)
8. (strain OR sprain* OR "sports injury").mp. (461094)
9. exp Musculoskeletal diseases/ (1041957)
10. (arthrit* OR rhemat* or osteoarth* OR tend?nitis OR sciatica OR lumbago OR fibrositis).mp. (222168)
11. 7 OR 8 OR 9 OR 10 (1505520)
12. (pain OR painful OR analgesi*).mp. (706918)
13. clinical trial.sh. (686097)
14. controlled clinical trial.sh. (340752)
15. randomized controlled trial.sh. (302635)
16. double-blind procedure.sh. (90931)
17. (clin* adj25 trial*).ab. (285240)
18. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab. (98024)
19. placebo*.ab. (151862)
20. random*.ab. (749790)
21. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22. 3 AND 6 AND 11 AND 12 AND 21
23. Limit 22 to yr="2008 - Current" (74)

Appendix 4. Summary of outcomes in individual studies: efficacy and use of rescue medication

		Analgesia		
Study ID	**Treatment**	**Outcome measure**	**Success**	**Rescue Medication**
Acute				
Diebschlag 1987	(1) Salicylate, adrenal extract, and mucopolysaccharide ointment (Mobilat) (2) Placebo ointment	Movement pain on 100 mm VAS at: (a) 8 days (b) 15 days	No dichotomous data (a) Significant difference in favour of (1) (b) Significant difference in favour of (1)	No data
Frahm 1993	(1) Salicylate and mucopolysaccharide cream (Movelat) (2) Placebo cream	Movement pain on 100 mm VAS at: (a) 9 days (b) 11 days	No dichotomous data (a) Significant difference in favour of (1) (b) No significant difference	No data
Ginsberg 1987	(1) Salicylate and capsicum oleoresin ointment (Rado-Salil) (2) Placebo ointment	Patient global assessment ('excellent' or 'good') at: (a) 3 days (b) 14 days	(a) (1) 5/20 (2) 0/20 (b)	Total number of rescue tablets (250 mg paracetamol) used: (1) 24 (2) 36

(Continued)

			(1) 10/20 (2) 2/20	
Ibanez 1988	(1) Salicylate spray (2) Fepradinol spray active control	"Cure" at 12 days	(1) 23/35 (2) 85/102	No data
Lester 1981	(1) Salicylate, adrenal extract, and mucopolysaccharide gel (Movelat) (2) Placebo gel	Relief of pain by 7 days	(1) 18/20 (2) 13/22	No data
Rothhaar 1982	(1) Salicylate gel (Reparil-Gel) (2) Placebo gel	Patient global assessment ('very good' or 'good') at 9 days	(1) 37/39 (2) 3/42	No data
Stam 2001	(1) Salicylate, nicotinate, capsicum oleoresin, and histamine gel (Cremor Capsici Compositus FNA) (2) Herbal gel (Spiroflor SRL) active control	80% reduction in pain on 100 mm VAS at 7 days	(1) 41/78 (2) 40/83	Number using rescue medication (paracetamol): (1) 65/82 (2) 56/75
Chronic				
Algozzine 1982	(1) Salicylate cream (Myoflex) (2) Placebo cream	Pain relief score at 7 days favours (1) or (2)	No first period data. Combined periods: (1) 10/25 (2) 8/25	No data
Camus 1975	(1) Salicylate and myrtecaine cream (Algesal Suractive) (2) Placebo cream	Improvement in rest pain score at 10 days	(1) 8/10 (2) 3/10	No data
Geller 1980	(1) Salicylate and heparin gel (Dolo-Menthoneurin) (2) Etofenamate gel active control	Patient global score ('very good' or 'good') after phase 1 at 7 days	First period data (1) 24/25 (2) 8/25	No data
Golden 1978	(1) Salicylate cream (Aspercreme) + placebo tablets (2) Aspirin tablets + placebo cream active control	Patient global assessment of pain relief ('excellent' or 'good') at 7 days	(1) 13/20 (2) 10/20	No data
Lobo 2004	(1) Salicylate cream (Theraflex-TMJ) (2) Placebo cream	Spontaneous pain VAS (10 cm) at: (a) 15 days (b) 10 days	No dichotomous data (a) Significant difference in favour of (1) (b) No significant difference	No data
Rutner 1995	(1) Salicylate gel (Phardol-Mono)	Dropout 'pain free' by day 14	(1) 21/54	No data

(Continued)

	(2) Placebo gel		(2) 18/59	
Shackel 1997	(1) Salicylate gel (2) Placebo gel	Patient global assessment ('very good' or 'good') at 28 days	(1) 22/58 (2) 21/56	Number using rescue medication (paracetamol): (1) 43/56 (2) 39/55 Average dose (mg/day): (1) 555 (2) 600
von Bach 1979	(1) Salicylate and nonivamide in heparin and salicylate ointment (Enelbin-Rheuma) (2) Salicylate in heparin and salicylate ointment active control	Global assessment ('very good' or 'good') at 14 days	(1) 27/50 (2) 10/50	No data
Wanet 1979	(1) Salicylate and myrtecaine cream (Algesal Suractive) (2) Placebo cream	Rest pain score at 15 days	(1) 15/32 (2) 4/24	No data
Zahmatkash 2011	(1) Salicylate ointment (2) Herbal (cinnamon, ginger, mastic, sesame oil) ointment	Reduction in pain intensity (group mean)	14 days (1) 13/100 (2) 13/100 28 days (1) 19/100 (2) 21/100 42 days (1) 22/100 (2) 25/100	No data

VAS: visual analogue scale

Appendix 5. Summary of outcomes in individual studies: adverse events and withdrawals

		Withdrawals and exclusions			Adverse events	
Study ID	**Treatment**	**All withdrawals and exclusions**	**Lack of efficacy**	**Adverse events**	**All adverse events**	**Local adverse events**

(Continued)

Algozzine 1982	(1) Salicylate cream (Myoflex) (2) Placebo cream	1/26 unrelated to study	(1) 0/25 (2) 0/25	(1) 0/25 (2) 0/25	(1) 0/25 (2) 0/25	(1) 0/25 (1) 0/25
Camus 1975	(1) Salicylate and myrtecaine cream (Algesal Suractive) (2) Placebo cream	No data	No data	No data	No data	No data
Diebschlag 1987	(1) Salicylate, adrenal extract, and mucopolysaccharide ointment (Mobilat) (2) Placebo ointment	No data	No data	(1) 0/40 (2) 0/40	(1) 0/40 (2) 0/40	(1) 0/40 (2) 0/40
Frahm 1993	(1) Salicylate and mucopolysaccharide cream (Movelat) (2) Placebo cream	7/16 violation of protocol	(1) 0/78 (2) 0/78	(1) 0/78 (2) 0/78	(1) 0/78 (2) 1/78	(1) 0/78 (2) 1/78
Geller 1980	(1) Salicylate and heparin gel (Dolo-Menthoneurin) (2) Etofenamate gel active control	Phase 1: (1) 0/25 (2) 0/25	Phase 1: (1) 0/25 (2) 0/25	Phase 1: (1) 0/25 (2) 0/25 Phase 2: (1) 0/25 (2) 0/25	Phases 1 and 2 combined: (1) 2/50 (2) 2/50	Phases 1 and 2 combined: (1) 2/50 (2) 2/50
Ginsberg 1987	(1) Salicylate and capsicum oleoresin ointment (Rado-Salil) (2) Placebo ointment	No data	No data	No data	(1) 4/20 (2) 1/20	(1) 4/20 (2) 1/20
Golden 1978	(1) Salicylate cream (Aspercreme) + placebo tablets (2) Aspirin tablets + placebo cream active control	(1) 1/20 (2) 8/20	(1) 1/20 (2) 2/20	(1) 0/20 (2) 6/20	(1) 3/20 (2) 12/20	(1) 0/20 (2) 0/20
Ibanez 1988	(1) Salicylate spray (2) Fepradinol spray active control	No data	No data	(1) 0/35 (2) 0/102	(1) 0/35 (2) 0/102	(1) 0/35 (2) 0/102
Lester 1981	(1) Salicylate, adrenal extract, and mucopolysaccharide gel (Movelat) (2) Placebo gel	8/50 4 excluded due to fractures, 4 lost to follow-up	No data	No data	(1) 0/20 (2) 2/22	(1) 0/20 (2) 2/22
Lobo 2004	(1) Salicylate cream (Theraflex-TMJ) (2) Placebo cream	No data	No data	No data	(1) 2/26 (2) 2/26	(1) 2/26 (2) 2/26
Rothhaar 1982	(1) Salicylate gel (Reparil-Gel) (2) Placebo gel	(1) 13/50	(1) 2/39 (2) 16/42	(1) 0/39 (2) 0/42	(1) 0/39 (2) 0/42	(1) 0/39 (2) 0/42

(Continued)

		11 with no data, rest lack of efficacy (2) 24/50 8 with no data, rest lack of efficacy				
Rutner 1995	(1) Salicylate gel (Phardol-Mono) (2) Placebo gel	7/136 lost to follow-up	No data	No data	(1) 1/54 unrelated disc prolapse (2) 0/59	(1) 0/54 (2) 0/59
Shackel 1997	(1) Salicylate gel (2) Placebo gel	(1) 15/58 14 withdrew during trial, 1 lost to follow-up (2) 10/58 2 withdrew before treatment, 7 withdrew during trial, 1 lost to follow-up	(1) 3/58 (2) 2/56	(1) 10/58 (2) 1/56	(1) 48/58 (2) 29/56	Total number of adverse events: (1) 80 (2) 27
Stam 2001	(1) Salicylate, nicotinate, capsicum oleoresin, and histamine gel (Cremor Capsici Compositus FNA) (2) Herbal gel (Spiroflor SRL) active control	(1) 4/78 lost to follow-up (2) 2/83 1 death, 1 lost to follow-up	No data	(1) 8/74 (2) 1/82 unrelated death	(1) 19/74 (2) 10/82	(1) 18/74 (2) 3/81
von Bach 1979	(1) Salicylate and nonivamide in heparin and salicylate ointment (Enelbin-Rheuma) (2) Salicylate in heparin and salicylate ointment active control	(1) 0/50 (2) 2/50	(1) 1/50 (2) 0/50	(1) 0/50 (2) 2/50	(1) 0/50 (2) 2/50	(1) 0/50 (2) 2/50
Wanet 1979	(1) Salicylate and myrtecaine cream (Algesal Suractive) (2) Placebo cream	No data	No data	No data	No data	No data
Zahmatkash 2011	(1) Salicylate ointment (2) Herbal (cinnamon, ginger, mastic, sesame oil) ointment	(1) 3/46 (2) 4/46 All lost to follow-up	No data	No data	No data	No data

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected.

HISTORY

Protocol first published: Issue 4, 2008
Review first published: Issue 3, 2009

Date	Event	Description
7 October 2016	Review declared as stable	See Published notes.
7 October 2014	New citation required but conclusions have not changed	Results not changed from 2009 review, but grading and interpretation of results now more cautious. PRISMA flow diagram, 'Risk of bias' assessment, and 'Summary of findings' table added.
22 August 2014	New search has been performed	New searches run in August 2014. This was ahead of the suggested update in 2015 because the review is to be included in an overview of topical analgesics. One new study added (Zahmatkash 2011, 92 participants), which contributed only to the analysis of withdrawals. Title changed from "rubefacients" to "salicylate-containing rubefacients" because all included studies used salicylates (alone or in combination with other compounds). We now also specify musculoskeletal pain because these products are used only for this type of pain.
15 September 2011	Review declared as stable	The authors of this review scanned the literature in August 2011 and are confident that there will be no change to conclusions and therefore a need to update the search until at least 2015.
24 September 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

For the original review PM and SD identified studies and carried out data extraction, analysis, and writing. RAM and HJM were involved in planning, acted as adjudicators, and were involved with writing the protocol and full review.

For this update SD and RAM carried out searches and data extraction. All authors were involved in writing the revised review.

SD will be responsible for conducting any update of this review.

DECLARATIONS OF INTEREST

SD has no conflicts relating to this review or any similar product.

PM has no conflicts relating to this review or any similar product.

PW has no conflicts relating to this review or any similar product.

RAM has no conflicts relating to this review or any similar product.

For transparency, SD, PW, and RAM have received research support from charities, government, and industry sources at various times, but none relate to this review. We are funded by the NIHR for work on a series of reviews informing the unmet need of chronic pain and providing the evidence for treatments of pain.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have changed the title of the review to better reflect the fact that all the studies investigate rubefacient containing salicylates, and treat musculoskeletal pain; rubefacients are not generally used for visceral, neuropathic, or cancer pain.

The earlier review assessed studies for 'validity', using a validated scale (Smith 2000). This has largely been superseded by the 'Risk of bias' assessment, which we have introduced in this update, and consequently we have amended the sensitivity analyses in the review. We no longer investigate high versus low quality and validity, or larger versus smaller studies. Instead, we have limited our sensitivity analyses to consideration of the baseline pain intensity, the outcome reported, and the time of outcome assessment.

We have also included a PRISMA flow diagram and a 'Summary of findings' table in this update.

NOTES

A restricted search in October 2016 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Topical; Chronic Disease; Irritants [*administration & dosage] [adverse effects]; Musculoskeletal Pain [*drug therapy]; Randomized Controlled Trials as Topic; Salicylates [*administration & dosage] [adverse effects]

MeSH check words

Adult; Humans