Topical treatments for cutaneous warts (Review)

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[Intervention Review]

Topical treatments for cutaneous warts

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ABSTRACT

Background

Viral warts are a common skin condition, which can range in severity from a minor nuisance that resolve spontaneously to a troublesome, chronic condition. Many different topical treatments are available.

Objectives

To evaluate the efficacy of local treatments for cutaneous non-genital warts in healthy, immunocompetent adults and children.

Search methods

We updated our searches of the following databases to May 2011: the Cochrane Skin Group Specialised Register, CENTRAL in *The Cochrane Library*, MEDLINE (from 2005), EMBASE (from 2010), AMED (from 1985), LILACS (from 1982), and CINAHL (from 1981). We searched reference lists of articles and online trials registries for ongoing trials.

Selection criteria

Randomised controlled trials (RCTs) of topical treatments for cutaneous non-genital warts.

Data collection and analysis

Two authors independently selected trials and extracted data; a third author resolved any disagreements.

Main results

We included 85 trials involving a total of 8815 randomised participants (26 new studies were included in this update). There was a wide range of different treatments and a variety of trial designs. Many of the studies were judged to be at high risk of bias in one or more areas of trial design.

Trials of salicylic acid (SA) versus placebo showed that the former significantly increased the chance of clearance of warts at all sites (RR (risk ratio) 1.56, 95% CI (confidence interval) 1.20 to 2.03). Subgroup analysis for different sites, hands (RR 2.67, 95% CI 1.43 to 5.01) and feet (RR 1.29, 95% CI 1.07 to 1.55), suggested it might be more effective for hands than feet.

A meta-analysis of cryotherapy versus placebo for warts at all sites favoured neither intervention nor control (RR 1.45, 95% CI 0.65 to 3.23). Subgroup analysis for different sites, hands (RR 2.63, 95% CI 0.43 to 15.94) and feet (RR 0.90, 95% CI 0.26 to 3.07), again

suggested better outcomes for hands than feet. One trial showed cryotherapy to be better than both placebo and SA, but only for hand warts.

There was no significant difference in cure rates between cryotherapy at 2-, 3-, and 4-weekly intervals.

Aggressive cryotherapy appeared more effective than gentle cryotherapy (RR 1.90, 95% CI 1.15 to 3.15), but with increased adverse effects.

Meta-analysis did not demonstrate a significant difference in effectiveness between cryotherapy and SA at all sites (RR 1.23, 95% CI 0.88 to 1.71) or in subgroup analyses for hands and feet.

Two trials with 328 participants showed that SA and cryotherapy combined appeared more effective than SA alone (RR 1.24, 95% CI 1.07 to 1.43).

The benefit of intralesional bleomycin remains uncertain as the evidence was inconsistent. The most informative trial with 31 participants showed no significant difference in cure rate between bleomycin and saline injections (RR 1.28, 95% CI 0.92 to 1.78).

Dinitrochlorobenzene was more than twice as effective as placebo in 2 trials with 80 participants (RR 2.12, 95% CI 1.38 to 3.26).

Two trials of clear duct tape with 193 participants demonstrated no advantage over placebo (RR 1.43, 95% CI 0.51 to 4.05).

We could not combine data from trials of the following treatments: intralesional 5-fluorouracil, topical zinc, silver nitrate (which demonstrated possible beneficial effects), topical 5-fluorouracil, pulsed dye laser, photodynamic therapy, 80% phenol, 5% imiquimod cream, intralesional antigen, and topical alpha-lactalbumin-oleic acid (which showed no advantage over placebo).

We did not identify any RCTs that evaluated surgery (curettage, excision), formaldehyde, podophyllotoxin, cantharidin, diphencyprone, or squaric acid dibutylester.

Authors' conclusions

Data from two new trials comparing SA and cryotherapy have allowed a better appraisal of their effectiveness. The evidence remains more consistent for SA, but only shows a modest therapeutic effect. Overall, trials comparing cryotherapy with placebo showed no significant difference in effectiveness, but the same was also true for trials comparing cryotherapy with SA. Only one trial showed cryotherapy to be better than both SA and placebo, and this was only for hand warts. Adverse effects, such as pain, blistering, and scarring, were not consistently reported but are probably more common with cryotherapy.

None of the other reviewed treatments appeared safer or more effective than SA and cryotherapy. Two trials of clear duct tape demonstrated no advantage over placebo. Dinitrochlorobenzene (and possibly other similar contact sensitisers) may be useful for the treatment of refractory warts.

PLAIN LANGUAGE SUMMARY

Topical treatments for skin warts

Viral warts are a common skin disease, most frequently affecting the hands and feet, caused by the human papilloma virus. While warts are not harmful and usually go away in time without any treatment, they can be unsightly and painful. Warts on the soles of the feet are also called 'plantar warts' or 'verrucas'.

This review did not cover the treatment of genital warts, and it only considered the evidence provided by the results of randomised controlled trials.

Salicylic acid (SA), a cheap and easily-available solution painted on to warts, had a definite but modest beneficial effect compared to placebo. It is effective for warts at all sites and has few adverse effects, but it may take several weeks of daily use to work.

Cryotherapy, usually using liquid nitrogen, is often used for the treatment of warts, but it is less convenient, more painful, and also more expensive. One study suggested that there is evidence that cryotherapy is better than SA for warts on the hands, but when we combined this study with our other results, we were unable to confirm this. We found that more aggressive cryotherapy appears to be more effective than gentle cryotherapy, but with an increased risk of adverse effects, such as pain, blistering, and scarring. We only looked at information from clinical trials of cryotherapy and not over-the-counter freezing treatments for warts, so we cannot say if these are as effective.

During the production of the last version of this review, duct tape had gained favour as it is a safe and simple treatment that is easy to apply; however, the trial on which this was based was relatively small. In this updated review, we found two further trials of duct tape that suggested that this treatment is not as effective as first thought.

Other treatments covered by this review include 5-fluorouracil, dinitrochlorobenzene, intralesional bleomycin, intralesional interferon, photodynamic therapy, and intralesional antigen. None of these treatments are used commonly, even by skin specialists, and there is much less evidence for their effectiveness. The limited available evidence we do have suggests that some of these treatments may be effective and could therefore be used for warts that have not responded to simpler, safer treatments, such as salicylic acid or cryotherapy.

Overall, providing a useful idea of 'what works' from such a wide range of studies was difficult as many studies were of poor quality.

BACKGROUND

Please see our glossary in Table 1 for an explanation of medical terms used throughout the text.

Description of the condition

Biology

Cutaneous viral warts are a very common skin condition caused by the human papilloma virus (HPV), and most people experience warts in one form or another at some point in their lives (Sterling 2004). There are over 100 types of HPV, which are all DNA viruses that infect epithelial cells. Viral replication and proliferation in fully-differentiated epithelium results in warty papules or plaques on the skin.

The appearance of warts is variable depending on the HPV type and the anatomical site infected; sometimes HPV does not result in visible warts but remains dormant within epithelial cells. The most common infections are with HPV type 2 on the hands and feet. HPV types 1, 4, 27, and 57 are also frequently found in common warts. Plane or flat warts, which are clinically distinct from common warts and usually occur on the distal limbs and face, are caused by HPV types 3 and 10. Genital warts, caused by a different group of HPV types (mainly 6 and 11), are also very common, but they were not considered within this review.

Epidemiology

There is limited high-quality epidemiological data on viral warts, and prevalence studies tend to focus on subsets of populations, such as dermatology outpatients or school children (Benton 1997). Two large population studies across all age groups in the USA and Russia produced markedly-different prevalence rates for viral warts: 0.84% (Johnson 1978) and 12.9% (Beliaeva 1990), respectively. The Lambeth study of skin disease in a stratified population of over 2000 adults aged 15 to 75 years reported an overall prevalence of warts of 3.3% (Rea 1976). Among school populations, reports of prevalence rates also appear variable with 3.9% to 4.7% reported in 11 to 16 year-olds in the UK (Williams 1993), 22% in 4 to 18 year-olds in Australia (Kilkenny 1998), and 33% in 3 to 12 year-olds in the Netherlands (van Haalen 2009).

Despite the lack of accurate and consistent data, it is generally agreed that visible viral warts are uncommon in infancy, common in childhood, and their prevalence declines fairly rapidly from the second decade of life onwards. There are many risk factors for the development of viral warts. For example, young people who regularly expose their bare feet in changing rooms and swimming pools are at greater risk of plantar warts, that is, warts on the soles of the feet (Johnson 1995). In addition, certain occupations have been identified as being at increased risk of acquiring hand warts: These include fishmongers, butchers, and other meat handlers (Keefe 1994). Immunosuppression, whether due to drugs or disease, also predisposes to HPV infection, but is beyond the remit of this review. In general, the same principles apply to treating warts in healthy individuals and immunosuppressed individuals, but in the latter group, success rates are often lower.

Natural history and morbidity (to treat or not to treat?)

Among immunocompetent individuals, non-genital warts are usually harmless and spontaneously resolve within months to years. A number of factors, such as host immunity, HPV type, and site of infection, all influence the rate of resolution. A frequently-cited study of an institutionalised population found that two-thirds resolved within a two-year period (Massing 1963). A number of trials included in the review clearly showed more rapid rates of cure in placebo and 'no active treatment' groups. With a relatively good chance of natural resolution, it can be argued that warts are best left untreated (Bridger 1996; Ordoukhanian 1997), and for some people, this may be the best option, perhaps especially when warts are not very symptomatic and have not been present for

a prolonged period of time. However, warts can persist for years and, untreated, represent a pool of HPV infection in the community. Furthermore, ordinary warts can be associated with very significant morbidity (Ciconte 2003), including an unsightly appearance (on the face and hands) and pain (on the soles of the feet). This morbidity is easily and frequently underestimated and dismissed.

Description of the intervention

A wide range of different interventions were considered in this review.

- Cryotherapy describes any treatment that induces cold damage to warts. The most common device used is a liquid nitrogen spray, but liquid nitrogen can also be applied to warts with a cotton bud.
- Salicylic acid is painted on to warts.
- Duct tape is stuck over warts.
- Bleomycin, interferons, and various antigens in solution are injected into warts (intralesional injection).
- 5-fluorouracil is either applied to warts as a cream or injected into warts as a solution.
- The immunotherapy treatments (including dinitrochlorobenzene, diphencyprone, and squaric acid dibutylester) are applied in a solution to warts.
- Photodynamic therapy and pulsed dye laser treatments are, essentially, destructive treatments that aim to destroy the infected tissues. Photodynamic therapy involves the application of a sensitising cream followed by a light shined on the skin. The pulsed dye laser consists of concentrated light energy that is directed on to individual warts.

How the intervention might work

Most topical treatments for viral warts are thought to work by selectively causing damage to cells infected with HPV. Completely-destroyed cells are obviously eradicated, but it is likely that partially-damaged cells expose HPV to the immune system encouraging natural immune-mediated eradication of the infection.

Salicylic acid is a keratolytic (softening/peeling) agent, but there is some uncertainty regarding its mechanism of action. It is believed to act by reducing cohesion between corneocytes, which leads to shedding of epidermal cells rather than lysis of keratin (Lin 1998). Salicylic acid is also an irritant and may help initiate an immune response, resulting in the eradication of HPV (Micali 2004).

The mode of action of duct tape is not well-understood, but it has been suggested that duct tape occlusion may produce a macerating and keratolytic environment, which may stimulate an immune response (Wenner 2007). However, it has also been suggested that it may have a psychological effect that works better in children than adults (Allen 2003).

Cryotherapy, usually with liquid nitrogen, is applied as a number of freezes at intervals of two to four weeks. The freeze causes tissue destruction by damaging cells and their vascular supply, and it is believed to also stimulate the immune system, so it can lead to resolution of warts at distant sites (Dawber 1997).

The mechanism of immunotherapy in the treatment of warts is unclear. One theory suggests that antigen exposure on a wart's surface causes a type IV hypersensitivity reaction, which causes inflammation that damages both virally-infected and normal cells (Brodell 2003). A second theory suggests that the substance applied acts as a hapten to wart virus proteins to induce an immune reaction to warts.

5-Fluorouracil has antineoplastic and antimetabolite properties that inhibit DNA and RNA synthesis, which is believed to be the mechanism that stops wart proliferation (Salk 2006).

The exact action of bleomycin on warts is unclear. Bleomycin has damaging effects on DNA and is also believed to have antiviral effects, which may result in wart resolution (Templeton 1994).

Photodynamic therapy and pulsed dye laser treatments are, essentially, all destructive treatments that aim to damage HPV-infected cells in a more accurate or targeted way than salicylic acid and cryotherapy. With photodynamic therapy, HPV-infected cells absorb more of a photosensitising chemical (usually 5-aminolevulinic acid) than normal cells and are therefore preferentially damaged by the visible light source that is subsequently used to irradiate lesions. The pulsed dye laser that preferentially targets vascularised tissues is thought to work by selectively damaging the blood supply to the warts.

Why it is important to do this review

Warts have a high prevalence in the general population. There are many local treatments for cutaneous warts, some of which are established and commonly-used. Local, or topical treatments, are defined as all treatments designed to be put on or in the wart, such as salicylic acid and cryotherapy, or removal of the wart by surgery. These are distinct from systemic (for example, medicines given by tablet or injection, which reach all parts of the body) or psychological treatments. Recent studies are exploring alternative treatments that may work as well as established treatments or may be used in difficult-to-treat or recurring warts when conventional treatments have failed.

In view of the potential for expensive treatment options, both in terms of the treatments and medical or nursing time spent on administering treatment, this updated review is necessary to summarise the current available evidence. This will help to provide guidance and identify areas for further research.

OBJECTIVES

To evaluate the efficacy of local treatments for cutaneous non-genital warts in healthy, immunocompetent adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of local treatments for non-genital viral warts (excluding molluscum contagiosum).

Types of participants

We included participants of any age or gender with clinically-observed non-genital viral warts.

Types of interventions

We included all local interventions aimed at eradicating viral warts. Local treatments were defined as all topical, intralesional, and surgical treatments, including cryotherapy, but not systemic or psychological treatments.

Types of outcome measures

Primary outcomes

1. Clinical cure at end of treatment period, where clinical cure is defined as complete disappearance of elevated/warty skin.
2. Participant satisfaction/dissatisfaction.
3. Quality of life measures.

Secondary outcomes

1. Adverse events, such as blistering, pain, or scarring.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

For this update, we revised the search strategies for MEDLINE, EMBASE, AMED, and CINAHL and re-ran our existing searches for the other databases. We searched the following databases up to 11 May 2011:

- the Cochrane Skin Group Specialised Register using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* using the search strategy in Appendix 2;
- MEDLINE (from 2005) using the strategy in Appendix 3;
- EMBASE (from 2010) using the strategy in Appendix 4;
- AMED (Allied and Complementary Medicine, from 1985) using the strategy in Appendix 5;
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 6; and
- CINAHL (Cumulative Index to Nursing and Allied Health Literature, from 1981) using the strategy in Appendix 7.

The UK and US Cochrane Centres have an ongoing project to systematically search MEDLINE and EMBASE for reports of trials that are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE from inception to 2004 and in EMBASE from inception to 2011. The Cochrane Skin Group undertook further searches to cover the years not searched by the UK and US Cochrane Centres for CENTRAL.

We searched the SIGLE (System for Information on Grey Literature in Europe) database in a previous version of this review, but not for this update as it only contains references to reports and other grey literature produced in Europe until 2005.

We undertook a final prepublication search for this review on 13 June 2012. Although it was not possible to incorporate potential RCTs identified through this search within the review, we listed relevant references under Studies awaiting classification. We will incorporate these into the next update of the review.

Ongoing Trials

We searched the following ongoing trials registries up to June 2012 using the broad search terms "warts" or "verruca". Although it was not possible to incorporate all the potentially eligible RCTs identified through this search within this review, we listed relevant references under Ongoing studies. We will incorporate these into the next update of the review.

- The metaRegister of Controlled Trials (www.controlled-trials.com).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).

- The World Health Organization International Clinical Trials Registry platform (http://www.who.int/trialsearch).
- The Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials).

Searching other resources

Reference searches

We also searched the references of all reviewed trials and selected review articles on wart treatments.

Correspondence

We contacted key clinicians, researchers, and pharmaceutical companies in an attempt to locate unpublished data (Table 2; Table 3).

Adverse events

We did not search separately for adverse events, but we considered adverse events in the data extraction and analysis of included trials.

Translations

We imposed no language restrictions on this review, and we translated those trials that were not published in English.

Data collection and analysis

Selection of studies

Two authors (CSK and RH) reviewed the abstracts of potentially relevant studies, independently, and where there was discrepancy over their inclusion, the third author (SG) determined if the study should be included.

Data extraction and management

All the authors (CSK and either SG or RH, with CB and RA) double-extracted data, including information on study design, interventions, and participants, and for 'Risk of bias' assessments. We collected additional data on participant attrition, patient flow, and outcomes.

Assessment of risk of bias in included studies

We assessed risk of bias using 'Risk of bias' tables completed according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). Risk of bias was assessed for each trial, and we considered the following: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; and incomplete outcome data. Where there was insufficient information in the trial report to make a judgement, we contacted trial investigators of studies that were 10 years old or less for further information. Two review authors (CB and CSK or SG) carried out 'Risk of bias' assessments independently. Where there was discrepancy, the third review author made the final decision.

Measures of treatment effect

Measures of treatment effect included cure rate, number of warts cured, partial cure rate, changes in wart size, and adverse events. We used cure rate and adverse events as the main measure of treatment effect.

Where appropriate, we reported number needed to treat (NNT) for cure rate outcomes and number needed to harm (NNH) for adverse events together with 95% CI. For the parallel group-designed trials, we used risk ratios with 95% confidence intervals (CI) as the main measure of effect. For the within-participant trials, we reported statistical analysis techniques used together with the resulting P value from the original publications, since no formal statistical pooling was possible.

Unit of analysis issues

Unit of analysis issues included groups of individuals randomised together, multiple observations for the same outcome, and individuals undergoing more than one intervention. For warts trials, left and right randomisation of two interventions may present a potential problem with the unit of analysis. While this method reduces bias due to baseline differences among participants, there is still the risk of bias as a result of choosing a less severe side for a particular intervention in unblinded studies and the possible systemic effects of local treatments.

Some trials considered individual warts as the unit of analysis, which made analysis problematic because a single individual could be assessed and treated multiple times.

We identified trials with these unit of analysis issues as possible sources of study heterogeneity. Furthermore, we identified trials with multiple treatment arms.

Dealing with missing data

We contacted trial investigators when there was insufficient data for analysis (Table 3).

Assessment of heterogeneity

The heterogeneity of the trials made it difficult to perform statistical pooling of the data or descriptive synthesis of information. There were many variables that distinguished trials, including both participant and treatment factors.

We assessed heterogeneity by considering various factors in each study. Elements considered included age of participants (children, adults), sites for wart lesions (hand, feet), types of lesions (plane and mosaic warts), previous treatment (untreated and refractory to previous treatment), and trial period (different periods of treatment and follow up). Treatment factors included differences in concentrations, formulations, and methods of application of salicylic acid and other topical agents. There were different delivery systems of cryotherapy and different concentrations, and for intralesional therapies, there were differences in vehicles and intervals between injections; different types of tape; problems with tape falling off and compliance; different wavelengths of pulsed light therapies, duration of exposure, and intervals between treatments; and different periods of treatment and periods before assessment of outcome.

Assessment of reporting biases

In future, if sufficient studies are included for each meta-analysis, we may formally evaluate publication bias with funnel plots.

Data synthesis

We examined the data from included studies for descriptive synthesis and pooling of dichotomous data where trials were sufficiently homogeneous in design, methodology, and outcomes. When data were pooled, we used the DerSimonian and Laird random-effects model because of anticipated heterogeneity between the included studies.

Subgroup analysis and investigation of heterogeneity

There were insufficient studies to perform subgroup analyses on most of the factors described above (e.g. children/adults, new warts/refractory warts), but we conducted some subgroup analyses comparing warts situated on the hands with warts on the feet (plantar warts). The small number of trials for many treatments and small sample sizes for each trial meant these subgroup analyses were of relatively limited value.

We investigated statistical heterogeneity using the I^2 statistic. An I^2 statistic of 30% to 60% represented a moderate level of heterogeneity; an I^2 statistic of 50% to 90% was treated as evidence of substantial heterogeneity; and an I^2 statistic of 75% to 100% was treated as considerable heterogeneity (Higgins 2009).

Sensitivity analysis

We intended to carry out sensitivity analyses on pooled results where there was substantial heterogeneity by evaluating the effect of removing each trial based on the I^2 statistic. We used random-effects models for analyses.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

We identified 1106 abstracts in total from our original and updated searches. The full text of 57 new trials (mostly published since 2005) were examined in detail, and of these, 26 were included in the review, and 31 were excluded. Thus, the total number of included trials was 85 (26 newly-included trials and 59 previously-included trials).

Included studies

We included 85 studies with a total of 8815 randomised participants. Full details of all the included studies are given in the tables of Characteristics of included studies. In this update, we included 26 new studies (Adalatkhah 2007; Aldara 3M 2000a; Aldara 3M 2000b; Aum 2006; Banihashemi 2008; Bruggink 2010; Chen 2008; Cockayne 2011; de Haen 2006; Dhar 2009; Faghihi 2010; Fuchs 2004; Huo 2010; Khattar 2007; Luk 2006; Nofal 2010; Passeron 2007; Rahimi 2008; Salk 2006; Sharquie 2007; Togsverd-Bo 2010; Vali 2007; Wenner 2007; Wu 2005; Yazar 1994; Yazdanfar 2008). We excluded the previously-included study, Fabbrocini 2001.

The previously-published review had 60 included studies with 6374 randomised participants (Gibbs 2006).

Design

All 85 included studies were randomised.

Fourteen studies employed a left/right or within-participant randomisation design (Adalatkhah 2007; Bunney 1984; Hursthouse 1975; Iscimen 2004; Lee 1990; Marroquin 1997; Niimura 1990; Pazin 1982; Stender 1999; Stender 2000; Vali 2007; Veien 1977; Wolff 1980; Yazdanfar 2008). As we were unable to extract individual data on participants, we could not pool this form of data.

Eight studies were multicentre in design (Abou-Auda 1987; Aldara 3M 2000a; Aldara 3M 2000b; Auken 1975; Cockayne 2011; Larsen 1996; Togsverd-Bo 2010; Vance 1986).

The main unit of analysis was the number of participants included in a study. Some trials evaluated individual warts as the base unit of analysis (Bunney 1984; Hayes 1986; Iscimen 2004; Marroquin 1997; Martinez 1996; Munkvad 1983; Rossi 1981; Stender 1999; Stender 2000; Vali 2007). However, it is difficult to make statistical inferences from such wart-based analyses (Altman 1997). And as we could not extract individual data on participants, we could not pool this form of data.

Sample sizes

We included 85 studies with a total of 8815 randomised participants. Details of all the studies are included in the 'Characteristics of included studies' tables. Sample sizes ranged from 1 (Pazin 1982, a study in which individual warts in 1 participant were randomised to different treatments) to 400 (Berth-Jones 1992a).

Setting

The majority of the studies were carried out in a secondary care setting (n = 71). The remainder were carried out in primary care (Abou-Auda 1987; Bruggink 2010; Erkens 1992; Hansen 1986; Marroquin 1997; Martinez 1996; Parton 1994; Salk 2006; Steele 1988a; Steele 1988b), including in podiatry clinics (Cockayne 2011), at home (de Haen 2006), or in the context of a phase II clinical trial (Aldara 3M 2000a; Aldara 3M 2000b) (see Table 1, Published notes).

Studies were carried out mostly, but not exclusively, in Europe and the USA: Seventeen studies were carried out in the USA; 21 in the UK; 2 in Turkey; 1 in Canada; 10 in Denmark; 4 in Iran; 2 in Italy; 2 in Korea; 1 in Singapore; 3 in the Netherlands; 6 in China; 1 in Mexico; 1 in Eire; 1 in Bangladesh; 2 in Germany; 1 in Sweden; 1 in Egypt; 1 in Japan; 1 in Spain; 1 in New Zealand; 1 in Guatemala; 1 in India; 1 in France; 1 in Iraq; and for 2 studies the location was unclear.

Participants

The participants in 45 studies were mixed groups of adults and children.

In four studies, the participants were children only (Cancino 1989; de Haen 2006; Felt 1998; Parton 1994).

In the following studies, the participants were adults only: Aldara 3M 2000a; Aldara 3M 2000b; Bart 1989; Berman 1986; Bunney 1984; Chen 2008; Fuchs 2004; Hayes 1986; Iscimen 2004; Luk 2006; Munkvad 1983; Nofal 2010; Passeron 2007; Pazin 1982; Robson 2000; Salk 2006; Schmidt 1981; Sonnex 1988; Spanos 1990; Stender 1999; Stender 2000; Vance 1986; Varnavides 1997; Wenner 2007; Wilson 1983; Wu 2005; Yazdanfar 2008.

In Adalatkhah 2007, Cockayne 2011, and Khattar 2007, the participants were described as being older than 12 years of age. In Banihashemi 2008, the intervention and control group mean ages were 15.6 and 16.4 years, respectively; in Vali 2007, the participant ages ranged from 10 to 50 years; and in Horn 2005, the average age was reported as ranging between 37 and 40. In Togsverd-Bo 2010, the age of the participants was not stated; however, the median ages ranged from 40 to 46 years. In Zhang 1999, the age of the participants was unclear, and we were unable to obtain further information. The age range was also unclear in Bunney 1973.

For the purposes of this review, we defined refractory warts as those that have not cleared with a standard course of treatment. Ordinary warts were defined as those that have not been treated.

The types of warts included were described as ordinary or common in 26 studies (Abou-Auda 1987; Adalatkhah 2007; Aldara 3M 2000a; Aldara 3M 2000b; Artese 1994; Banihashemi 2008; Bart 1989; Bruggink 2010; Erkens 1992; Felt 1998; Focht 2002; Hansen 1986; Larsen 1996; Martinez 1996; Nofal 2010; Parton 1994; Passeron 2007; Sharquie 2007; Stahl 1979; Steele 1988a; Steele 1988b; Wang 2002; Wilson 1983; Wolff 1980; Yazar 1994; Zhang 1999), mosaic in 3 studies (Bunney 1973; Bunney 1976d; Bunney 1976e), refractory in 18 studies (Aum 2006; Berman 1986; Berth-Jones 1992b; Bunney 1984; Cancino 1989; Fuchs 2004; Gustafsson 2004; Hayes 1986; Horn 2005; Lee 1990; Pazin 1982; Rossi 1981; Sonnex 1988; Stender 1999; Stender 2000; Togsverd-Bo 2010; Varnavides 1997; Veien 1977), or mixed, that is ordinary and refractory, in 4 studies (Berth-Jones 1992a; Berth-Jones 1994; Bourke 1995; Robson 2000). In Vali 2007, the type of warts included were described as plane warts; in Rahimi 2008, the warts were described as common, flat, or plantar. In the 32 remaining studies, the type was not specified (Auken 1975; Bunney 1971; Bunney 1976a; Bunney 1976b; Bunney 1976c; Chen 2008; Cockayne 2011; Connolly 1999; de Haen 2006; Dhar 2009; Faghihi 2010; Flindt-Hansen 1984; Gibson 1984; Huo 2010; Hursthouse 1975; Iscimen 2004; Khan 1999; Khan 2000; Khattar 2007; Luk 2006; Marroquin 1997; Munkvad 1983; Niimura 1990; Perez 1992; Salk 2006; Schmidt 1981; Spanos 1990; Vance 1986; Veien 1991; Wenner 2007; Wu 2005; Yazdanfar 2008).

Thirty-four studies described the site of the warts as hands and feet (Abou-Auda 1987; Adalatkhah 2007; Artese 1994; Auken 1975; Berth-Jones 1992a; Berth-Jones 1992b; Berth-Jones 1994; Bourke 1995; Connolly 1999; Flindt-Hansen 1984; Focht 2002; Fuchs 2004; Gustafsson 2004; Hursthouse 1975; Lee 1990; Marroquin 1997; Munkvad 1983; Niimura 1990; Passeron 2007; Pazin 1982; Perez 1992; Rahimi 2008; Robson 2000; Schmidt 1981: Sonnex 1988; Spanos 1990; Stahl 1979; Steele 1988a; Stender 1999; Stender 2000; Togsverd-Bo 2010; Varnavides 1997; Veien 1977; Wolff 1980). The site was periungual in Aum 2006; not feet or periungual in Yazdanfar 2008; and it was on the hands only in nine studies (Banihashemi 2008; Bart 1989; Bunney 1976a; Bunney 1976b; Bunney 1984; Erkens 1992; Hayes 1986; Larsen

1996; Wilson 1983). Eighteen studies only treated feet or plantar warts (Aldara 3M 2000a; Bunney 1971; Bunney 1973; Bunney 1976c; Bunney 1976d; Bunney 1976e; Cockayne 2011; Gibson 1984; Hansen 1986; Huo 2010; Khan 1999; Khan 2000; Parton 1994; Salk 2006; Steele 1988b; Vance 1986; Veien 1991; Zhang 1999). The remaining 22 studies included warts at multiple sites or unspecified sites (Aldara 3M 2000b; Berman 1986; Bruggink 2010; Cancino 1989; Chen 2008; de Haen 2006; Dhar 2009); warts on the hands, neck, lower extremities, and trunk (Faghihi 2010; Felt 1998; Horn 2005; Iscimen 2004; Khattar 2007; Luk 2006; Martinez 1996; Nofal 2010; Rossi 1981; Sharquie 2007; Vali 2007; Wang 2002; Wu 2005; Yazar 1994); and non-genital warts (Wenner 2007).

Interventions

The included trials fell into 12 broad therapeutic categories, although some trials compared more than 1 therapy, so we have counted them below. Further information about interventions, results, and outcomes can be found in the additional data tables, Analysis 13.1 to Analysis 13.12, which are tables of non-numerical data. We found the following:

- 14 trials of topical salicylic acid with or without lactic acid (Analysis 13.1). (Salicylic acid was combined with lactic acid in some of the older trials (Auken 1975; Bunney 1976e; Felt 1998; Flindt-Hansen 1984; Veien 1991). In this review, we referred to salicylic acid with or without lactic acid as SA);
- 21 trials of cryotherapy (Analysis 13.2);
- 7 trials of intralesional bleomycin (Analysis 13.3);
- 7 trials of intralesional interferons (Analysis 13.4);
- 2 trials of dinitrochlorobenzene (Analysis 13.5);
- 5 trials of photodynamic therapy (Analysis 13.6);
- 3 trials of duct tape (Analysis 13.7);
- 3 trials of pulsed dye laser (Analysis 13.8);
- 7 trials of topical 5-fluorouracil (Analysis 13.10);
- 2 trials of intralesional 5-fluorouracil (Analysis 13.11);
- 2 trials of topical zinc (Analysis 13.9); and
- 13 trials of other interventions (Analysis 13.12), including topical imiquimod (Aldara 3M 2000a; Aldara 3M 2000b), formic acid puncture (Faghihi 2010), traditional Chinese medicine (Wang 2002; Wu 2005; Zhang 1999), aciclovir cream (Gibson 1984), hyperthermia (Huo 2010), topical Thuja (Khan 1999; Khan 2000), intralesional MMR (mumps, measles, and rubella) vaccine (Nofal 2010), and silver nitrate (Yazar 1994).

Outcomes

All the studies reported the outcome of cure ('successful treatment' in Abou-Auda 1987; wart area in Fuchs 2004, Horn 2005, and Stender 2000). The earliest that cure was assessed was 2 weeks (Martinez 1996; Sharquie 2007), with participants followed up to 26 weeks (Aum 2006; Bruggink 2010; Iscimen 2004; Larsen 1996; Salk 2006; Steele 1988a; Steele 1988b; Yazdanfar 2008) (up to 18 months in Felt 1998) after treatment. Most studies assessed cure at between six weeks and six months after treatment.

Aum 2006, Dhar 2009, Steele 1988a, and Wenner 2007 assessed recurrence as an outcome at six months. In Aldara 3M 2000a and Aldara 3M 2000b, recurrence was during a 12-week treatment-free follow-up period, after 12 weeks of intervention.

Some studies also considered other measures of treatment efficacy, such as number of warts cured, partial cure rate, and changes in wart size, but we did not include these in our meta-analyses. The reason for this is that from a clinician's and a participant's perspective, the ideal treatment should completely cure all warts. So, partial response, change in size, or reduced number of warts is less satisfactory than complete cure.

Few studies reported adverse effects: Adalatkhah 2007; Aldara 3M 2000a; Aldara 3M 2000b; Bruggink 2010; Cockayne 2011; Connolly 1999; Dhar 2009; Horn 2005; Munkvad 1983; Togsverd-Bo 2010; Vance 1986.

Excluded studies

Two authors (CSK and RH) independently examined and excluded the studies. Many of the studies that were not relevant discussed the human papilloma virus vaccine. The relevant excluded studies are further described in the 'Characteristics of excluded studies' tables.

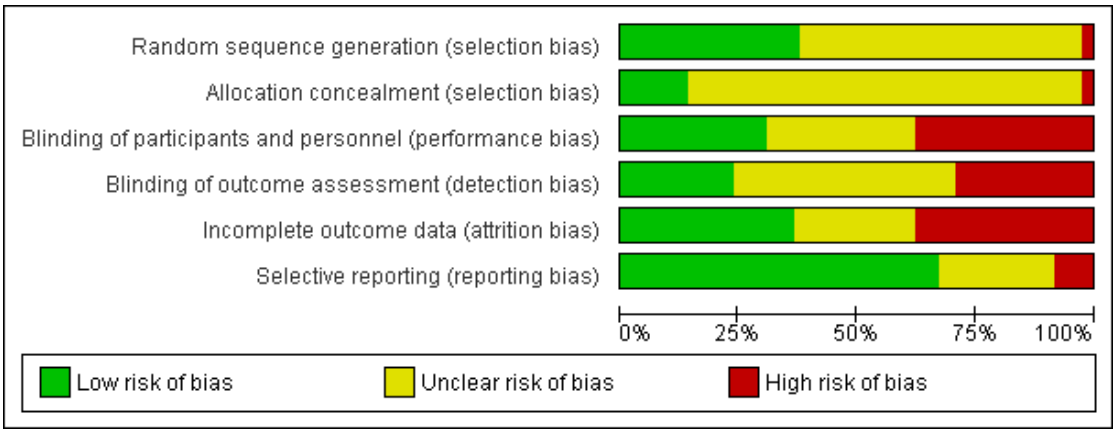
In total, we excluded 47 studies. Reasons for their exclusion were as follows: On inspection of the full text of the report they were controlled clinical trials, employed inadequate or quasi-randomisation, or reported systemic or psychological therapies.

In this updated review, we excluded one study (Fabbrocini 2001), which had previously been included. This was a trial of photodynamic therapy (PDT) versus placebo, and unpublished data obtained from the author showed cure rates of 26/34 participants (76%) with PDT versus (vs) 13/33 (42%) with placebo at 22 months. Following further correspondence with the author, it emerged that this was a quasi-randomised trial rather than a true RCT; therefore, it was moved onto the list of excluded trials.

Risk of bias in included studies

In this update of the review, we included more detailed 'Risk of bias' assessments. Please see Figure 1, which shows our judgements about each 'Risk of bias' item presented as percentages across all included studies. Where 'Risk of bias' information was not found in the trial report, we contacted authors of studies published from 2001 onwards to ask for missing information. For studies judged as 'unclear', we requested clarification from the trial investigators, but no further information was available at the time this review was prepared.

Figure 1. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies



Allocation

The randomisation process and concealment of allocation are the most important and sensitive indicators that bias has been minimised in clinical trials (Schulz 1995). In the majority of the trials reviewed, the method of randomisation was not described or was unclear. Out of all 85 included studies, only 32 trials clearly described adequate randomisation methods (Bart 1989; Bruggink 2010; Bunney 1971; Bunney 1973; Chen 2008; Cockayne 2011; de Haen 2006; Dhar 2009; Felt 1998; Focht 2002; Fuchs 2004; Hayes 1986; Horn 2005; Huo 2010; Hursthouse 1975; Iscimen 2004; Khan 1999; Khan 2000; Larsen 1996; Luk 2006; Nofal 2010; Parton 1994; Passeron 2007; Sharquie 2007; Steele 1988a; Steele 1988b; Stender 2000; Togsverd-Bo 2010; Vali 2007; Varnavides 1997; Veien 1991; Wenner 2007).

Twelve studies demonstrated adequate concealment of allocation (Bruggink 2010; Bunney 1984; Cockayne 2011; de Haen 2006; Dhar 2009; Fuchs 2004; Huo 2010; Hursthouse 1975; Nofal 2010; Stender 2000; Togsverd-Bo 2010; Wenner 2007).

Blinding

Twenty-six trials blinded the participants or personnel (Berman 1986; Bunney 1971; Bunney 1976a; Bunney 1984; de Haen 2006; Dhar 2009; Erkens 1992; Hayes 1986; Huo 2010; Hursthouse 1975; Iscimen 2004; Khattar 2007; Luk 2006; Niimura 1990; Nofal 2010; Perez 1992; Rossi 1981; Sharquie 2007; Spanos 1990; Steele 1988b; Stender 2000; Vance 1986; Varnavides 1997; Wenner 2007; Wolff 1980; Yazdanfar 2008).

In trials comparing treatments that are entirely different, such as a trial comparing intralesional bleomycin to cryotherapy, adequate time should be given after the intervention to ensure any acute effects of treatment are not visible. Ideally, an independent person should assess the outcome who was not aware of the treatment group to which the participant was allocated. Only 20 of the trials demonstrated blinding of outcome assessment (Auken 1975; Banihashemi 2008; Bunney 1971; Bunney 1984; Cockayne 2011; de Haen 2006; Focht 2002; Gustafsson 2004; Hayes 1986; Iscimen 2004; Khattar 2007; Luk 2006; Martinez 1996; Nofal 2010; Rahimi 2008; Spanos 1990; Stender 2000; Togsverd-Bo 2010; Varnavides 1997; Wenner 2007).

Incomplete outcome data

Some authors analysed their data to show that the numbers of participants who dropped out or were withdrawn were not significantly different from the groups analysed, but this did not mean that bias was excluded, as the reason for dropout might have differed between the two groups (e.g. adverse events and lack of efficacy). Many authors made efforts to retain participants by writing or telephoning them, but the results may be less reliable than interview and clinical assessment.

The high rate of attrition in the trials was a problem and a potential source of bias. For many of the trials, analysis was only carried out on participants who had completed the trial, and in 34 of the trials, the distribution of or high number of dropouts or losses to follow up could have introduced bias (Abou-Auda 1987; Adalatkhah 2007; Banihashemi 2008; Bart 1989; Berth-Jones 1992a; Berth-Jones 1992b; Berth-Jones 1994; Bourke 1995; Bruggink 2010; Bunney 1971; Bunney 1976a; Bunney 1976b; Bunney 1976c; Bunney 1976d; Bunney 1976e; Connolly 1999; Dhar 2009; Faghihi 2010; Focht 2002; Fuchs 2004; Hayes 1986; Horn 2005; Munkvad 1983; Niimura 1990; Parton 1994; Rahimi 2008; Schmidt 1981; Sharquie 2007; Stahl 1979; Vance 1986; Varnavides 1997; Veien 1991; Wolff 1980; Wu 2005).

In many trials, the attrition data was poorly-reported or absent, despite our attempts to request further information from trial investigators; we judged these as unclear.

Intention-to-treat (ITT)

Intention-to-treat analysis was only reported in 12 trials (Artese 1994; Berth-Jones 1994; de Haen 2006; Erkens 1992; Hansen 1986; Khattar 2007; Larsen 1996; Luk 2006; Stender 1999; Stender 2000; Wenner 2007; Veien 1991).

Selective reporting

Most of the trials requested all of the prespecified trial outcomes. We judged that only seven studies could have introduced an element of bias by selective outcome reporting: Adalatkhah 2007 (incomplete adverse event reporting); Aum 2006 (length of study and adverse effects not reported); Focht 2002 (time to resolution of warts not reported); Hayes 1986 (insufficient follow up for 1 treatment group); Marroquin 1997 (no 30-day results reported); Parton 1994 (cure rate by group not reported); Passeron 2007 (percentages of warts rather than participants). In 21 trials, there was insufficient information to make a judgement. Unfortunately, no further data were available from these trials to clarify these issues.

Other potential sources of bias

Human papilloma virus can remain dormant in epithelial cells without any visible abnormality. The natural immunity of the person and the effects of any wart treatment used may mean that it takes time for the wart to develop or recur. One study used a questionnaire to look at long-term outcomes (Keefe 1990), and it found that 83% of participants believed they were cured at the end of the treatment period, but only 57% were cleared of warts after a median follow-up time of 19 months. For these reasons, it seems sensible that the results of any treatment for common warts should be assessed after a reasonable interval to allow for gradual resolution of warts or recurrence of disease. In 18 included trials (Adalatkhah 2007; Banihashemi 2008; Bunney 1984; de Haen 2006; Hursthouse 1975; Lee 1990; Passeron 2007; Perez 1992; Marroquin 1997; Martinez 1996; Rossi 1981; Schmidt 1981; Spanos 1990; Sonnex 1988; Stender 1999; Wolff 1980; Vali 2007; Yazar 1994), the period of outcome assessment was six weeks or less. Most clinicians would agree that this period is inadequate to properly assess cure of warts, and they would recommend follow up at about six months. For some trials, it was unclear whether the period of assessment was measured from the beginning or the end of the treatment period. Lack of clarity on this point and a short assessment interval reduced the weight of evidence provided by these studies.

Effects of interventions

This section is organised into two parts. In the first part, we present the results of meta-analyses; in the second part, we summarise the results of included studies that could not be combined in meta-analyses, because of differences between studies in terms of study design. We present the results of studies that could not be pooled in meta-analyses or presented graphically as summary tables.

1. Meta-analysis results

In the text below, an I^2 statistic value for heterogeneity is only reported as high if it exceeds 50%. Numbers given are the total number of participants in the analysis. Where it was possible to calculate an effect size, we reported these with 95% confidence intervals. Where the calculated effect size was statistically significant ($P < 0.05$), we stated whether the result favours the intervention or control condition.

For numerical data (Analyses 1 to 12), we have summarised results below under headings corresponding to the primary and secondary outcomes outlined in the section entitled Types of outcome measures. Where possible, we presented the results according to site of the wart (for example, hands or feet or all sites). Under each heading, any results of sensitivity analyses or subgroup analyses (site of warts) are included where these were conducted.

Comparison: topical salicylic acid versus placebo

Clinical cure

Trials of topical preparations containing SA (with or without additional lactic acid) are summarised in the additional data table, Analysis 13.1. Meta-analysis of 6 of these studies (with 486 participants) in Analysis 1.1 showed a statistically-significant result favouring the topical application of SA for warts at all sites (RR 1.56, 95% CI 1.20 to 2.03). We used a random-effects model as heterogeneity between studies was moderate (I^2 statistic = 35%).

We conducted subgroup analyses to investigate the effects of therapy at specific sites. The results showed a larger size of effect for warts on the hands (2 studies, n = 120 participants) (RR 2.67, 95% CI 1.43 to 5.01; Analysis 1.2; P = 0.002) than on the feet (2 studies, n = 139 participants) (RR 1.29, 95% CI 1.07 to 1.55; Analysis 1.2).

The overall result for those studies that reported results for warts on both hands and feet combined also significantly favoured the intervention, with a size of effect intermediate between that for hands alone and feet alone (RR 1.62, 95% CI 1.15 to 2.30; Analysis 1.2).

However, as the confidence intervals for all these subgroup analyses overlapped, the suggested differences in efficacy between sites (hands and feet) were not, in fact, statistically significant.

Satisfaction and quality of life

Participant satisfaction and quality of life measures were reported in Bruggink 2010; 24% of participants were satisfied with treatment (95% CI 13 to 39) after SA treatment and 22% (95% CI 12 to 38) in the placebo group. The report of the study also stated, "In the plantar wart group, there were no differences in treatment burden or satisfaction between the three treatment groups."

Adverse events

In one trial (Steele 1988b) that compared a mixture of monochloroacetic acid and 60% SA with placebo, 1 of the 29 participants in the active treatment group developed cellulitis. Minor skin irritation was reported occasionally in some of the other trials, but generally, no significant harmful effects of topical SA were identified.

Comparison: cryotherapy versus placebo or no treatment

We included 21 trials of cryotherapy (Analysis 13.2).

Bruggink 2010 and two small trials (Gibson 1984; Wilson 1983) contained a cryotherapy and no-treatment or placebo group, and both Wilson 1983 and Gibson 1984 included another arm of a topical treatment (dinitrochlorobenzene in Wilson 1983 and aciclovir in Gibson 1984). Meta-analysis of these 3 studies (n = 227) is shown in Analysis 2.1 and showed, surprisingly, no advantage of cryotherapy over placebo (RR 1.45, 95% CI 0.65 to 3.23) using a random-effects model (I^2 statistic = 60%). One of these trials (Gibson 1984) showed an unusually low cure rate (1/11) for cryotherapy consisting of 4 double freezes at intervals of 2 weeks. And the other (Wilson 1983) showed a relatively high cure rate (8/20) in its no-treatment group after 4 months of 'wait and see'. Subgroup analysis for hands and feet are shown in Analysis 2.2. Meta-analysis using data from 2 studies (Bruggink 2010; Wilson 1983) for hands only (n = 104) favoured neither intervention nor control (RR 2.63, 95% CI 0.43 to 15.94). The same analysis for data from Bruggink 2010 and Gibson 1984 (n = 110) on plantar warts (warts on the soles of the feet) likewise favoured neither intervention nor control (RR 0.90, 95% CI 0.26 to 3.07).

Satisfaction and quality of life

In Bruggink 2010, 69% (95% CI 53% to 82%) of participants were satisfied with treatment after cryotherapy. Only 22% (95% CI 12% to 38%) reported satisfaction after the wait-and-see (no treatment) protocol.

Adverse effects

Gibson 1984 and Wilson 1983 did not report adverse effects, but Gibson commented that cryotherapy can often be a painful treatment. In Bruggink 2010, 31% of participants reported considerable treatment burden after cryotherapy.

Comparison cryotherapy versus salicylic acid

Clinical cure

Four studies of 707 participants contributed to a meta-analysis of clinical cure of warts at all sites (Bruggink 2010; Bunney 1976b; Cockayne 2011; Steele 1988a). The results using a random-effects model showed the difference in cure rate between the 2 treatments was not statistically significant (RR 1.23, 95% CI 0.88 to 1.71; Analysis 3.1).

Subgroup analyses for hands and feet are shown in Analysis 3.2. Three studies (Bruggink 2010; Bunney 1976b; Steele 1988a) provided data for hands alone (n = 346), and neither treatment was superior (RR 1.17, 95% CI 0.80 to 1.70). Three studies (Bruggink 2010; Cockayne 2011; Steele 1988a) provided data for feet alone (n = 347), and again, no treatment appeared superior (RR 1.09, 95% CI 0.76 to 1.57). Bruggink 2010 was the only trial to show cryotherapy to be more effective than SA, and this was only in the 'common warts' subgroup. This subgroup (n = 78) included all non-plantar warts and was mostly made up of participants with warts on the hands (n = 70). The study results of both Cockayne 2011 and Bruggink 2010 appeared to show that SA is similar in efficacy to cryotherapy for foot warts, but in fact, neither SA nor cryotherapy was any better than no treatment for warts on the soles of the feet in Bruggink 2010.

Overall, there appeared to be no significant difference in terms of effectiveness between hands and feet (assessed comparing the overlapping of confidence intervals and the test for subgroup differences: P = 0.78).

Satisfaction and quality of life

Only Bruggink 2010 and Cockayne 2011 reported this outcome. Participants reported greater satisfaction with cryotherapy than SA in Bruggink 2010 (69% were satisfied after cryotherapy; 24%, after SA).

In Cockayne 2011, participants were asked to rate levels of satisfaction with treatment. The trial investigators reported this as follows: "At week 1, more patients were happy with SA than cryotherapy but also more patients were very happy with cryotherapy than SA. At week 3, more patients were unhappy with SA than with cryotherapy (none), and more patients were very happy with cryotherapy than SA. At week 12, more patients were unhappy with SA than with cryotherapy, and more were very happy with cryotherapy than with SA."

Adverse effects

In Bruggink 2010, participants experienced more adverse effects after cryotherapy than after topical SA application. In the report of the study, the adverse effects included "pain, blistering, scarring, skin irritation, skin pigmentation and crust. In the common wart

group, 31% (95% CI 19% - 46%) of the participants reported considerable treatment burden after cryotherapy and 54% (95% CI 39% - 68%) after SA treatment (P = 0.040)."

Comparison: cryotherapy treatment intervals (at 2, 3, and 4 weeks)

Clinical cure

Three trials of 313 participants (Bourke 1995; Bunney 1976a; Larsen 1996) examined the optimum treatment interval and showed no significant difference in long-term cure rates between treatment at 2-, 3-, and 4-weekly intervals. The results favoured neither a 3-week interval between cryotherapy treatments nor a 2-week interval (RR 1.03, 95% CI 0.77 to 1.37; Analysis 4.1). Similarly, the results favoured neither intervention nor control when comparing cryotherapy at 3 weeks versus 4 weeks (RR 1.42, 95% CI 0.76 to 2.63; Analysis 4.2) in 161 participants from 2 trials (Bunney 1976a; Larsen 1996); or 2 weeks versus 4 weeks (RR 1.29, 95% CI 0.70 to 2.38; Analysis 4.3) in 167 participants from the same 2 trials.

Only one trial (Berth-Jones 1992b) examined the important question of the optimum number of treatments, and this showed no significant benefit of prolonging three-weekly cryotherapy beyond three months (approximately four freezes) in a large population of adults and children with warts on the hands and feet.

Participant satisfaction

No study reported this as an outcome.

Adverse effects

In Bourke 1995, pain, blistering, or both, was reported in 29%, 7%, and 0% of those treated at 1-, 2-, and 3-weekly intervals, respectively. The higher percentage of reported adverse effects with a shorter interval between treatments might have been a reporting artefact due to participants being seen sooner after each treatment. Generally, data on adverse effects were sparse.

Comparison: aggressive versus gentle cryotherapy

Clinical cure

Four trials (Berth-Jones 1994; Connolly 1999; Hansen 1986; Sonnex 1988) examined the benefit of 'aggressive' versus 'gentle' cryotherapy. Although these trials were in different populations, on different types of warts, and used different definitions of aggressive and gentle (see below), we decided that the studies were similar enough to combine them in an analysis:

- Berth-Jones 1994 - double versus single freeze
- Connolly 1999 - 10-second freeze versus a gentle freeze
- Hansen 1986 - 2 minutes versus 15 seconds with a cryoprobe
- Sonnex 1988 - 20- or 30-second freeze with local anaesthesia versus 10- or 15-second freeze (hands and feet, respectively)

Pooling of data from the above 4 trials of 532 participants showed aggressive cryotherapy to be significantly more effective (RR 1.90, 95% CI 1.15 to 3.15; Analysis 5.1).

Participant satisfaction

No study reported this outcome.

Adverse events

Unfortunately, reporting of adverse effects was less complete, and pooling of data on pain and blistering was not possible. The impression from those trials that did comment on adverse effects was that, not surprisingly, pain and blistering were more frequent with aggressive cryotherapy.

One trial (Connolly 1999) of 126 participants noted increased morbidity in the aggressive freeze group, including 2 participants who required additional treatment for severe blistering. Pain was noted in more participants treated with an 'aggressive' freezing regime (10 seconds) compared with those treated with a 'gentle' regime (brief freeze) regime (RR 1.45, 95% CI 0.96 to 2.19; Analysis 5.2). And those treated with the aggressive regime had more blistering (RR 1.25, 95% CI 0.84 to 1.87; Analysis 5.2), although neither of these were statistically significant.

This translates to a 45% increase in pain, blistering, or both, in the 'aggressive' group and a number needed to harm (NNH) of 6.2 for pain and 10.3 for blistering. Five participants withdrew from the aggressive group and one from the gentle group due to pain and blistering.

Comparison: cryotherapy + salicylic acid/lactic acid (SA/LA) versus SA/LA alone

Clinical cure

Two trials (Bunney 1976b; Steele 1988a) compared cryotherapy plus SA/LA with topical SA/LA alone on hand and foot warts. For hand warts only (n = 271), cryotherapy + SA/LA was significantly better in terms of cure of warts than SA/LA alone (RR 1.25, 95% CI 1.02 to 1.53; Analysis 6.1), but this was not the case for foot warts (n = 47) where neither the intervention nor the control was favoured. There were much smaller numbers for feet than for hands; the CIs were wide, and so there was less power to detect a difference should one have existed (RR 1.37, 95% CI 0.74 to 2.52; Analysis 6.1). Overall, for hand and foot warts (n = 328),

cryotherapy + SA/LA was more effective than cryotherapy alone (RR 1.24, 95% CI 1.07 to 1.43; Analysis 6.1). There appeared to be no significant difference in terms of effectiveness between the different sites (assessed comparing the overlapping of confidence intervals and the test for subgroup differences: P = 0.78).

Participant satisfaction

No trials reported this outcome.

Adverse events

Steele 1988a reported that 22.5% of participants receiving liquid nitrogen suffered pain after the first week of treatment compared with 15.8% receiving combined treatment and only 2.6% receiving paint only (P < 0.05). Reports of adverse effects were similar after the second week of treatment (there were no significant differences between the groups).

Comparison: cryotherapy + SA/LA versus cryotherapy

Clinical cure

Two trials (Bunney 1976b; Steele 1988a) compared cryotherapy plus SA/LA with cryotherapy alone on hand and foot warts. There was some heterogeneity between studies (I^2 statistic = 52%), and the result favoured neither the intervention nor the control for hand warts (RR 1.25, 95% CI 0.99 to 1.57; Analysis 7.1). For the treatment of foot warts, in 1 study (Steele 1988a) of 51 participants, there was no significant difference between the 2 treatments (RR 0.97, 95% CI 0.60 to 1.57; Analysis 7.1). Overall, for both hands and feet (n = 328), the difference was not statistically significant (RR 1.20, 95% CI 0.99 to 1.45; Analysis 7.1).

Participant satisfaction

This outcome was not reported in any trial.

Adverse events

Steele 1988a reported adverse events (see above).

Comparison: intralesional interferon versus placebo

Cure rate

Of the six trials (Analysis 13.4), four were with interferon-alpha and one each with interferon-beta and interferon-gamma. The latter two trials (Lee 1990; Niimura 1990) both used a within-participant design. Four of the six trials involved refractory warts. Pooled data from 3 of the interferon-alpha trials, which contributed 150 participants, failed to show any significant advantage over placebo (RR 0.87, 95% CI 0.56 to 1.33; Analysis 8.1; random-effects model; I^2 statistic = 0%). The fourth interferon-alpha trial (Pazin 1982) involved only one participant in whom individual warts were randomised to treatment or placebo injections; the results of this study (see Analysis 13.4) should be treated with extreme caution.

Participant satisfaction

This outcome was not reported in any study.

Adverse events

The Varnavides 1997 study, which used a relatively low-dose interferon-alpha, noted flu-like symptoms that lasted for a few hours in all participants in the active treatment group and 1.5% of the placebo group.

Lee 1990 reported flu-like symptoms in 71% and 26% of participants in the high- and low-dose groups, respectively.

In Vance 1986, there was local pain from the injections. In the high-dose group, 33 participants (80%) noted adverse reactions, 16 of whom complained of local pain. In the low-dose group, 20 (51%) had reactions, 11 of whom described local pain. In the placebo group, 26 participants (62%) had reactions, 11 of whom had local pain. Transient (during therapy) minor depression in white blood cell count was also noted as well as an elevation in the hematocrit and aminotransferase levels.

Redness and itching alone was reported in 7 of 64 warts (11%) in the Niimura study (Niimura 1990).

Comparison: topical dinitrochlorobenzene (DNCB) versus placebo

Cure rate

Pooled data from the 2 small trials (Cancino 1989; Wilson 1983) comparing DNCB with placebo (Analysis 13.5) showed DNCB to be more than twice as effective than placebo (RR 2.12, 95% CI 1.38 to 3.26; Analysis 9.1). There was some evidence of efficacy, but this was based on limited data from 80 participants.

Participant satisfaction

This outcome was not reported in any study.

Adverse events

There were no precise data concerning adverse effects in either of these trials.

Cancino 1989 commented that 6/20 (30%) participants treated with DNCB were sensitised only after the second application of

2% DNCB to the warts. All of them subsequently experienced significant local irritation with or without blistering when they were treated with 1% DNCB. None withdrew from the study.

Comparison: duct tape versus placebo

Cure rate

Two trials evaluated duct tape versus placebo (Analysis 13.7). One trial (de Haen 2006) investigated duct tape compared to a non-medicated corn pad (used as the placebo) in a community setting among 103 children. The second trial (Wenner 2007) compared duct tape with moleskin to moleskin (a non-medicated dressing used as the placebo) alone in 90 adults. The results of these 2 trials were pooled together (n = 198 participants) and identified no significant effect of duct tape (RR 1.43, 95% CI 0.51 to 4.05; Analysis 10.1).

Participant satisfaction

de Haen 2006 assessed participant satisfaction with the therapy. Of the child participants, 81% noted that the duct tape would not stick.

Adverse events

de Haen 2006 reported a higher incidence of adverse events in the duct tape group (data were reported for only 47 out of 51 participants in this group; the discrepancy in numbers was accounted for by "missing values"). All 52 participants in the placebo group were accounted for.

In the intervention group, skin reaction caused by the tape led to adverse events. Three participants reported erythema; three reported itching; one reported eczema; one reported bleeding; and one other participant was reported as having a skin reaction classed as "other". This was compared with no reports of skin reactions caused by the placebo intervention.

All participants were instructed to soak and rub the wart with a pumice stone once a week. Elevan participants had pain, and 8 participants had bleeding associated with pumice stone use in the intervention group, compared with 9 who had pain and 4 who had bleeding associated with pumice stone in the placebo group.

Wenner 2007 reported two cases of either numbness of the finger or bleeding, but the number of events in each group was unclear.

2. Individual study results

A number of studies were not combined in meta-analyses because the study designs were too dissimilar in terms of participants or the intervention used, or they compared more than one intervention or new non-established interventions. These studies did not contribute data to the meta-analyses, but we present an overview of the main study results, organised by intervention type, below.

Duct tape versus cryotherapy

Cure rate

One trial (Focht 2002; see Analysis 13.7) compared cryotherapy and occlusive treatment with duct tape in 61 children and young adults. The duct tape was applied for 6.5 days every 7 days, and cryotherapy was given for 10 seconds every 2 to 3 weeks up to a maximum of 6 times. Cure rates were 22/30 (71%) and 15/31 (46%), respectively, which translates to a 52% increase in cure rate in the participants using the duct tape (RR 1.52, 95% CI 0.99 to 2.31; Analysis 11.1).

Participant satisfaction

No quantitative data were reported, but duct tape treatment was generally well-received by the participants.

Adverse events

Focht 2002 reported pain (ranging from mild to severe) in all 25 cryotherapy participants.

Pulsed dye laser

Cure rate

Three trials evaluated the use of pulse dye laser treatment (Analysis 13.8). One trial (Robson 2000) involving 40 participants showed no significant difference in cure rates between 4 pulsed dye laser treatments at monthly intervals and 'conventional treatment' with either cryotherapy or cantharidin (66% vs 70% of warts, respectively). Another study (Aum 2006) investigated pulsed dye laser treatment or no laser treatment after intralesional bleomycin in 24 participants with recalcitrant periungual warts. This small study found that all the participants treated were cured in both arms, which may suggest the treatment effect was due to intralesional bleomycin.

The other study (Passeron 2007) investigated pulsed dye laser treatment or no laser treatment after cryotherapy in 35 participants. It assessed ordinary warts of the hands and feet and found the cure rate in the laser and cryotherapy group was 6/19 (32%) compared to 3/16 (19%) in the cryotherapy-only group, which was also not statistically significant (P = 0.46). These studies provided further evidence to suggest the cure rate for cryotherapy generally lies between 20% and 50%.

Adverse events

Robson 2000 reported no significant adverse effects in either treatment group.

Aum 2006 reported less pain (the visual analogue score was 15.75 compared to 18.42) and haemorrhagic blistering in the intralesional bleomycin and laser treatment group compared to the bleomycin-only treatment group.

Passeron 2007 found increased pain (the visual analogue score was 4.7/10 compared to 1.5/10) and less tolerance (8.31 compared to 9.81) in the laser treatment group. Crusting, purpura, and petechiae was also reported in the pulsed dye laser group.

Intralesional bleomycin versus placebo

Cure rate

Evaluation of four of the seven included trials (Analysis 13.3) of intralesional bleomycin was hampered by the fact that they used warts rather than participants as the unit of analysis. The results of these 4 trials (Bunney 1984; Hayes 1986; Rossi 1981; Munkvad 1983) varied widely, with cure rates between 16% and 94% of warts, and should be interpreted with considerable caution (Analysis 13.3). The trials used different concentrations, delivery systems, and total doses of bleomycin, but none of these factors seem to correlate with their rates of success.

Two trials (Perez 1992; Munkvad 1983) of the four trials (Bunney 1984; Munkvad 1983; Perez 1992; Rossi 1981) that compared bleomycin with placebo reported that bleomycin was ineffective compared with placebo.

Munkvad 1983, used a within-participant randomised design on 108 warts in 62 participants, and bleomycin achieved a cure in 4/22 in the bleomycin + saline group (18%), 5/36 in the bleomycin in oil group (14%), 8/19 in the saline placebo group (42%), and 10/22 in the oil placebo group (45%) for warts assessed at 3 months. Only 1 trial of 31 participants (Perez 1992) used participants as the unit of analysis and demonstrated a cure rate of 15/16 (94%) that was not significantly different from the 11/15 (73%) achieved with placebo injections of saline (RR 1.28, 95% CI 0.92 to 1.78; Analysis 12.1).

Adverse events

No precise data on adverse effects were provided in any of the trials. Munkvad 1983 reported 'adverse events' in 19/62 (31%) of all participants, but did not specify what the adverse events were or their distribution between the active treatment and placebo groups. Three of the trials (Bunney 1984; Hayes 1986; Rossi 1981) reported that pain was experienced by most participants. In two of the trials (Perez 1992; Rossi 1981), local anaesthetic was used routinely prior to the injection of bleomycin. Hayes 1986 reported pain in most participants irrespective of dose. In the trial by Bunney 1984 in which all 24 participants received bleomycin, 1 withdrew because of the pain of the injections, and 1 withdrew because of pain following injections.

Intralesional bleomycin versus cryotherapy

Cure rate

Two trials (Adalatkhah 2007; Dhar 2009), both using a left/right within-participant design, evaluated the use of bleomycin compared to cryotherapy . Both trials (n = 161 participants) reported that bleomycin was more effective than cryotherapy. Participant satisfaction with the therapy was not reported in either trial. Adverse events resulting from bleomycin therapy were observed. In Adalatkhah 2007, there were 3 reported significant adverse events (7%) in the bleomycin group and 2 significant adverse events (5%) in the cryotherapy group, but the type of event was unclear. In Dhar 2009, every participant reported some pain (5% in the bleomycin group and 12% in the cryotherapy group). Dyspigmentation developed in 91% of the participants in the cryotherapy group and 46% of the bleomycin participants.

Topical 5-fluorouracil (5-FU)

Cure rate

Seven trials (Analysis 13.10) evaluated the efficacy of topical 5-FU, but one trial did not report statistical analysis of the results (Artese 1994). The three trials (Hursthouse 1975; Schmidt 1981; Wolff 1980) that compared 5-FU with placebo (Analysis 13.10) showed it to be superior with cure rates in the order of 50%, but 1 of these trials (Hursthouse 1975) used a left/right within-participant design preventing meaningful pooling of data. Schmidt 1981 used a preparation of 5-FU and SA combined, yielding cure rates of 46% versus 19%. In Wolff 1980, 5-FU plus SA treatment gave a significantly better cure rate of 57% in the intervention group versus 43% in the placebo group.

In one trial (Bunney 1973) involving 95 participants, 2 different concentrations of 5-FU were compared with standard topical SA/LA for mosaic plantar warts (warts on the feet). The cure rates for all 3 treatments were close to 50% and not significantly different. A more recent trial (Salk 2006) of 40 participants compared 5-FU to tape occlusion and found that there was a high cure rate at 6 months in the 5-FU group: 17/20 (85%) compared to 2/20 (10%) in the tape occlusion group.

One trial compared topical 5-FU to placebo after cryotherapy (Luk 2006). This study of 80 participants found a cure rate of 12/40 (30%) in the 5-FU group versus 17/40 (43%) in the placebo group. This was not statistically significant and implies no additional benefit of 5-FU. Artese 1994 compared 5-FU with cautery and found that cure rates were better in the 5-FU group (85% versus 66%).

Adverse events

Hursthouse 1975 noted onycholysis (nail detachment) in 11 of 64 participants using 5-FU, especially when it was used for warts near the nails. Artese 1994 reported that local irritation was noticed by most participants, but gave no precise figures. This may have been due to SA or the combination of SA and 5-FU. Luk 2006 reported 21 episodes of blistering (53%) and 19 episodes of moderate/severe pain (48%) among 40 participants in the cryotherapy and 5-FU group, while there were 14 episodes of blistering (35%) and 11 episodes of moderate/severe pain (28%) among 40 participants receiving cryotherapy only. Salk 2006 reported more episodes of pain (12/20, i.e. 60%) in the 5-FU treatment group compared to (9/20, i.e. 45%) in the tape occlusion group. The other two studies did not mention adverse effects.

Intralesional 5-fluorouracil

Cure rate

Two trials evaluated the efficacy of intralesional 5-FU compared to placebo (Analysis 13.11). One trial (Yazdanfar 2008) used a left/right within-participant design (which cannot be easily presented in Review Manager (RevMan)), but found cure rates of 22/34 (64%) in the 5-FU group versus 12/34 (35%) in the placebo group. A larger trial (Iscimen 2004) found a much higher cure rate in the treatment group: 118/169 (70%) compared to 43/146 (29%) in the control group, and this was statistically significant ($P < 0.001$). Data from these two studies could not be pooled in a meta-analysis due to differences in study design.

Adverse events

Yazdanfar 2008 reported 6 cases of pain, erythema, and oedema (18%); 6 cases of hyperpigmentation (18%); 1 case of hypopigmentation (3%); 2 cases of ulceration (6%); and 2 cases of scarring (6%) in the 5-FU group, while in the placebo group there were 3 cases of pain, erythema, and oedema (9%) and 1 case of hypopigmentation (3%).

Iscimen 2004 reported no significant systemic or local adverse events, only pain and burning immediately at the injection site.

Photodynamic therapy (PDT)

Five RCTs of PDT were included in the review (Analysis 13.6); methodological heterogeneity prevented pooling of any of the data.

Cure rate

The 2 older trials from the 1970s used different dyes with dimethyl sulphoxide (DMSO) and different light sources. One of the trials (Veien 1977) used a left/right within-participant design and reported complete resolution (100%) of the placebo PDT half compared to 40% resolution in the PDT-treated half. The other (Stahl 1979) showed equally disappointing results with PDT and topical SA with creosote.

Two more recent studies evaluated PDT with aminolevulinic acid (ALA) for refractory warts. Both trials used warts as the unit of analysis. The first trial (Stender 1999), described as a pilot study, compared a number of different light sources with 4 treatments of cryotherapy and showed PDT to be superior, with cure rates of up to 73% of warts compared with 20% in the cryotherapy group. The second study (Stender 2000) from the same research team involved 45 adults with refractory warts and compared ALA-PDT with placebo PDT and showed cure rates of 64/114 (56% of warts) and 47/113 (42% of warts), respectively, which was statistically significant ($P < 0.05$). All warts were also treated with paring and topical SA ('Verucid'). Wart area was also measured photographically and shown to be significantly more reduced in the active group compared to the placebo group.

Another trial (Fuchs 2004) was an article that the trial investigator sent to the review authors after we identified his conference abstract. This trial was a study of 80 participants with SA and curettage pretreatment followed by randomisation to 4 different treatment arms, including (a) 5-aminolevulinic acid (5-ALA) and visible light, (b) 5-ALA and water-filtered infrared-A (wIRA), (c) placebo cream and visible light, and (d) placebo cream and wIRA. There were higher cure rates with placebo cream (2/16 (12.5%)) than with 5-ALA cream (0/14 (0%)), which suggests that PDT did not improve cure rate. They found that those treated with wIRA had a much higher cure rate (16/38 (42%)) compared to those treated with visible light (2/30 (7%)).

Adverse events

Only three of these trials commented on adverse events. Precise data were provided by 1 trial only (Stender 2000) in which severe or unbearable pain during treatment was reported in an average of 17% of warts with active treatment and an average of 4.2% of warts with placebo PDT. Burning and itching during treatment and mild discomfort afterwards were reported universally with ALA PDT. All participants with warts on the feet were able to walk after treatment. Fuchs 2004 evaluated pain using a visual analogue score (VAS), and they found that the wIRA group experienced high pain compared to the participants that were not treated with wIRA (mean VAS = 92 vs 41 out of 100).

Topical zinc

Cure rate

Two trials evaluated topical zinc treatments for cutaneous warts (Analysis 13.9). One trial (Sharquie 2007) evaluated zinc sulphate treatment compared to water placebo, and it found that there was

a higher cure rate with topical zinc compared to water, which appeared to be dependent on the concentration of zinc solution used (10% zinc sulphate: 7/16 (44%), 5% zinc sulphate: 4/29 (14%), placebo: 1/22 (5%)). The other trial (Khattar 2007) studied 20% zinc oxide compared to 15% SA in 44 participants, and it found a similar cure rate in both groups: 8/22 (36%) and 8/22 (36%).

Adverse events

Sharquie 2007 reported adverse events only in the zinc sulphate treatment group; 7 participants had itching or pain (16%), and 6 participants had hypopigmentation (13%). Khattar 2007 reported numerous adverse events, including 10 participants with erythema (45%), 12 participants with swelling (55%), 7 reporting scaling (32%), and 4 participants with blackening in the zinc oxide treatment group (18%). In the SA group, 17 participants experienced erythema (77%); 5 participants experienced swelling (23%); 14 participants experienced scaling (64%); 1 participant experienced itching (5%), 1 participant experienced tenderness (5%); and 2 participants experienced blackening (9%).

Miscellaneous treatments

This group contains a heterogeneous collection of trials of less commonly-used topical treatments, few of which of which appear to be of any great relevance to everyday practice. For most of these trials, there was little evidence of effectiveness of the intervention assessed (Analysis 13.12). Some of these trials warrant further brief comment.

Phenol versus cryotherapy

Of the 21 trials that evaluated cryotherapy (Analysis 13.2), 1 study (Banihashemi 2008) evaluated the use of 80% phenol compared to cryotherapy, and the cure rate was similar in the 2 groups: 20/30 (67%) in the cryotherapy group and 19/30 (63%) in the 80% phenol group. Banihashemi 2008 reported an increased incidence of adverse events with phenol treatment (15/30, i.e. 50%) compared to cryotherapy (9/30, i.e. 30%). In the phenol-treated group, these events included burning in 7 participants (23%), which led to 3 (10%) dropping out of the study; erythema; and hypopigmentation; and in the cryotherapy group, there were reports of pain, hyperpigmentation, and hypopigmentation.

Smoke exposure versus cryotherapy

A pilot study (Rahimi 2008) that studied cryotherapy compared to smoke from burnt *Populus euphratica* leaves found that the cure rate was 13/30 (43%) in the cryotherapy group and 16/30 (53%) in the exposure-to-smoke group. This difference was not statistically significant. There were 11 cases (37%) of pain; 6 cases (20%) of blistering in the cryotherapy group; and 3 cases (10%) of pruritus in the smoke-exposure group.

Silver nitrate

Silver nitrate remains a fairly popular topical treatment for viral warts, particularly amongst podiatrists, although evidence for its efficacy remains fairly scant. We found one RCT (Yazar 1994) that should be mentioned. From the paper, this appears to have been a randomised and, at best, single-blind, placebo-controlled trial in which silver nitrate (percentage concentration not given) was applied every three days for an unspecified period with the placebo being black ink. The outcome was assessed one month after the last application. The complete cure rate was 15/35 (43%) in the treatment group and 4/35 (11%) in the placebo group.

Alpha-lactalbumin-oleic acid (ALOA)

Gustafsson 2004 compared alpha-lactalbumin-oleic acid (ALOA) with placebo. This employed the topical application of an unusual hybrid molecule (consisting of a combination of alpha-lactalbumin from human breast milk and oleic acid) said to be lethal to a wide range of transformed cells, but harmless to normal ones. The trial appeared to have been properly randomised and double-blind, but the analysis focused on the main outcome of > 75% reduction in wart volume rather than the more relevant complete clearance of warts. Unfortunately, the trial defaulted to an open-label design after three months making the long-term follow-up data potentially biased. Reported data showed that whilst 100% of those in the active treatment group experienced > 75% reduction in wart volume, only 21% of lesions in the treatment group resolved completely, and only 9/20 (45%) participants with active treatment experienced the resolution of at least 1 wart compared with 3/20 (15%) in the placebo group (RR 3.0, 95% CI 0.95 to 9.48).

Intralesional antigen injection

Horn 2005 was an RCT of the use of intralesional antigen injection for warts (a form of local immunotherapy designed to elicit an immune reaction in warts injected with candida, mumps, or trichophyton antigens). This was a complex study with four treatment arms (antigen with and without interferon (IFN) and placebo with and without IFN), which involved up to five injections given at three-weekly intervals into the largest wart on each participant. Blinding involved only the participants and not the investigators, introducing a source of potentially-significant bias. The main outcome reported was > 75% reduction in wart surface area at the end of treatment. This is of questionable relevance to participants. Participants were evaluated at each episode of treatment, and no long-term follow up was reported. Two hundred and one participants with refractory warts completed the trial. Of the participants, 57/95 (60%) injected with antigen with or without additional interferon experienced the resolution of at least 1 wart compared with 25/106 (24%) of participants injected with saline or IFN alone. The number of participants who experienced

complete clearance of all warts was difficult to ascertain from the study, but it appeared to have been 21/95 (22%) in the treatment groups and 11/106 (10%) in the 'placebo' groups.

Imiquimod

Topical imiquimod, a novel immunomodulator drug, is an established treatment for genital warts. Two dose-finding RCTs for non-genital warts were obtained from 3M, the manufacturers of imiquimod. There was no significant difference in the proportion of participants whose warts were cured when analysed by ITT or per protocol when comparing different treatment regimens of 5% imiquimod cream (Aldara) for either common warts (Aldara 3M 2000b) or 'plantar' (feet) warts (Aldara 3M 2000a). For 'plantar' warts, complete clearance ranged from 10.0% to 12.8% in the active treatment groups, compared with 2.9% in the vehicle control group (Aldara 3M 2000a). For common warts, clearance ranged from 9.5% to 10% in the active treatment groups, compared with 4.9% in the control group. Therefore, there was no evidence for effectiveness of this intervention.

One other trial (Erbagci 2005) reported as a conference abstract suggested that 5% topical imiquimod showed a significant reduction in the average number of warts compared to vehicle cream ($P < 0.05$), but no numbers regarding cure rate were reported. We contacted the author, but there was no response.

Surgery (curettage and excision)

Surgical excision and curettage with cautery have certainly been recognised treatments for common warts in the past, but fewer dermatologists advocate these treatments now due to the morbidity of the procedure, particularly scarring, and the anecdotal experience of high rates of recurrence. We did not identify any controlled trials or RCTs that evaluated these treatments.

Glutaraldehyde, formaldehyde, podophyllotoxin, cantharidin, diphencyprone, and squaric acid dibutylester

No RCTs studying these treatments were identified by our searches.

Sensitivity analysis

The limited evidence for each comparison available meant that a sensitivity analysis of findings according to risk of bias would have been of limited value; therefore, we did not carry out sensitivity analyses.

DISCUSSION

Summary of main results

There were many more trials (85 studies with a total of 8724 participants) and a much wider variety of treatments and trial designs included in this review than in previous versions. This heterogeneity and the fact that much of the data were at high risk of bias made a meaningful synthesis of the results problematic. In many studies, outcomes other than those we specified were reported, or results were presented in such a way that data could not be extracted and used in calculations (and no further information was available to us). For these reasons, many trial results could not be put into graphs, and we presented them as summary tables.

Trials of topical salicylic acid (SA) showed a definite but modest effect for warts at all sites, possibly more marked for warts on the hands than for warts on the feet (often described as 'plantar warts' in the studies), although statistical tests confirmed that there was no significant difference in effectiveness between the different sites. Adverse effects occurred as a result of treatment. In 1 trial (Steele 1988b) that compared a mixture of monochloroacetic acid and 60% SA with placebo, 1 of the 29 participants in the active treatment group developed cellulitis. This is the only study that reported cellulitis as an adverse effect of SA, and as it was a single event, it was difficult to be sure of its significance, especially since the SA was mixed with monochloroacetic acid in this study.

Data from trials of cryotherapy were less consistent and more difficult to interpret. Bruggink 2010 was a new study included for this update, and its results taken on their own clearly supported the use of cryotherapy over SA or no treatment for hand warts, but not for 'plantar warts' (feet). In fact, neither SA nor cryotherapy was any better than no treatment for warts on the soles of the feet in this trial. Results from Cockayne 2011 showed no statistically-significant difference between cryotherapy and SA for plantar warts. This trial did not include a control group.

When data from these newer trials were pooled with all the previously-included data, there remained no clear, statistically-significant difference in effectiveness between cryotherapy and placebo (or no treatment) for all sites and also in separate subgroup analyses for hands and feet. Likewise, all the data combined showed no clear statistically-significant difference in effectiveness between cryotherapy and SA for all sites and also in separate subgroup analyses for hands and feet. It was difficult to draw firm conclusions when looking at all of these meta-analyses together.

There was no significant difference between 2-, 3-, or 4-week cryotherapy treatment intervals. Aggressive cryotherapy was more effective, but with increased morbidity in the aggressive freeze group.

In Bruggink 2010, participants reported a significant burden of adverse effects after cryotherapy, including pain, blistering, and scarring; however, participants reported greater satisfaction with cryotherapy than SA. In Cockayne 2011, as the study progressed, more participants were happy with cryotherapy than SA.

A meta-analysis of three trials showed no significant advantage of intralesional interferon-alpha compared with placebo.

Two new trials (Adalatkhah 2007; Dhar 2009) of intralesional bleomycin versus cryotherapy using within-participant, left/right comparisons were included in this review. Both trials showed bleomycin to be significantly more effective than cryotherapy. Pain and depigmentation occurred with both therapies. The effectiveness of bleomycin remains uncertain, however, as the design of these trials makes their results more difficult to interpret. The data from other trials of intralesional bleomycin are both heterogeneous and inconsistent (Analysis 13.3). The only trial of intralesional bleomycin that used participants rather than warts as the unit of analysis (Perez 1992) favoured neither intralesional bleomycin nor control.

Two trials in 80 participants, comparing topical dinitrochlorobenzene with placebo, showed that it was more than twice as effective as placebo, but with a risk of local irritation due to sensitisation by the dinitrochlorobenzene.

Duct tape gained considerable favour following the publication of Focht 2002 as it is a safe and simple treatment that is easy to apply. However, the trial was relatively small, and the length of freeze in the cryotherapy group was considered by some to be inadequate (Abramovits 2003; Buccolo 2003). An unspecified number of outcome assessments were carried out over the telephone, and it is not entirely clear how long after the treatment period this was done. In updating this review, two trials of clear duct tape occlusive treatment versus placebo (de Haen 2006; Wenner 2007) were included, which show fairly convincingly that this treatment is not as effective as the single earlier trial (Focht 2002) might have suggested. These two later trials (de Haen 2006; Wenner 2007) were not without methodological problems either. van Cleave 2006 reviewed the methodology used in de Haen 2006, highlighting the small sample size (making the study underpowered). The Wenner 2007 study had a number of limitations, which were discussed by the investigator in the study report; the mechanism of action of duct tape is unknown but may be related to the type of adhesive used. The two interventions may not have been directly comparable as some commentators have pointed out that the adhesive used in clear duct tape is not the same as standard silver duct tape (industrial, contractor grade duct tape) (Samlaska 2011). It seem this debate is likely to continue (Gibbs 2012).

We summarised the results of studies that could not be combined by meta-analysis. Cure rates for pulsed dye laser treatments were not statistically significant. The efficacy of topical 5-fluorouracil was unclear. Intralesional 5-fluorouracil was investigated in 2 within-participant design trials in which there was higher cure rate in the 5-fluorouracil groups.

Two trials evaluated topical zinc treatments; there was a higher cure rate with topical zinc compared to water and a similar cure rate when compared to topical SA acid in both groups: 8/22 (36%) and 8/22 (36%).

One study evaluated the use of 80% phenol compared with cryotherapy; the cure rate was similar in the 2 groups but with more adverse events with phenol treatment.

A pilot study compared cryotherapy to smoke from burnt *Populus euphratica* leaves. The cure rate was not statistically significant.

There is scant evidence for silver nitrate, which was used in 1 RCT; the complete cure rate was 15/35 (43%) in the treatment group and 4/35 (11%) in the placebo group.

Different treatment regimens of topical imiquimod were tested with no significant difference in the proportion of participants whose warts were cured with each regimen.

Comment on the other two trials (Gustafsson 2004; Horn 2005) was made because they were both published RCTs and seemed to promise new and effective treatments. Gustafsson 2004 compared alpha-lactalbumin-oleic acid (ALOA) with placebo; the main outcome was a > 75% reduction in wart volume. All of those in the active treatment group experienced > 75% reduction in wart volume, but only 21% of lesions in the treatment group resolved completely. The number of participants whose warts completely cleared is not clear from the data, and overall, there is little to support the trial authors' optimistic conclusion that 'ALOA has potential as a novel therapeutic tool in the treatment of papillomas and other tumours'.

Sandra Johnson and Thomas Horn's group was the first to publish an RCT (Horn 2005) of the use of intralesional antigen injection for warts (a form of local immunotherapy designed to elicit an immune reaction in warts injected with candida, mumps, or trichophyton antigens). The cure rate for intralesional antigen injection for warts was 21/95 (22%) in the treatment groups and 11/106 (10%) in the placebo groups. For an elaborate and presumably fairly painful and expensive treatment, this does not appear to be a treatment with any striking advantages.

We did not identify any RCTs that evaluated surgery (curettage, excision), glutaraldehyde, formaldehyde, podophyllotoxin, or cantharidin.

Overall completeness and applicability of evidence

There were 13 trials of topical SA with or without placebo and 20 trials of cryotherapy. Two new trials (Bruggink 2010; Cockayne 2011) have furnished a fuller and more realistic picture than we had previously about the effectiveness of SA and particularly cryotherapy. There is now a reasonable number of trials for SA versus placebo. The evidence for cryotherapy is a little less complete but enough to suggest that it has a place in the routine treatment of warts.

Many of the treatments were unusual and are unlikely to be used in regular clinical practice (e.g. intralesional antigen, interferons, smoke box using smoke from burnt *Populus euphratica* leaves).

Quality of the evidence

We identified several limitations in the body of evidence identified, and as a result, we were unable to draw robust conclusions. Although we included 85 trials, the very wide range of treatments used and methodological heterogeneity of many of the trials made pooling of data in meta-analyses problematic; therefore, each of our comparisons use data derived from relatively few trials.

The methodological quality of the evidence was poor. Despite a large number of published trials, only a minority were properly randomised (we excluded quasi-randomised studies from this review), and the majority of the trials that fit our inclusion criteria had unclear or inadequate allocation concealment. We were also unable to obtain further information from the trial investigators. The beneficial effects of treatments in these trials were likely to have been overstated. Also, many trials employed the use of within-participant randomisation (left and right randomisation), using individual warts or change in size of warts as the unit of analysis, which prevented the use of these data in our meta-analyses. Many trials also employed inadequate blinding of participants or outcome assessors, which is also likely to have exaggerated intervention effects.

For all these reasons, the conclusions of this review cannot be robust, and we discuss the implication of this for future research (Implications for research). There are tentative but definite pointers from individual studies to suggest that two widely-used therapies, cryotherapy and SA, are effective, although, overall, our analyses of pooled data did not support the supposition that these therapies are more effective for hand warts than warts on the feet.

Potential biases in the review process

Steps were taken to reduce bias in the review process. We expanded our search to include additional databases in addition to contacting noted experts in the field and companies for additional trials. In the trial selection process, two authors independently screened all titles and abstracts for suitable trials, and where there was discrepancy in inclusion, the third author made the decision.

Agreements and disagreements with other studies or reviews

Most of our conclusions were unchanged from the previous publication of this Cochrane systematic review (Gibbs 2006) and a previous publication that incorporates data from the studies included in this review (Kwok 2011). Important new data on cryotherapy and SA were included in this update, and there was new evidence for the efficacy of SA and cryotherapy from two large studies (Bruggink 2010; Cockayne 2011).

Our findings are also largely consistent with a recently-published Clinical Evidence review (Loo 2009), with the important exception of the newer data on cryotherapy and SA, which were not included in Loo 2009.

AUTHORS' CONCLUSIONS

Implications for practice

More recent data from trials of cryotherapy and SA have provided better evidence for the use of these treatments. The relatively high rate of cure in control groups supports the notion that no treatment and awaiting spontaneous resolution is a very reasonable option, especially for recently-acquired warts that are not causing too much bother. Warts that do not resolve spontaneously after many months to a year are probably less likely to do so without treatment.

Salicylic acid appeared to be both effective and safe, but only modestly effective in terms of size of effect, and this is particularly true for plantar warts. Overall, the data for SA remains the most consistent.

The data on cryotherapy is more limited and less consistent, with only one trial (Bruggink 2010) showing it to be superior to placebo or no treatment, and this was only for warts on the hands; the same trial showed cryotherapy to be more effective than SA for hand warts.

The EVERT study (Cockayne 2011), which compared cryotherapy versus SA (with no placebo arm), showed that SA is similar in efficacy to cryotherapy for plantar warts.

No trial showed cryotherapy to be any more effective than placebo for plantar warts alone, and in view of this, the continued use of cryotherapy for plantar warts is highly questionable. Indeed, only one trial (Bunney 1971, of SA) showed any treatment to be effective compared to placebo for plantar warts, and even then the size of effect was modest. Thus, no treatment seems to be particularly effective for plantar warts.

Pooled data from all relevant trials involving the treatment of warts at all sites showed no significant difference between cryotherapy and placebo, but also no difference between cryotherapy and SA; the latter suggesting that cryotherapy can also, like SA, be modestly effective.

It is difficult to draw firm conclusions from all these contradictory data about the different roles of SA and cryotherapy, but it remains true that there is still only limited evidence to support the use of cryotherapy, especially considering it is a more painful, hazardous, and expensive treatment when compared with SA. On the other hand, even though there is less evidence for its effectiveness, cryotherapy may work where SA has failed, and data from one trial (Bruggink 2010) showed this to be the case for warts on the hands.

The limited data on adverse effects, such as pain and blistering, suggest that these are more common with cryotherapy than with SA. However, it is also important to point out that participant satisfaction data suggest that these adverse effects do not seem to worry participants. More aggressive cryotherapy appears to be

more effective than gentle cryotherapy, but with an increased risk of adverse effects. There is some evidence that SA combined with cryotherapy is more effective than SA alone.

Good quality data for most other treatments are still lacking.

Evidence for the efficacy of intralesional bleomycin remains limited. Two more recent left-right studies showed it to be more effective than cryotherapy, so taking into account the fact that caution is required when interpreting trials with this sort of design, there may be a place for bleomycin in selected people with refractory warts.

Topical immunotherapy with dinitrochlorobenzene, intralesional 5-fluorouracil, topical zinc, and silver nitrate are not commonly-used treatments. The limited available evidence suggest that these treatments may have a therapeutic effect, but none have any clear advantage over SA and cryotherapy. The limited data on dinitrochlorobenzene suggest that it might be substantially more effective than cryotherapy and SA (see Implications for research), and so, again, there may be a place for topical immunotherapy with dinitrochlorobenzene (or other contact sensitisers, such as diphencyprone or squaric acid dibutylester, now probably in more common use than DNCB for refractory warts in specialist centres). The risk of troublesome allergic contact dermatitis (in the personnel who apply treatment, as well as those treated) needs to be taken into account when considering this treatment.

There is insufficient evidence to support the use of topical 5-fluorouracil, pulsed dye laser, photodynamic therapy, 80% phenol, 5% imiquimod cream, intralesional antigen, and topical alpha-lactalbumin-oleic acid.

Intralesional interferon did not appear to be effective.

There is no very convincing evidence that occlusive treatment with various types of duct tape is effective, and two relatively-recent trials that were newly included (de Haen 2006; Wenner 2007) showed no significant difference in effectiveness between clear duct tape and placebo.

Implications for research

The problem of cutaneous warts lends itself well to randomised control trials because it is common and not-life threatening.

Despite a large number of published trials, only a minority are properly randomised and have an overall low risk of bias.

This updated review highlighted an apparent difference in response to treatment of warts at different body sites. Plantar warts (on the soles of the feet) appear to be a particular challenge, and any new trials should either concentrate on one body site or recruit sufficient numbers of participants with warts at each site to produce statistically-meaningful results.

A reasonable amount of data are now available for the most commonly-used treatments of cryotherapy and SA, although many of the included trials are small and have a significant risk of bias. Furthermore, larger studies of these treatments compared with each other and with placebo (using standardised treatment regimens) would be helpful.

Second- and third-line treatments are treatment for warts used after the initial treatment (first-line treatment) has failed. Finding treatments for refractory warts, such as those which fail first-line therapy, is a challenge. Data on many of the second- or third-line treatments mentioned above for refractory warts showed no advantage over cryotherapy or SA (which are generally used as first-line therapies). Perhaps the controlled studies with such first-line topical therapies have not been performed (and moreover are unlikely to be performed) because, generally, such second- or third-line treatments are reserved for those who have already failed first-line therapies.

Good quality studies of the more hazardous second-line treatments, such as intralesional bleomycin and topical immunotherapy (with dinitrochlorobenzene, diphencyprone, or squaric acid dibutylester), are definitely needed to provide clearer guidance for their use. Finally, the more 'surgical' treatments, such as photodynamic therapy, pulsed dye laser, and even the carbon dioxide laser (for which no randomised trials were found), require further study.

Trials using within-participant randomisation (e.g. left and right randomisation) and using individual warts as the unit of analysis are fraught with statistical and biological difficulties (Altman 1997; Altman 2002) and should be discouraged. Quasi-randomised studies where allocation may be made alternately on the basis of birth date or hospital number are easy to manipulate. We excluded quasi-randomised studies from this review for that reason, and future studies should be conducted using adequate randomisation and allocation concealment methods, to minimise selection bias.

A reduced area or volume of warts is not a clinically-relevant end point, and sustained clearance of warts after a reasonable follow-up period of at least three months and preferably six months is to be encouraged as the standard end point. As none of the trials evaluated quality of life outcomes, quality of life issues related to treatment for warts remains an area that requires future research.

This review was updated in 2011 and will be updated as new trials become available.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abou-Auda 1987

Methods	This study was carried out in a primary care setting, and it was multicentre This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in the USA.
Participants	100 participants were recruited. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the hands or feet
Interventions	• 15% SA patch • Placebo patch The wart was abraded with a file prior to each treatment and treated until wart resolution or for 12 weeks
Outcomes	**Outcomes of the trial** 1. 'Successful treatment' at 12 weeks
Notes	This study measured 'successful treatment' rather than cure and number of withdrawals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was described as 'double blind', but no details were given. An identical placebo was used Comment: The participants were probably blinded to the intervention given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear; no details were given.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 54 participants were included in the analysis. 46 dropped out. There was a high dropout rate for the control group (54%) stated in the discussion

Abou-Auda 1987 (*Continued*)

		Comment: The numbers of dropouts by intervention group was not given
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported.

Adalatkhah 2007

Methods	This study was carried out in a secondary care setting. This was a left-right study. The blinding within this study was unclear. Intention-to-treat analysis was not carried out. This study was conducted in the USA.
Participants	52 participants were recruited: 8 dropped out. **Inclusion criteria of the trial** • Participants aged > 12 • Ordinary warts • Warts on the hands or feet
Interventions	• Cryotherapy versus • Cryotherapy plus bleomycin Treatment was allocated up to 3 times if necessary.
Outcomes	**Outcomes of the trial** 1. Cure at 6 weeks
Notes	The adequacy of cryotherapy was uncertain as 'the wart was sprayed until the ice ball formation had spread from the centre to include the edge of the wart and a 1 mm margin.'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 2): "Two treatment types were randomly allocated to either right sided or left sided warts", but the method of randomisation was unclear Comment: There was insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	It was unclear if allocation was concealed. Comment: This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details were given, but as the treatments were very different, it would have been difficult to fully blind

Adalatkhah 2007 (*Continued*)

		Comment: This was unclear; no details were given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details were given; the treatment and assessment was done by different dermatologists Comment: This was unclear; no details were given.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote (page 2): "Most patients (44 of 52) continued participation." It was unclear if the dropouts were balanced across the groups, and no reasons were given for the dropouts
Selective reporting (reporting bias)	High risk	Quote (page 4): "Only five cases of significant adverse complications were encountered, three of which belonged to bleomycin. Minor complications were not recorded." There was risk of bias from incomplete adverse event reporting

Aldara 3M 2000a

Methods	This was a phase II research trial; the setting was unclear. This study was blinded. Intention-to-treat analysis was carried out. This study was conducted in the USA.
Participants	191 participants were recruited. **Inclusion criteria of the trial** • Adults • Ordinary warts • Warts on the feet
Interventions	• 5% imiquimod cream versus • Placebo cream Four dosing regimens were included - 3 times weekly with tape occlusion, daily with tape occulusion, 3 times weekly with no tape occulusion, daily with no tape occlusion - versus placebo groups with and without tape occlusion. Warts were pared at interval visits (1- to 2-week intervals). There was 12 weeks of treatment
Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks 2. Wart recurrence 3. Adverse effects

Aldara 3M 2000a (*Continued*)

Notes	This was unpublished trial data on 'Aldara' cream.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was randomised.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	'Modified blind' was stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	'Modified blind' was stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This was unclear: Intention-to-treat analysis and PP analyses were discussed, but the number of dropouts was not stated
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Aldara 3M 2000b

Methods	This was a phase II research trial. The setting was unclear, but it was multicentre This study was blinded. Intention-to-treat analysis was carried out. This study was conducted in the USA.
Participants	200 participants were recruited. **Inclusion criteria of the trial** • Adults • Ordinary warts • 'Common warts'
Interventions	• 5% imiquimod cream • Placebo cream Four dosing regimens were included - 3 times weekly with tape occlusion, daily with tape occulusion, 3 times weekly with no tape occulusion, daily with no tape occlusion - versus placebo groups with and without tape occlusion. Warts were pared at interval visits (1- to 2-week intervals). There was 12 weeks of treatment
Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks 2. Wart recurrence

Aldara 3M 2000b (*Continued*)

	3. Adverse effects
Notes	This was unpublished trial data on 'Aldara' cream.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This study was randomised.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	'Modified blind' was stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	'Modified blind' was stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This was unclear: Intention-to-treat analysis and PP analyses were discussed, but the number of dropouts was not stated
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Artese 1994

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was carried out. This study was conducted in Italy.
Participants	300 participants were recruited: 6 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the hands or feet
Interventions	• 5-FU for 12 hours and SA/LA elastic collodion-based preparation for the following 30 days versus • Cautery (single session)
Outcomes	**Outcomes of the trial** 1. Cure at 75 days
Notes	There was no statistical analysis of the results.

Artese 1994 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was described as randomised, but no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was not blinded, as blinding was not possible because of the nature of the therapy
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was not blinded, as blinding was not possible because of the nature of the therapy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 participants left the study. (No details were given about which intervention group they had been allocated to.)
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported.

Auken 1975

Methods	This study was carried out in a secondary care setting, and it was multicentre This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in Denmark.
Participants	240 participants were recruited: 55 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory wart type not specified • Warts on the hands or feet
Interventions	• LA/SA (Verucid) • 'conventional' treatment (= anything else or no treatment)
Outcomes	**Outcomes of the trial** 1. Cure at 3 months
Notes	The control group were treated with 3 different treatments. No details were given about the treatment methods or how many participants were treated with each method
Risk of bias	

Auken 1975 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 3): "The trial was carried out as a double-blind trial with roughly half the patients being treated by the traditional, conservative methods…" "The patients were chosen randomly and only the treating nurse knew which treatment applied to the number the patient had been given". The method of randomisation was not stated
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only the treating nurse knew which treatment had been given. Comment: Although some attempt at blinding was made, it was unclear if both participants and personnel were blinded adequately. This was judged as unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 3): "After paring away the wart and also removing any remaining ointment (so the preparation could not be seen), one of us was called to assess the result." Comment: This was probably at low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	55/240 participants dropped out: 27 from the intervention group and 28 from the control group. Reasons for dropout were not stated
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Aum 2006

Methods	This study was carried out in a secondary care setting. The blinding within this study was unclear. Intention-to-treat analysis was not carried out. This study was conducted in Korea.
Participants	24 participants were recruited. **Inclusion criteria of the trial** • Adults and children • Refractory warts • Periungual warts

Aum 2006 (*Continued*)

Interventions	• Intralesional bleomycin (dose unclear) versus • Pulsed dye laser with intralesional bleomycin every 3 weeks. The total duration of therapy was unclear.
Outcomes	**Outcomes of the trial** 1. Cure rate
Notes	Follow-up time was unclear. Recurrence was assessed at 6 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; the method of randomisation was not clear
Allocation concealment (selection bias)	Unclear risk	It was unclear if allocation was concealed; no information was given in the trial report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was unclear if the study was blinded. Comment: Blinding was unlikely given the nature of the treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	It was unclear if the study was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were apparently lost to follow up, but the numbers completing and available for assessment were not given Comment: The minimisation of attrition bias was adequate.
Selective reporting (reporting bias)	High risk	The length of the study was not documented. Tolerability, adverse effects, and practicality of PDL were not reported on

Banihashemi 2008

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in Singapore.
Participants	60 participants were recruited: 7 dropped out. The average age of the participant was 15.6 years in the intervention group and 16.4 years in the control group

	Inclusion criteria of the trial • Adults or children not specified • Ordinary warts • Warts on the hands only
Interventions	• Cryotherapy (cryotherapy was done with a cotton swab dipped into liquid nitrogen and then applied on the warts for 10 to 20 seconds every week) • 80% phenol was applied on the dry lesions with a cotton swab every week.
Outcomes	**Outcomes of the trial** 1. Cure at 6 weeks
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 1035): "Patients were randomly divided into two groups." Comment: The method used was simple randomisation according to the method of Lachin 1981 (additional information came from the trial investigator).
Allocation concealment (selection bias)	Unclear risk	The allocation concealment was unclear; no information was given
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial investigators said: "Patients and the first dermatologist who treated them were alert about the medication." Comment: This was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to the treatment (additional information came from the trial investigator)
Incomplete outcome data (attrition bias) All outcomes	High risk	7 cases in the phenol group were not followed up. Quote (page 1036): "Four did not complete the follow-up period and three could not tolerate burning sensation." Comment: Uneven distribution across the groups was likely to introduce bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Bart 1989

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in the USA.
Participants	61 participants were recruited: 8 dropped out. **Inclusion criteria of the trial** • Adults • Ordinary warts • Warts on the hands only
Interventions	• SA patch • Placebo patch The wart was abraded before treatment; the patch was applied nightly up to resolution of the wart or for 12 weeks of treatment
Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 75): "A block random allocation procedure stratified by wart count was used to balance the two groups." Comment: This was probably done.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was described as double-blind. Quote (page 74): "Patients were randomly assigned medicated patches in a double blind manner." And the patches used were identical; however, it was unclear how the investigators were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was described as double-blind, but no details were given regarding outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	53/61 participants completed; it was unclear how many were randomised to each group initially, so the number of dropouts from each group can only be estimated. There were more dropouts from the control group (failure to comply with protocol) -

Bart 1989 (*Continued*)

		this was possibly because of the failure of the warts to clear
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Berman 1986

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This study was conducted in the USA.
Participants	8 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults • Refractory warts • The site was not stated
Interventions	• Intralesional IFN-alpha (0.1 mls of 1 millionU/ml 3 times a week for 3 weeks) • Placebo (phosphate-buffered isotonic saline containing human serum albumin and glycine) The treatment schedules for the intervention and control groups were identical
Outcomes	**Outcomes of the trial** 1. Cure at 8 weeks
Notes	There was no apparent 'systemic' effect on untreated warts.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random assignment to 2 groups was described, but no further details were given
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 328): "Neither the patient nor the investigator knew the identity of the injected material."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was stated as double-blind, but no details were given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 8 participants completed the trial and were available for follow up

Berman 1986 (*Continued*)

Selective reporting (reporting bias)	Low risk	Clinical laboratory tests were also reported as remaining within the normal range ('Materials and Methods', page 328)

Berth-Jones 1992a

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	400 participants were recruited: 77 dropped out. **Inclusion criteria of the trial** • Adults and children • Mixed types of warts • Warts on the hands or feet
Interventions	• 3-weekly cryotherapy • No cryotherapy 3-weekly cryotherapy was applied with a cotton wool bud + SA/LA versus no cryotherapy
Outcomes	**Outcomes of the trial** 1. Cure at 3 months
Notes	Cure rates were expressed as percentages only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that the trial was randomised, but no details were given
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was inadequate; there was no blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was inadequate; there was no blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	77 randomised participants were lost to follow up at 3 months with no reasons given, although they were balanced demographically and across the treatment groups

Berth-Jones 1992a (*Continued*)

Selective reporting (reporting bias)	Low risk	The only outcome, 'cure rate', was reported.

Berth-Jones 1992b

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	155 participants were recruited: 40 dropped out. **Inclusion criteria of the trial** • Adults and children • Refractory warts • Warts on the hands or feet
Interventions	• 3-weekly cotton wool bud cryotherapy • No cryotherapy 3-weekly cryotherapy was applied with cotton wool bud + SA/LA with paring, versus without paring
Outcomes	**Outcomes of the trial** 1. Cure after a further 3 months
Notes	This is the second part of Berth-Jones 1992a. Systemic inosine pranobex was also used for some participants with no apparent impact

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that the trial was randomised ('Methods', page 262), but no details were given
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was inadequate; there was no blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was inadequate; there was no blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	77/400 randomised participants were lost to follow up at 3 months ('Table 2', page 264) with no reasons given. They were classed as defaulters, and results were only

Berth-Jones 1992b (*Continued*)

		presented for defaulters Comment: This was inadequate and represented a potentially high risk of bias
Selective reporting (reporting bias)	Low risk	The only outcome, 'cure rate', was reported.

Berth-Jones 1994

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was carried out. This study was conducted in the UK.
Participants	300 participants were recruited: 93 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary/refractory warts • Warts on the hands or feet
Interventions	• 3-weekly cotton wool bud cryotherapy + SA/LA: 2 freeze/thaw cycles at each visit for up to 3 months • Cryotherapy as above, single freeze
Outcomes	**Outcomes of the trial** 1. Cure at 3 months
Notes	There was a high attrition rate.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was described as randomised ('Methods', page 883); no details were given Comment: This was inadequate.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding (described as 'open'). .
Blinding of outcome assessment (detection bias) All outcomes	High risk	There was no blinding (described as 'open'). .

Berth-Jones 1994 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	93/300 participants (page 884) were recruited and withdrawn before 3 months; no reasons were given
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Bourke 1995

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat and per-protocol analyses were carried out This study was conducted in the UK.
Participants	225 participants were recruited: 143 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary/refractory warts • Warts on the hands or feet
Interventions	• Cotton wool bud cryotherapy + SA/LA 1- vs 2- vs 3-week intervals between freezes The intervals between cryotherapy were compared at 1, 2, and 3 weeks. Treatment continued until withdrawal or the wart was cured
Outcomes	**Outcomes of the trial** 1. Cure after 12 treatments 2. Response times 3. Departmental workload
Notes	There was a very high attrition rate. Cure rates were only given as percentages Cryotherapy was applied with a cotton bud.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was described as randomised ('Methods', page 433). No details were given
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was not blinded.

Bourke 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	143/225 participants ('Results', page 434) did not complete the therapy. The high withdrawal rate was explained as failure to attend. It was unclear how the numbers of withdrawals were balanced across the intervention groups or the reasons for non-attendance
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Bruggink 2010

Methods	This study was carried out in a primary care setting, and it was open Intention-to-treat and per-protocol analyses were carried out This study was conducted in the Netherlands.
Participants	250 participants were recruited: 16 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the hands, feet ('plantar'), or other
Interventions	• Cryotherapy applied with cotton swab - 1 session every 2 weeks • SA petroleum jelly applied topically daily • Wait-and-see group
Outcomes	**Outcomes of the trial** 1. Cure at 13 weeks and adverse effects 2. Newly-developed warts 3. Adherence at 4 weeks, 13 weeks, and 26 weeks
Notes	This was a 3-arm trial. Cryotherapy was applied with cotton wool.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1625): "Random allocation of participants to treatment groups was done without blocking." Comment: This was computerised.
Allocation concealment (selection bias)	Low risk	Quote (page 1625): "We used opaque, sealed envelopes that were numbered based on a computerized randomisation list delivered by an independent statistician to con-

Bruggink 2010 (*Continued*)

		ceal allocation."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not possible as the cryotherapy and alicyclic acid treatments were different Quote (page 1625): "Research nurses, family physicians and participants were not blinded to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 1625): "Research nurses, family physicians and participants were not blinded to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	High risk	All dropouts were accounted for with reasons. More participants stopped treatment in the SA (50/84) and cryotherapy (37/80) groups compared with the observation group (18/80)
Selective reporting (reporting bias)	Low risk	All outcomes were reported except for the use of OTC medication, which was permitted but not explicitly reported

Bunney 1971

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	382 participants were recruited: 86 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the feet only
Interventions	• SA/LA • Collodion • Callusolve • 50% podophyllin
Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks
Notes	There were lower cure rates for mosaic as opposed to simple plantar warts with all treatments: 58% vs 75%

Bunney 1971 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The paper described allocation to treatment as according to a random table (page 199)
Allocation concealment (selection bias)	High risk	There was no allocation concealment; allocation was by a secretary to a random numbers table (page 199)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was described as double-blind. Wart treatments were prepared in the hospital pharmacy and (quote, page 198) "dispensed in identical bottles with plastic applicators, numbered by the pharmacist who held the key to the code until the end of trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This was unclear; no details were given. Comment: It was possibly done as the code was held by the pharmacist who had no role in assessing outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	336/382 participants completed the trial. Analysis was conducted on 348, as 16 defaulted because of severe pain, but they were included in the analysis
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported.

Bunney 1973

Methods	This study was carried out in a secondary care setting. The blinding within this study was unclear. Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	95 participants were analysed. **Inclusion criteria of the trial** • Adults and children not specified • Ordinary or refractory warts not specified • Warts on the feet - mosaic
Interventions	• 2% 5-FU ointment • 5% 5-FU ointment • SA/LA

Bunney 1973 (*Continued*)

	• Idoxuridine The exact treatment conditions were unclear in terms of dosage and duration
Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks
Notes	The report of the trial was very brief. Further data appeared in Bunney 1976d (page 675).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number table was used.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not specified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of the study was not specified.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of the outcome assessment was not specified.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This was unclear.
Selective reporting (reporting bias)	Unclear risk	This was unclear.

Bunney 1976a

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	100 participants were recruited: 28 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the hands only
Interventions	• Cotton wool bud cryotherapy - 2-week, 3-week, and 4-week intervals The effects of the intervals between freezes were compared up to 12 weeks of therapy
Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks

Bunney 1976a (*Continued*)

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was done using a random (numbers) table.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatments were allocated blind. Quote (page 668): "...the key being held by the hospital pharmacy."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	28/100 participants (page 670) dropped out or withdrew; it was unclear how they were distributed across the intervention groups Comment: Minimalisation of attrition bias was inadequate. There was a possibility of a high risk of bias
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Bunney 1976b

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	389 participants were recruited: 95 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the hands only
Interventions	• 3-weekly cotton wool bud cryotherapy • SA/LA nightly • Cryotherapy and SA/LA Therapy continued for up to 12 weeks.

Bunney 1976b (*Continued*)

Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was done using a random (numbers) table.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not specified, but it was likely that this study was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not specified, but it was likely that this study was not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	134 participants were rejected because of irregular attendance, and only 31 defaulters remained untraced. (Quote: "134 patients were rejected on irregular attendance and only 31 defaulters remained untraced. ") However, results for 294 were presented for which we were unable to find an explanation
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Bunney 1976c

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	156 participants were recruited: 18 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the feet (simple plantar)

Bunney 1976c (*Continued*)

Interventions	• SA/LA • SA/LA + polyethylene Therapy continued for up to 12 weeks.
Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was done using a random (numbers) table.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not specified, but it was likely that the study was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not specified, but it was likely that the study was not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote (page 674): "Twelve patients were rejected because they failed to attend or to carry out treatment regularly. Only one patient in each treatment group was rejected on account of persistent pain or failure to improve. Six defaulters could not be traced. "
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Bunney 1976d

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	94 participants were recruited: 13 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the feet (mosaic plantar)

Bunney 1976d (*Continued*)

Interventions	• 10% glutaraldehyde paint • SA/LA paint Therapy continued for up to 12 weeks. It was unclear how therapy was applied, but it may have been during clinic visits
Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was done using a random (numbers) table.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 participants were rejected, and 1 remained untraced. It was unclear how many participants were lost from each treatment group
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Bunney 1976e

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	110 participants were recruited: 17 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the feet (mosaic plantar)

Bunney 1976e (*Continued*)

Interventions	• 40% SA • SA/LA paint Therapy continued for up to 12 weeks. It was unclear how therapy was applied
Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was done using a random (numbers) table.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13 participants were rejected, and 4 remained untraced at the end of the trial. It was unclear how many participants were lost from each treatment group
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Bunney 1984

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This was a left-right study. This study was conducted in the UK.
Participants	24 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults • Refractory warts • Warts on the hands

Bunney 1984 (*Continued*)

Interventions	• 0.1% bleomycin intralesional injection versus • Intralesional saline injection There were up to 3 injections per wart if necessary.
Outcomes	**Outcomes of the trial** 1. Cure at 6 weeks
Notes	The main unit of analysis was warts rather than participants Participants switched to active treatment after 6 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not specified.
Allocation concealment (selection bias)	Low risk	This was adequate, as on entry, each participant received a trial number; randomisation lists were held by the pharmacist and statistician only; and the code was not broken until the end of the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants received bleomycin solution or normal saline; randomisation lists were held by the pharmacist and statistician only; and the code was not broken until the end of the trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants received bleomycin solution or normal saline; randomisation lists were held by the pharmacist and statistician only; and the code was not broken until the end of the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow up.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Cancino 1989

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was carried out. This study was conducted in Mexico.

Cancino 1989 (*Continued*)

Participants	40 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Children • Refractory warts • Warts at any site
Interventions	• 2% DNCB in acetone • Placebo (acetone only) DCNB treatment was repeated after 15 days if no signs of sensitisation occurred
Outcomes	**Outcomes of the trial** 1. Cure (time period not stated)
Notes	The period of the trial was unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was stated that blinding was impossible because of the effect of the DNCB intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	It was stated that blinding was impossible because of the effect of the DNCB intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear if there were dropouts or how they were distributed across the groups. No details were given
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported. The time period of the study was not stated. The number of participants experiencing adverse effects were not reported

Chen 2008

Methods	This study was carried out in a secondary care setting. This study was not blinded. It was unclear if ITT analysis was carried out. This study was conducted in China.
Participants	120 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults aged 16 to 35 • Ordinary or refractory warts not specified • Wart site not specified
Interventions	• Traditional Chinese medicine cream "Xiao You Gao" versus • 0.1% tretinoin cream applied daily Cream was applied daily by the participant for up to 30 days
Outcomes	**Outcomes of the trial** 1. Cure, but time of follow up was unclear
Notes	There was a potential conflict of interest (see translation from TX Wu) and risk of other bias (conflict of interest) as the drug used was prepared by the author himself and made by his hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The allocation sequence was generated by a computer software; the random number matched the recruitment order; and an eligible participant took a relative numbered envelope containing the treatment method
Allocation concealment (selection bias)	Unclear risk	There were sealed envelopes corresponding to the participant randomisation number. It was unclear if these were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The results for 120/120 participants were reported; it was unclear if there were any dropouts (with reasons)

Chen 2008 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	This was unclear. Cure rates were reported.

Cockayne 2011

Methods	This study was carried out in a primary care setting, as well as podiatry clinics, and it was multicentre This study was not blinded. Intention-to-treat analysis was carried out. This study was conducted in the UK.
Participants	242 participants were randomised: 240 entered the trial, and 11 went missing or were withdrawn **Inclusion criteria of the trial** • Aged 12 or over • Ordinary or refractory warts not specified • 'Plantar' warts
Interventions	• Cryotherapy every 2 to 3 weeks for a maximum of 4 treatments • SA applied daily with pumicing or filing for 8 weeks
Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2): "Randomisation was performed by a member of the research team either telephoning an independent, secure, remote, telephone randomisation service (York Trials Unit) or accessing a secure online web randomisation programme..."
Allocation concealment (selection bias)	Low risk	Quote (page 2): "...thereby concealing treatment allocation until the moment of randomisation."
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not possible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 2): "Digital photographs... were assessed by two assessors who were blind to treatment allocation. If no photographs were available,...the patient's self

		reported outcome...was used." Comment: This was probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All dropouts and losses to follow up were accounted for and balanced between the groups
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Connolly 1999

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was not carried out. This study was conducted in Eire.
Participants	200 participants were recruited: 54 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the hands or feet
Interventions	• 10 second freeze with cryogun versus • 'gentle' cryogun freeze There was a maximum of 5 treatments at 2-weekly intervals.
Outcomes	**Outcomes of the trial** 1. Cure at 8 weeks
Notes	This was a very brief trial report.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an open study.

Connolly 1999 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants in the deep freeze group required antibiotics, analgesia, and daily dressings for severe blistering Comment: No details were given about adverse events; more participants in the aggressive therapy group had severe adverse events
Selective reporting (reporting bias)	Unclear risk	This was unclear.

de Haen 2006

Methods	The study was carried out in a primary care setting (in the participants' homes) This study was blinded. Intention-to-treat analysis was carried out. This study was conducted in Netherlands.
Participants	103 participants were recruited: 11 dropped out. **Inclusion criteria of the trial** • Children • Ordinary or refractory warts not specified • Warts at any site
Interventions	• Duct tape • Placebo All participants (both groups) were asked to soak and rub the wart with a pumice stone once a week. Treatment continued for up to 6 weeks
Outcomes	**Outcomes of the trial** 1. Cure at 6 weeks
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 1122): "Randomization was performed in blocks of 10 stratified in 2 groups (single or multiple warts)." No further information was given on the method of randomisation Comment: This was probably done.
Allocation concealment (selection bias)	Low risk	Quote (page 1122): A "central randomisation office that assigned the intervention and kept the randomisation key" was used in the study

de Haen 2006 (*Continued*)

		Comment: This was adequate.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded. Quote (page 1122): "Patients were blinded to the hypothesis of the study." "Because it is unknown how duct tape achieves its possible effect, it was impossible to fabricate a placebo copy. Therefore, participants were not informed about the specific treatment investigated in this study." "To blind the assessor a second researcher who was not involved in the follow-up measurements, applied the first treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 1122): "One researcher performed the outcome measurements at school." This researcher was blind to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	From 103 randomised participants, 11 children discontinued treatment: 8 in the duct tape group and 3 in the placebo group. Reasons were given; 3 in the treatment group stopped because of adverse effects Comment: Table 3 on page 1124 of the study report reports adverse effects for only 47 out of 51 randomised to duct tape because of "missing values". All 52 participants in the placebo group were accounted for. This was not thought to introduce significant bias into the study
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Dhar 2009

Methods	This study was carried out in a secondary care setting, and the study was blinded Intention-to-treat analysis was carried out. This study was conducted in Bangladesh.
Participants	80 participants were recruited: 7 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Wart site not specified
Interventions	• Cryotherapy (group C), 1 to 4 sessions, versus • 0.1% intralesional bleomycin injection (group B) evaluated at 3-weekly intervals

Dhar 2009 (*Continued*)

Outcomes	**Outcomes of the trial** 1. Cure at 8 weeks (total study time was 8 to 17 weeks) after completion of treatment using a 7-point scale, where 0 = exacerbation and 6 = normal skin after cure of wart Scores 5 and 6 were regarded as treatment success; other scores were regarded as treatment failure Recurrence was not counted as a treatment failure, if there was an initial response to treatment and scores 5 or 6 on the 7-point scale given above
Notes	This was a head-to-head trial, reporting pain and depigmentation as adverse effects The cryotherapy was inadequate: "The wart was sprayed until the ice-ball formation had spread from the centre to include the edge of the wart and a 1-mm margin."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 263): "Patients were randomised using computer generated codes."
Allocation concealment (selection bias)	Low risk	Every selected consecutive participant was given a serial ID, and that ID was set in a computer-generated randomised table to allocate either bleomycin or cryotherapy, which was known to the study physician after selecting the case not before selection. Further details were obtained from the trial investigator
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and the study physician were blind to the intervention until selection of the case and first intervention of therapy. Further details were obtained from the trial investigator
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was not possible because of the nature of the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	1/40 participants in the bleomycin group and 6/40 participants in the cryotherapy group withdrew because of "infrequent follow up" (page 264)
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Erkens 1992

Methods	This study was carried out in a primary care setting, and it was open Intention-to-treat analysis was carried out. This study was conducted in Netherlands.
Participants	93 participants were recruited: 18 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the hands
Interventions	• Monthly cotton wool bud cryotherapy versus • Bimonthly Histofreezer Treatment continued for up to 2.5 months.
Outcomes	**Outcomes of the trial** 1. Cure at 2.5 months
Notes	Cryotherapy was applied with a cotton tip.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	This was adequate; sealed envelopes were used. It was unclear if they were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 193): "Neither the doctor nor the patient knew beforehand which treatment was to be used." Comment: This was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details were given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	17/93 participants withdrew (7/17 in the cryotherapy group and 10/17 in the Histofreezer group): The reason given was that they 'did not comply fully with protocol' Comment: Reasons for dropouts were given; there was equal distribution between the groups
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Faghihi 2010

Methods	This study was carried out in a secondary care setting. The blinding within this study was unclear. It was unclear if ITT analysis was carried out This study was conducted in Iran.
Participants	34 participants were recruited: The number of dropouts was unclear **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the hands, neck, lower extremities, or trunk
Interventions	• After cleaning the lesion with alcohol, 85% formic acid in distilled water was applied on the surface of the wart with a cotton swab. On alternate days the lesion was punctured on the contralateral part using a 30-gauge disposable needle about 6 to 10 times each lesion with 2 mm intervals between punctures versus • Distilled water, which was applied as above Treatment continued for 12 sessions or until complete recovery
Outcomes	**Outcomes of the trial** 1. Cure at 3 months
Notes	One side of the body received the intervention; the other side was treated with placebo (saline)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given. Each person acted as their own control (body-part randomisation)
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details were given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details were given.
Incomplete outcome data (attrition bias) All outcomes	High risk	No details were given; 34 participants were randomised, but the numbers completing therapy or available for follow up were not given

Selective reporting (reporting bias)	Low risk	All outcomes were reported. Exact numbers were not stated - only percentages. Therefore, this was difficult to interpret

Felt 1998

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was not carried out. This study was conducted in the USA.
Participants	61 participants were recruited: 10 dropped out. **Inclusion criteria of the trial** • Children • Ordinary warts • Warts anywhere
Interventions	• Relaxation imagery • SA • No treatment
Outcomes	**Outcomes of the trial** 1. Cure at 6 to 18 months
Notes	Only 1 index wart was treated in each child. A quote on page 134 related to performance bias: "A similar percentage of children across experimental groups reported use of topical treatments after the initial 8 weeks." The authors commented that "spontaneous regression within 2 years is thought to occur for about half to two thirds of warts"; yet, they used 6 to 18 months as the timeframe for follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment was conducted by picking a study number from a hat. (page 132) Comment: This was probably adequate.
Allocation concealment (selection bias)	Unclear risk	It was unclear if any attempt was made to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt was made at blinding.

Felt 1998 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt was made at blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	51/61 participants completed. Dropouts were distributed across groups. The reasons for dropout were not given Comment: This was probably adequate.
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported.

Flindt-Hansen 1984

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was not carried out. This study was conducted in the USA.
Participants	72 participants were recruited: 14 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordnary or refractory warts not specified • Warts on the hands or feet
Interventions	• Anthralin • LA/SA Participants applied 1 of the preparations twice daily, with paring done in clinic every 2 weeks. Treatment continued for 2 months
Outcomes	**Outcomes of the trial** 1. Cure at 2 months
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not apparently blinded; no details were given.

Flindt-Hansen 1984 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	This was not apparently blinded; no details were given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	58/72 participants completed: 14 were excluded, 10 did not follow instructions, and 4 did not present for assessment Quote (page 178): "No difference in the distribution of drop outs between the two groups of treatment was found."
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Focht 2002

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in the USA.
Participants	61 participants were recruited: 10 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the hands or feet
Interventions	• Duct tape occlusion for 6 days then replaced with new tape for up to 2 months versus • 2- to 3-weekly cryotherapy (maximum of 6 sessions)
Outcomes	**Outcomes of the trial** 1. Cure at 2 months
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated. Quote (page 972): "Patients were then randomised, using a computer-generated code, to 1 of 2 treatment arms: cryotherapy or duct tape." Comment: This was adequate.

Focht 2002 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No method of allocation concealment was described. However, nurses had access to the data sheet (which may be the allocation sequence), which suggests it was not adequately concealed. (page 972)
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is unclear if participants were blinded, but because of the nature of the intervention, this was unlikely. Quote (page 972): "Study physicians and nursing personnel were blinded to the therapy being used." "Patients in the duct tape arm were instructed to remove all tape prior to making a return clinic visit. This was effective in keeping nursing personnel blinded to which treatment arm a patient was in until after they measured the study wart. Nursing personnel then checked the data sheet to see which arm the patient was in for further therapy." Comment: Although some attempt at blinding was made, the nursing personnel had knowledge of the treatment group. Therefore, blinding was probably not adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded. Quote (page 972): "Study physicians and nursing personnel were blinded to the therapy being used. Patients in the duct tape arm were instructed to remove all tape prior to making a return clinic visit. This was effective in keeping nursing personnel blinded to which treatment arm a patient was in until after they measured the study wart." Comment: There were multiple follow-up visits, so it was possible that nursing personnel knew which treatment arm a participant was in
Incomplete outcome data (attrition bias) All outcomes	High risk	10/61 participants were not available for follow up, and they were not included in the investigators' analyses: 3 from the duct tape group and 6 from the cryotherapy group; no reasons were given. 1 wart was lost in an accident. There was discrepancy between the 2 groups

Focht 2002 (*Continued*)

		Quote (page 973): "...had to rely on parental report of resolution over the telephone." Comment: This may have introduced detection bias by relying on parent reports (parent not blinded), and parents may not have had the incentive to return for a follow-up appointment
Selective reporting (reporting bias)	High risk	The outcomes included complete resolution of the study wart and time to resolution of the warts Time to resolution of the wart was not accurately recorded because of variability in when the contact or follow-up appointments were made. (see page 974)

Fuchs 2004

Methods	This study was carried out in a secondary care setting. The blinding within this study was unclear. It was unclear if ITT analysis was carried out This study was conducted in Germany.
Participants	80 participants were recruited: 12 dropped out. **Inclusion criteria of the trial** • Adults • Refractory warts • Warts on the hands or feet
Interventions	• 20% 5-aminolevulinic acid (5-ALA) + visible light (VIS) + water-filtered infrared-A (wIRA) versus • Placebo + visible light + wIRA versus • 20% 5-ALA + visible light versus • Placebo + visible light There were 1 to 3 therapy cycles every 3 weeks for a total duration of 18 weeks
Outcomes	**Outcomes of the trial** 1. Per cent change in wart area at 0, 3, 6, 9, 12, and 18 weeks
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2): "80 patients were randomised within 10 time blocks of 8 patients

Fuchs 2004 (*Continued*)

		to 4 therapy groups purely on sequence of the patients being included in the study." Comment: This was probably done.
Allocation concealment (selection bias)	Low risk	Quote (page 5): "...smallest possible block size which allows no information about the allocation of another patient of the same time block to a therapy group, not even that he or she belongs to a different therapy group." Comment: The method of allocation concealment was unclear, but randomisation was done in blocks, preventing knowledge of allocation. Therefore, this was probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1): "...prospective randomised controlled blind study." No further information was given in the published trial report other than that the placebo could not be distinguished by inspection nor by smell from the treatment cream Quote (page 6): "Presence or absence of wIRA can be felt by the treating physician by comparing the radiation, the study was performed single instead of double blind."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1): "...prospective randomised controlled blind study." No further information was given in the published trial report
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote (page 9): "Out of the 80 patients, 68 completed the entire study." Comment: The reasons for attrition were given in the trial report (page 8). The dropout rate between the groups was similar
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Gibson 1984

Methods	This study was carried out in a secondary care setting and was blinded with respect to the creams used, i.e. participant-blinded Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	52 participants were recruited: 5 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the feet
Interventions	• Topical aciclovir once-daily versus • Placebo cream versus • 2-weekly cryotherapy plus glutarol Treatment continued for up to 6 weeks.
Outcomes	**Outcomes of the trial** 1. Cure at 8 weeks
Notes	Quote (page 179): "Liquid nitrogen was used as a positive control during the first phase of the trial but after the entry of 33 patients it was discontinued as an initial therapy in order to obtain maximal numbers of patients on the cream treatments."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised. (page 189)
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The creams used were identical, but it would not be possible to blind the cryotherapy treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear; no details were given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	47/52 participants completed the trial. The distribution of dropouts in the groups was reported. Reasons for dropouts were unclear Comment: This was probably low risk of bias.
Selective reporting (reporting bias)	Unclear risk	Adverse effects were not reported.

Gustafsson 2004

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This study was conducted in Sweden.
Participants	40 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults and children • Refractory warts • Warts on the hands or feet
Interventions	• α-lactalbumin-oleic acid in saline (1 drop per lesion) • Placebo (saline) Applied once a day for 3 weeks.
Outcomes	**Outcomes of the trial** 1. > 75% reduction in wart volume at 2 months
Notes	The trial converted to open-label after the first 3 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised, and a randomisation code was mentioned, but no further details were given
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Bottles of the intervention were coded, but no further details were given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 2665): "The randomisation code was broken one month after all patients had completed three weeks of the randomly assigned treatment." Comment: This was probably adequate.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 participants entered the trial; 34 were available for follow up at the end of the trial. There were no withdrawals from the first phase of the study. There were 2/40 withdrawals from the second phase - who were lost to follow up (LFU) (1 from each of the original 2 groups). No reasons were given for dropouts Comment: This was unlikely to introduce

Gustafsson 2004 (*Continued*)

		a high risk of risk of bias
Selective reporting (reporting bias)	Low risk	All outcomes (lesion volume and number of lesions) were reported

Hansen 1986

Methods	This study was carried out in a primary care setting, and it was open Intention-to-treat analysis was carried out. The country in which this study was conducted was unclear.
Participants	77 participants were recruited: 17 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Feet
Interventions	• Cryoprobe for 2 minutes versus • Cryoprobe for 15 seconds Warts were treated 3 times with an interval of 3 weeks.
Outcomes	**Outcomes of the trial** 1. Cure at 9 weeks
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as 'chosen randomly' in the 'Materials and methods' section of the report
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was described as 'single blind', so the participants may have been blind to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was not done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	60/77 participants completed: 3 did not want to take part; 14 dropped out, 11 of which because of non-compliance, 2 because of wart growth or increase in number of warts, and 1 because of pain. If the

Hansen 1986 (*Continued*)

		groups contained equal numbers at randomisation, most dropouts appeared to be in the 15-seconds group (27/33) compared with the 2-minute treatment group (33/34) Comment: This was possibly high risk of bias, but there was insufficient information to reach a judgement
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Hayes 1986

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This study was conducted in the USA.
Participants	26 participants were recruited: The number of dropouts was unclear **Inclusion criteria of the trial** • Adults • Refractory warts • Warts on the hands
Interventions	• Bleomycin intralesional injection: 0.25 U/ml versus • 0.5 U/ml versus • 1.0 U/ml Each wart was treated up to 3 times at 3-weekly intervals for up to 3 months
Outcomes	**Outcomes of the trial** 1. Cure at 3 months
Notes	The main unit of analysis was warts rather than participants The number of dropouts was not disclosed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	This was described as randomly-assigned (page 1003), using a randomisation code Comment: This was probably done.
Allocation concealment (selection bias)	Unclear risk	This was unclear; a randomisation code was described, but there was no report of adequate allocation concealment being employed

Hayes 1986 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was described as double-blinded. The contents of the vials of treatment medication were blinded from participants and investigators. (page 1003)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The randomisation code was broken at the end of the study (page 1003); it was stated that the investigators were unaware of allocation Comment: This was probably done.
Incomplete outcome data (attrition bias) All outcomes	High risk	23/26 participants were included in the results. (3 were spontaneously cured.) The final results show a disparity between the numbers of warts in the subgroups (page 1004). Adequate follow up was not possible for sufficient numbers of participants, although it is stated that those who left the study did so for reasons unrelated to the success of treatment
Selective reporting (reporting bias)	High risk	Quote (page 1003): "Unfortunately plantar warts treated with bleomycin x could not be included because of the small numbers of warts in this group and because of insufficient follow up."

Horn 2005

Methods	This study was carried out in a secondary care setting. The participants were blinded, but not the investigators. Intention-to-treat analysis was not carried out. This study was conducted in the USA.
Participants	233 participants were recruited: 32 dropped out. **Inclusion criteria of the trial** • The age group was not specified • Mostly refractory warts • The site was not specified
Interventions	• Intralesional skin test antigens versus • Intralesional interferon-alpha 2b versus • Antigen plus interferon-alpha 2b versus • Placebo (saline) All subjects received injections every 3 weeks into the same wart until complete clearing of the treated wart was achieved or for a maximum of 5 treatments

Outcomes	**Outcomes of the trial** 1. > 75% reduction in surface area of warts during the trial only
Notes	Only 1 index wart was treated per participant. Participants were evaluated at each episode of treatment, and there was no long-term follow up Quote: "The initial design included treatment arms using GM-CSF instead of interferon alfa-2b. Because of serious adverse events experienced by subjects receiving GM-CSF, these arms were discontinued and the trial proceeded using interferon alfa-2b in place of GM-CSF."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was computer-generated, using randomised blocks of random block sizes. However, 1 arm of the study was discontinued
Allocation concealment (selection bias)	Unclear risk	Quote (page 591): "The sequence was provided to the investigators in sealed envelopes." It was unclear if they were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was single-blind in that the participants, but not the study investigators, were blinded to an individuals' treatment assignment Comment: Personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The investigators (outcome assessors) were not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	233 participants were randomised: 201 were available for analysis. 23 were not included in the analysis because the trial arm was discontinued because of safety concerns. 9 were randomised but did not receive treatment Comment: This was judged as high risk of bias as data were not presented for the group that received GM-CSF, because of discontinuation of this arm
Selective reporting (reporting bias)	Low risk	The only specified outcome was reported.

Huo 2010

Methods	This study was carried out in a secondary care setting. This study was blinded in terms of participants, but it was unclear if the investigators were blinded Intention-to-treat analysis was carried out. This study was conducted in China.
Participants	60 participants were recruited: 6 dropped out. **Inclusion criteria of the trial** • Adults and children aged 10 to 43 years • Ordinary or refractory warts not specified • Feet only
Interventions	• Hyperthermia/local hyperthermia (44 C for 30 minutes from an infrared-emitting source causing red dot with hyperthermia) versus • Red spot device without heat sensation These were applied once a day for 30 minutes for 3 days and again for 2 days 2 weeks later
Outcomes	**Outcomes of the trial** 1. Complete disappearance of warts up to 3 months, followed up monthly and then contacted at 6 months by telephone call or visit
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1170): "A computer-generated randomisation table was used to serially allocate patients to the treatment or control group."
Allocation concealment (selection bias)	Low risk	Quote (additional information from the trial investigators): "We used opaque, sealed envelopes that were numbered based on a computerized randomisation list to conceal allocation."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants were blinded. The investigators were not blinded Quote (page 1170): "To keep the patients blinded to the treatment received, they were individually informed that a warty lesion would receive a red spot with or without a heating sensation."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors examined the pre- and post-treatment photography or made a

		phone call to the participants (6 months after treatment) to evaluate the treatment responses independent of the treating physicians. Additional information came from the trial investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	54/60 participants completed. Quote (page 1170): "Of the 6 patients, 2 were from the treatment group: 1 received a lesional interferon injection after 3 sessions of local hyperthermia, and 1 lost contact immediately after finishing the last treatment session. Four of the 6 patients were from the control group: 2 dropped out after 1 or 2 treatment sessions, 1 received cryotherapy after 2 months of follow-up visits, and 1 received a lesional interferon injection after 2 treatment sessions." The remaining participants were well-matched demographically
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Hursthouse 1975

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This was a left-right study. This study was conducted in New Zealand.
Participants	66 participants were recruited: 2 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the hands or feet
Interventions	• 5% 5-FU cream • Placebo cream Treatment was applied daily to the wart and covered with a plaster for up to 4 weeks of treatment
Outcomes	**Outcomes of the trial** 1. Cure at 4 weeks
Notes	-
Risk of bias	

Hursthouse 1975 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables were used.
Allocation concealment (selection bias)	Low risk	Quote (page 93): "A sealed code was provided. The packaged pairs of tubes were chosen from their case in random fashion by a nurse at the clinic."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 93): "...matching 10 g tubes of active and dummy cream." Comment: This was probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear; no details were given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	64/66 participants were assessed; it was unclear which group the 2 defaulters were assigned to Comment: This was unlikely to introduce a significant risk of bias
Selective reporting (reporting bias)	Unclear risk	There were adverse effects in 11/66 participants (it was not stated in which groups)

Iscimen 2004

Methods	This study was carried out in a secondary care setting, and it was open It was unclear if an ITT analysis was carried out A within-participant randomisation design was employed. This study was conducted in Turkey.
Participants	79 participants were recruited: 3 dropped out. **Inclusion criteria of the trial** • Adults • Ordinary or refractory warts not specified • Warts on any site
Interventions	• Intralesional 5-FU 50ng/ml, lidocaine, and epinephrine • Saline Each lesion was infiltrated with either of the solutions once a week for up to a maximum of 4 weeks
Outcomes	**Outcomes of the trial** 1. Complete response at 1 month and 6 months

Iscimen 2004 (*Continued*)

Notes	The main unit of analysis was warts rather than participants	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	This was randomised by coin flip (additional information was supplied by the trial investigator)
Allocation concealment (selection bias)	Unclear risk	The method was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was described as "single blind". 1 investigator applied the injections and the other investigator evaluated the clinical response. Also, the participants were unaware of the application substance (additional information was supplied by the trial investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 456): "One investigator applied the injections and the other investigator evaluated the clinical response." Comment: This was probably adequate; no details were given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (page 456): "The three drop outs (out of 79 recruited) gave limited time as the reason for discontinuation", but it was unclear which groups these belonged to or how many warts each participant contributed. These participants were deleted from the analyses Comment: This was unlikely to introduce serious risk of bias
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported.

Khan 1999

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This study was conducted in the UK.
Participants	30 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults and children

Khan 1999 (*Continued*)

	• Ordinary or refractory warts not specified • Warts on the feet
Interventions	• Topical Thuja • Placebo The extract (or placebo) was applied weekly for 3 weeks.
Outcomes	**Outcomes of the trial** 1. Resolution at 1 month and 3 months
Notes	This was a conference abstract only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment was carried out using a randomisation table
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was described as double-blind; no details were given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details were given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants who dropped out (from 30 participants) - if any - was unclear
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Khan 2000

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This study was conducted in the UK.
Participants	30 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the feet

Khan 2000 (*Continued*)

Interventions	• Comparison of 3 different fractions of Thuja (hexane, chloroform, or ethyl acetate) applied topically. The duration of therapy was unclear.
Outcomes	**Outcomes of the trial** 1. Resolution
Notes	This was a conference abstract only. The timescale was not clear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatments were assigned according to a randomisation table.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was described as double-blind; no details were given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was described as double-blind; no details were given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow up.
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported.

Khattar 2007

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was carried out. This study was conducted in the USA.
Participants	44 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Participants aged > 12 • Ordinary or refractory warts not specified • The site was not specified
Interventions	• 15% salicylic acid and 15% lactic acid combination ointment versus • 20% zinc oxide These were applied twice daily, over 3 months.

Outcomes	**Outcomes of the trial** 1. Cure at 3 months
Notes	The number of warts per participant ranged from 1 to 41, and the study was aiming for cure of all warts in each participant. There was a higher mean number of warts in the zinc oxide group (5.1 versus 4.3), and participant compliance was not assessed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 427): "Patients were assigned randomly to two groups." Comment: The method of randomisation was unclear.
Allocation concealment (selection bias)	Unclear risk	The allocation concealment was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The medication was labelled A or B; therefore, participants were unaware which treatment they were receiving Personnel were blinded. Quote (page 427): "At the end of the study the pharmacist informed the primary investigator that arm A was 20% zinc oxide and arm B was the 15% alicyclic acid." Comment: This was probably done for both participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was not specifically stated that outcome assessors were blinded Comment: This was judged as probably done as the personnel were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	9/44 participants withdrew: 6/22 in the zinc oxide group and 3/22 in the SA-LA group. Reasons were not stated There be may be a source of bias arising from 1 participant with 41 warts who withdrew
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Larsen 1996

Methods	This study was carried out in a secondary care setting; it was multicentre; and it was open Intention-to-treat analysis was carried out. This study was conducted in Denmark.
Participants	185 participants were recruited: 41 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the hands
Interventions	• Cotton wool bud cryotherapy - 2-weekly intervals versus 3-weekly intervals versus 4-weekly intervals between freezes Treatment continued until wart resolution or a maximum of 6 freezes had been applied
Outcomes	**Outcomes of the trial** 1. Cure at 6 months
Notes	The study was done on 1 index wart per participant only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A table of random numbers was used ('Materials and methods', page 29)
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was attempted (an open trial) .
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding was attempted (an open trial) .
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for attrition were given. Quote (page 29): "There were no significant differences in the age, sex, duration of disease or number of warts among the patients who left the study and the 144 (of 185) patients who completed the treatment schedule." It was unclear how the dropouts were distributed across the treatment groups
Selective reporting (reporting bias)	Unclear risk	Quote (page 29): "For some patients not all the information on treatment results was

		available 3 and 6 months after initiation of treatment."

Lee 1990

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This was a left-right study. This study was conducted in Korea.
Participants	74 participants were recruited: The number of dropouts was unclear **Inclusion criteria of the trial** • Adults and children • Refractory warts • Warts on the hands or feet
Interventions	• IFN-gamma: high-dose (5 millionU/ml) versus • Low-dose (1 millionU/ml) versus • Placebo Intralesional injections were given twice-weekly for 3 weeks
Outcomes	**Outcomes of the trial** 1. Cure at 4 weeks
Notes	The numbers of withdrawals and dropouts were not clear from the text The placebo group (group C) consisted of participants with multiple warts; therefore, they may not be valid

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 78): "...randomly divided in to two groups." No details were given The method was not stated. Also, there was a large discrepancy between the numbers in each group: group A (n = 36), group B (n = 53). Therefore, this was not appropriately randomised
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was unclear if blinding was attempted.

Lee 1990 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear if blinding was attempted.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants out of 74 dropped out; there were no details Comment: This was judged as high risk because of lack of information
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Luk 2006

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was carried out. This study was conducted in China.
Participants	80 participants were recruited: 3 dropped out. **Inclusion criteria of the trial** • Adults • Ordinary or refractory warts not specified • Warts on any site
Interventions	• Cryotherapy using Cryojet once every 3 weeks versus • Cryotherapy as above plus 5% 5-FU ointment applied twice daily Cryotherapy was continued every 3 weeks for a maximum of 5 treatments
Outcomes	**Outcomes of the trial** 1. Number of participants with wart clearance
Notes	The duration of follow up was unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 395): "The patients were randomised into two treatment groups", but the method of randomisation was unclear Comment: Block randomisation was used, with coin flipping (additional information came from the trial investigator)
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes were used (additional information came from the trial investigator) . It was unclear if they were sequentially numbered and opaque

Luk 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 395): "Doctors and nurses who participated in the study were blinded to the exact nature of the medication throughout the study." The participants were blinded (additional information came from the trial investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessors were blinded (additional information came from the trial investigator)
Incomplete outcome data (attrition bias) All outcomes	Low risk	77/80 participants completed. 3 participants - 2 from the cryotherapy + 5-FU group and 1 from the cryotherapy + placebo group - dropped out, although no reasons for dropout were given Comment: This was unlikely to introduce a high risk of bias.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Marroquin 1997

Methods	This study was carried out in a primary care setting, and it was open Intention-to-treat analysis was not applicable. A within-participant randomisation design was employed. This study was conducted in Guatemala.
Participants	30 participants were recruited: The number of dropouts was unclear **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the hands or feet
Interventions	• *Jatropha* sap (twice a day for 15 to 20 days) versus • Cryotherapy (single session) versus • Petrolatum gel (twice a day for 15 to 20 days)
Outcomes	**Outcomes of the trial** 1. Cure at 30 days
Notes	The main unit of analysis was warts rather than participants Only 3 warts per participant were treated. The results were poorly reported. The cryotherapy technique was not described in detail (reference given). *Jatropha* curcas sap was an unknown active ingredient and may have varied in concentration

Marroquin 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was described as a random experimental design. (page 160)
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not attempted.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not attempted.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear if there were dropouts or from which groups. Comment: This was judged as unclear risk as no information was available
Selective reporting (reporting bias)	High risk	The lesions were evaluated at 30 days, but these results were not stated

Martinez 1996

Methods	This study was carried out in a primary care setting, and it was open Intention-to-treat analysis was not carried out. This study was conducted in Spain.
Participants	124 participants were recruited: 3 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts anywhere
Interventions	• Dimethyl ether propane (DMEP) applied by swab • Cotton wool bud cryotherapy, 3 freezes per case at 1-week intervals
Outcomes	**Outcomes of the trial** 1. Cure 15 days after last treatment
Notes	The main unit of analysis was warts rather than participants It was not clear whether warts or participants were randomised. Molluscum and solar keratosis were also included in the study. Liquid nitrogen was applied with gauze
Risk of bias	

Martinez 1996 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as random allocation.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was unclear; no details were given.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blind assessment was made by a doctor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/124 participants completed (there were 3 voluntary withdrawals and no withdrawals because of adverse effects)
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Munkvad 1983

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This study was conducted in Denmark.
Participants	62 participants were recruited: The number of dropouts was unclear **Inclusion criteria of the trial** • Adults • Ordinary or refractory warts not specified • Warts on the hands or feet
Interventions	• 0.2 ml per wart of 1% bleomycin in saline injection in oil versus • Saline alone versus • Oil alone Injections were carried out using Dermajet. 1 to 3 shots were applied depending on the size of the wart. This was repeated 3 times with an interval of 2 weeks
Outcomes	**Outcomes of the trial** 1. Cure at 3 months
Notes	The main unit of analysis was warts rather than participants

Risk of bias

Bias	Authors' judgement	Support for judgement

Munkvad 1983 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was described as double-blind. Comment: Given the different application of the treatments, blinding would have been difficult
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear; no details were given.
Incomplete outcome data (attrition bias) All outcomes	High risk	Out of 62 participants, it was unclear how many dropped out and which groups they were in. The results were reported by wart and not by participants Comment: This was judged as high risk of bias as insufficient information was given about the number of participants completing The numbers did not add up: • bleomycin in oil/feet group: 22 participants in table 1 and 23 participants in table 2; • bleomycin in oil/hands group: 12 participants in table 1 and 11 participants in table 2; and • sesame oil/feet group: 11 (10) participants in table 1 and 10 participants in table 2.
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported. Quote (page 87): "Adverse effects were observed in a total of 19/62 patients in the 4 treatment modalities."

Niimura 1990

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This was a left-right study. This study was conducted in Japan.
Participants	80 participants were recruited: 16 dropped out. **Inclusion criteria of the trial**

Niimura 1990 (*Continued*)

	• Adults and children • Ordinary or refractory warts not specified • Warts on the hands or feet
Interventions	• Intralesional injection of IFN-beta (0.1 mls of 1 millionU/ml weekly) • Placebo (saline injection) Therapy continued until 1 extremity had cleared or the participant had received 10 weekly injections
Outcomes	**Outcomes of the trial** 1. Cure at 10 weeks
Notes	1 wart per participant was injected.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was unclear if true randomisation occurred. No further details were available about the method of randomisation
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 1495): "(Identical) vials were labelled A or B by a controller who maintained the code until the experiment was completed." Comment: This was probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear (stated to be 'double blind').
Incomplete outcome data (attrition bias) All outcomes	High risk	16/80 participants left the study; no reasons were given. The numbers of dropouts by intervention group were not given
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Nofal 2010

Methods	The site was not specified. The blinding within this study was unclear. It was unclear if an ITT analysis was carried out. This study was conducted in Egypt.

Participants	135 participants were recruited: 25 dropped out. **Inclusion criteria of the trial** • Adults • Common warts • Warts on any site
Interventions	• Intralesional MMR vaccine versus • Saline injection Injections were every 2 weeks for a maximum of 5 treatments.
Outcomes	**Outcomes of the trial** 1. Complete or partial response of warts at 6 months
Notes	It was unclear if ethical approval was obtained. There was a difference in numbers between the groups (85 versus 50)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	This was described as randomly-assigned; the sequence was generated by coin flip (additional details were supplied by the investigator)
Allocation concealment (selection bias)	Low risk	The allocation sequence was concealed by sealed envelope (additional details were supplied by the investigator)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants were blinded to the intervention (additional details were supplied by the investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessors were blinded to the intervention (additional details were supplied by the investigator)
Incomplete outcome data (attrition bias) All outcomes	Low risk	110/135 participants completed. Quote (page 1167): "The remaining patients (15 in the MMR group and 10 in the control group) discontinued at different times for different causes, including failure to follow up, and adverse effects, such as pain of the procedure or flu-like symptoms. "
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Parton 1994

Methods	This study was carried out in a primary care setting, and it was open Intention-to-treat analysis was not applicable. This study was conducted in the UK.
Participants	49 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Children • Ordinary warts • Warts on the feet
Interventions	• Abrasion (using fine glass paper) • SA (Duofilm), lesions painted daily It was unclear how long treatment was continued for.
Outcomes	**Outcomes of the trial** 1. Mean time to cure
Notes	The cure rate was not reported (a 100% cure rate was implied in the text) This was a brief report. SA is usually used in combination with paring down of the lesion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 205): This was randomised by "drawing a card from a closed box containing equal numbers of cards marked 'C' control or 'A' abrasion."
Allocation concealment (selection bias)	High risk	This was inadequate as the markings on the cards were visible; therefore, allocation to group was potentially open to manipulation
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not done; it was not possible. Quote (page 205): "The treatment performed would have been obvious at the first return visit."
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was not done; it was not possible to have another assessor present as the trial was performed in a rural, single-handed clinic
Incomplete outcome data (attrition bias) All outcomes	High risk	Out of 49 participants, it was unclear how many dropped out.
Selective reporting (reporting bias)	High risk	The cure rate by group was not adequately reported. Time to cure in months appeared

		to be the main outcome. The length of the study was not stated only 'the patients were reassessed at two weekly intervals by the same practitioner until the lesions resolved', and the time range of the control group was up to 38 weeks

Passeron 2007

Methods	This study was carried out in a secondary care setting. The blinding within this study was unclear. It was unclear if ITT analysis was carried out. This study was conducted in France.
Participants	36 participants were recruited: 1 dropped out. **Inclusion criteria of the trial** • Adults • Ordinary warts • Warts on the hands or feet
Interventions	• Cryotherapy plus 595 nm pulsed dye laser irradiation (595 nm PDL) using a spot diameter 5 mm, pulse duration 0.45 ms, fluence 9 J/cm2 with 5 passes at a frequency of 1 Hz. Cryogen spray cooling (system incorporated in the machine) was given at a rate of 50 spurts of 40 ms prior to each laser pulse) versus • Cryotherapy (cooling pulses alone) These were gIven for up to 3 treatments at 3-weekly intervals
Outcomes	**Outcomes of the trial** 1. Cure at 5 weeks
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The method of randomisation was central randomisation generated by a computer (additional information was supplied by the principal investigator)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was achieved by sending the type of treatment by fax after randomisation (performed by the Department of Clinical Research of the hospital) . (Additional information was supplied by the principal investigator.) Comment: It was unclear if allocation was concealed until treatment

Passeron 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants were blinded. The investigators were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded (additional information was supplied by the principal investigator)
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant out of 35 did not complete the study; this was because of a change in the participant's personal life (additional information was supplied by the principal investigator) Comment: This was unlikely to introduce a high risk of bias.
Selective reporting (reporting bias)	High risk	The type and number of warts was specified as an outcome, but only the percentage of resolved warts was reported (along with self-assessed safety scores). 75 warts were treated in the PDL group (19 patients) and 30 in the placebo group (16 participants)

Pazin 1982

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This study was conducted in the USA and Finland.
Participants	1 participant was recruited; this person did not dropout (described as patient 2 'WK') **Inclusion criteria of the trial** • Adults • Refractory warts • Warts on the hands or feet
Interventions	• Intralesional injection of IFN-alpha • Placebo (Various regimes and doses)
Outcomes	**Outcomes of the trial** 1. Cure at 15.5 weeks
Notes	The inclusion of multiple and resistant warts may introduce bias and clinical heterogeneity. A previous course of intramuscular interferon had been tried with 'modest effects'

Risk of bias

Pazin 1982 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	There was no random allocation (because of there only being 2 participants). This was described as 'coded double blind manner'
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was stated to be double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants (n = 2) completed.
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported.

Perez 1992

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. It was not clear in which country the study was conducted.
Participants	37 participants were recruited: 6 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Warts on the hands or feet
Interventions	• Intralesional injection of 0.1% bleomycin • Saline 2 cycles (at days 14 and 30) were injected if necessary.
Outcomes	**Outcomes of the trial** 1. Cure at 30 days
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Perez 1992 (*Continued*)

Random sequence generation (selection bias)	High risk	Quote: "Patients were distributed in 2 groups". It was unclear what method, if any, was used to randomise
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "During the trial the researchers and the parents didn't know which treatment was used"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear; no details were given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	31/37 participants competed: 15 in the saline group and 11 in the bleomycin group. The reasons for dropout were unclear
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Rahimi 2008

Methods	This study was carried out in a secondary care setting, and it was open It was unclear if ITT analysis was carried out This study was conducted in Iran.
Participants	60 participants were recruited: 8 dropped out. **Inclusion criteria of the trial** • Adults and children • Common, flat, and plantar • Warts on the hands or feet
Interventions	• Cryotherapy applied by cotton wool bud • Burnt leaves of *Populus euphratica* (using a smoke box for 10 minutes at a time) These were applied for up to 10 cycles if necessary for the smoke treatment, but the total number of cryotherapy cycles was unclear
Outcomes	**Outcomes of the trial** 1. Cure at 6, 12, and 2 weeks
Notes	The cryotherapy treatment may not have been adequate.

Risk of bias

Bias	Authors' judgement	Support for judgement

Rahimi 2008 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote (page 393): "Patients were randomly assigned to either smoke (group A) or cryotherapy (group B)." Comment: The method of randomisation was unclear.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 393): "...single blind prospective study". However, it was not stated who was blinded and how Comment: The participants were probably not blinded given the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 394): "The physician measuring the lesion size during follow-up was blind to the nature of therapy."
Incomplete outcome data (attrition bias) All outcomes	High risk	8/60 participants were not analysed (described as 'defaulters'): 6 in the smoke group and 2 in the cryotherapy group; no reasons were given
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Robson 2000

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in the USA.
Participants	40 participants were recruited: 5 dropped out. **Inclusion criteria of the trial** • Adults • Mixed • Warts on the hands or feet
Interventions	• Pulsed dye laser (585 nm) • 'Conventional' treatment (cotton wool bud cryotherapy or cantharidin (1% cantharidin, 30% salicylic acid, and 5% podophyllin under occlusion for 3 to 4 hours) Either intervention was applied for a maximum of 4 sessions. All participants used SA at home
Outcomes	**Outcomes of the trial** 1. Cure at approximately 16 weeks

Robson 2000 (*Continued*)

Notes	The following quote was from the trial report: "Preliminary testing for outcome clustering within subjects demonstrated a significant dependence in wart treatment outcomes. Hence, most statistical investigations were performed using subjects and not warts as the unit of analysis. Statistical analysis was performed by means of analysis of variance and tests of association."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised. (page 276)
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was described. Comment: This was unlikely given the differences in the application of the treatments
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding was described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The 5/40 participants who withdrew were all from the PDT group, but they withdrew for reasons unrelated to treatment
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Rossi 1981

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This study was conducted in Italy.
Participants	16 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults and children • Refractory warts • The wart site was not specified
Interventions	• Intralesional bleomycin 0.1% injection versus • Placebo (saline) injection
Outcomes	**Outcomes of the trial** 1. Cure at 1 month

Rossi 1981 (*Continued*)

Notes	The main unit of analysis was warts rather than participants. As 12/16 warts cured in the placebo group were from 1 participant, this may have introduced a source of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 3): "Patients were randomised to two groups of treatment."
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	It was stated that the trial was double-blinded. Quote (page 3): "Neither the patients nor the researchers were aware of the contents of the treatment which was only revealed at the end if the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear; no specific details were given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	16/16 participants completed. No details were given regarding adverse effects
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported.

Salk 2006

Methods	This study was carried out in a primary care setting. The blinding within this study was unclear. It was unclear if ITT analysis was carried out This study was conducted in the USA.
Participants	40 participants were recruited: 2 dropped out. **Inclusion criteria of the trial** • Adults only • Ordinary or refractory warts not specified • Warts on the feet only
Interventions	• Tape occlusion versus • 5% 5-FU cream under tape occlusion every 2 weeks for up to 12 weeks applied twice daily Both groups were instructed to debride the wart daily with a pumice stone. Treatment continued for up to 12 weeks

Salk 2006 (*Continued*)

Outcomes	**Outcomes of the trial** 1. Cure at 6 months
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly separated into 2 treatment groups." Comment: The method was unclear.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was unclear if blinding was used. Comment: No placebo cream was applied instead of 5-FU; therefore, blinding was unlikely
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear if blinding was used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	38/40 enrolled participants completed the study. Both dropouts were from the tape group; reasons were given
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Schmidt 1981

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in Denmark.
Participants	60 participants were recruited: 5 dropped out. **Inclusion criteria of the trial** • Adults • Ordinary or refractory warts not specified • Warts on the hands or feet
Interventions	• 5-FU/SA • Placebo (vehicle alone) Treatment was applied daily for 6 weeks.

Schmidt 1981 (*Continued*)

Outcomes	**Outcomes of the trial** 1. Cure (presumably at 6 weeks)
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was unclear. This was described as double-blind; the placebo appeared to be identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear; no details were given.
Incomplete outcome data (attrition bias) All outcomes	High risk	5/60 participants completed. The results for 5 dropouts (2/30 Verrumal and 3/30 placebo) "could not be analysed" (page 1). No reasons were given Also, it was not stated how many participants were randomised to each group - it was presumed that there were 30 in each group
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Sharquie 2007

Methods	This study was carried out in a secondary care setting. This study was blinded. It was unclear if ITT analysis was carried out This study was conducted in Iraq.
Participants	90 participants were recruited: 23 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • The site was not specified

Sharquie 2007 (*Continued*)

Interventions	• 5% zinc sulphate or • 10% zinc sulphate versus • Distilled water These were applied 3 times daily for 4 weeks.
Outcomes	**Outcomes of the trial** 1. Cure at 2 weeks, 4 weeks, and 6 months
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computerised (additional information came from the trial investigator)
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote ('Methods', page 1418): "...double blinded study." Containers were labelled by a third person and the contents were unknown by the treating doctor or participant until the end of the study. (page 1419)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote ('Methods', page 1418): "...double blinded study." No further details were given about the blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	23/90 participants dropped out (did not complete therapy). It was unclear which intervention group(s) the dropouts belonged to
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Sonnex 1988

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was not applicable. This study was conducted in the UK.
Participants	31 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults

	• Refractory warts • Warts on the hands or feet
Interventions	• Cryogun cryotherapy: aggressive "two 20 s freezes (hand) or two 30 s freezes (foot)" versus • Standard cryotherapy "single 10 s liquid nitrogen freeze (hand) or two 15 s freezes (foot)" It was unclear if the treatment sessions were repeated. LA was also applied
Outcomes	**Outcomes of the trial** 1. Cure at 4 weeks
Notes	This was published as an abstract only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was described as randomised, but no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding was described. Comment: It was unlikely given the difference in freeze times
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding was described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The report of the trial was silent with respect to dropouts or losses to follow up; however, the number of warts randomised and assessed after treatment was the same Commment: This was assessed as at low risk of bias.
Selective reporting (reporting bias)	Low risk	The single outcome of wart clearance was reported. Adverse effects were not stated; there was only a quote on page 38: "...there was no significant scarring."

Spanos 1990

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This study was conducted in Canada.
Participants	40 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults • Ordinary or refractory warts not specified • Warts on the hands or feet
Interventions	• Hypnosis versus • SA (Dermacyl, aka 'Compound W' for up to 2 weeks) versus • Placebo versus • Nil (no intervention) The duration of the intervention was unclear.
Outcomes	**Outcomes of the trial** 1. 'Loss of warts' at 6 weeks
Notes	The strength and frequency of application of SA was not reported, so there may have been inadequate treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that participants were randomly assigned, but no details were given
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Salicyclic acid was compared with an identical placebo. Hypnosis was compared with a waiting list control. Therefore, this was probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 110): "...all subjects had their warts recounted by a technician who was blind to their treatment." Comment: This was assessed as 'low risk'.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information is given about dropouts or reasons for dropout or loss to follow up
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Stahl 1979

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was not carried out. This study was conducted in Denmark.
Participants	149 participants were recruited: 29 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the hands or feet
Interventions	• Methylene blue/DMSO PDT, once a week for 8 weeks (0.1% methylene blue (absorption maximum 664 nm) in 80% DMSO and 20% alcohol was applied with a cotton-tipped applicator) • SA/creosote ointment (16 % salicylic acid and 24% creosote), dally application for 8 weeks.
Outcomes	**Outcomes of the trial** 1. Cure at 8 weeks and presence of complement-fixing antibodies
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was apparently attempted. It was unlikely because of differences in treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding was apparently attempted.
Incomplete outcome data (attrition bias) All outcomes	High risk	9/74 participants did not complete treatment in the PDA (intervention) group, and 20/75 participants did not complete treatment in the control group, with no reasons given Comment: This was judged as high risk of bias because of an uneven distribution of dropouts
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported. Complement level data were only available

		for 106/149 participants

Steele 1988a

Methods	This study was carried out in a primary care setting, and it was open Intention-to-treat analysis was not carried out. This study was conducted in the UK and Germany.
Participants	207 participants were recruited: 18 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the hands or feet
Interventions	• Weekly cotton wool bud cryotherapy versus • SA/LA paint daily versus • Both cryotherapy and SA/LA On alternate days, participants in all 3 treatment groups were instructed to soak their warts in warm water and abrade then with a pumice stone or emery board
Outcomes	**Outcomes of the trial** 1. Cure at 6 months
Notes	Multiple and mosaic plantar warts were excluded. Adverse effects were not assessed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	This was randomly assigned using a random number tables. (page 256)
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was unlikely because of the application of the intervention Quote (page 257): "Liquid nitrogen does not lend itself to a double blind trial."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear; no details were given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 13/129 withdrawals from the hand-wart trial: 10/13 were irregular attendees; 2/13 withdrew because of pain; and 1/13 hospital were admissions, but it was not clear which groups the withdrawals were

Steele 1988a (*Continued*)

		from There were 5/78 withdrawals from the plantar-wart trial: 4/5 were irregular attendees; 1/5 withdrew because of pain (groups not stated). (page 257)
Selective reporting (reporting bias)	Unclear risk	Adverse effects were not reported.

Steele 1988b

Methods	This study was carried out in a primary care setting. This study was blinded. Intention-to-treat analysis was not applicable. This study was conducted in the UK and Germany.
Participants	57 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the feet (simple plantar)
Interventions	• Monochloracetic acid crystals + 60% SA • Placebo The wart was covered with a dressing and left in place for 1 week, then it was pared and debrided. No further therapies or dressings were applied
Outcomes	**Outcomes of the trial** 1. Cure at 6 weeks and 6 months
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random number table was used.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was described as 'double blind'. Quote (page 538): "Containers containing placebo were dabbed with acetic acid to prevent recognition of the active preparation by smell." Quote (page 539): "Preparations were made up, dispensed and allocated using a random numbers table, by the health cen-

Steele 1988b (*Continued*)

		tre pharmacist." Comment: This was probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear, although the trial was described as 'double blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 57 participants who were recruited completed the trial.
Selective reporting (reporting bias)	Low risk	All stated outcomes were reported.

Stender 1999

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was carried out. A within-participant randomisation design was employed. This study was conducted in Denmark.
Participants	30 participants were recruited: 2 dropped out. **Inclusion criteria of the trial** • Adults • Refractory warts • Warts on the hands or feet
Interventions	• PDT: white, red, and blue light was applied 3 times within 10 days and white light once in 10 days (Kodak, fluence rate 22 mW/cm2 in 30 minutes) • Cryotherapy (liquid nitrogen spray) up to 4 times within a 2-month period
Outcomes	**Outcomes of the trial** 1. Cure at 4 to 6 weeks
Notes	Warts were the unit of analysis. Results were given as percentages only. There was no placebo group; SA was used in all groups.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not, apparently, attempted in this pilot study as the discussion stated that the results should be "verified in a double

Stender 1999 (*Continued*)

		blinded placebo-controlled study." (page 158)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 155): "Clearance of the warts was assessed clinically, and not blinded." Also, the discussion stated that the results should be "verified in a double blinded placebo-controlled study."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All warts that were entered into the study were reported in Table 8 Quote (page 156): "Three patients had to discontinue treatment because of intolerable pain during the first minutes of R3, B3 and W3 exposure. One patient randomised to W3 did not return after a single treatment. One patient randomised to CRYO discontinued after a single treatment because of pain." Comment: It is unclear how treatment response was assessed for dropouts
Selective reporting (reporting bias)	Low risk	Wart clearance was reported, as stated.

Stender 2000

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was carried out. A within-participant randomisation design was employed. This study was conducted in Denmark.
Participants	45 participants were recruited: 5 dropped out. **Inclusion criteria of the trial** • Adults • Refractory warts • Warts on the hands or feet
Interventions	• ALA photodynamic therapy versus • Placebo PDT • Both with paring and Verrucid Prior to treatment, all warts were pared by a scalpel. A topical application of 20% ALA cream or placebo cream was applied. 4 hours later all warts were irradiated with a red light source or placebo photodynamic therapy repeated at 1 week and 2 weeks The ALA-PDT and placebo-PDT interventions were repeated after 1 and 2 weeks. If the warts persisted at week 7, ALA-PDT or placebo-PDT were applied again 3 times at 1-week intervals.

	Participants were instructed to pare all their warts with a scalpel twice a week during the whole study and then apply SA/LA
Outcomes	**Outcomes of the trial** 1. Cure at 18 weeks
Notes	Warts were used as the unit of analysis. SA was also used in both groups.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 963): "...independent, centralised, computer generated block randomisation. A block size of two (unknown to the clinical investigators) was chosen, ensuring the application of both treatments for patients with more than one wart."
Allocation concealment (selection bias)	Low risk	Quote (page 963): "All warts were consecutively numbered and the treatments were allocated blindly to intervention...independent, centralised, computer generated block randomisation" Comment: This was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Particpants were blinded (cream or identical placebo). Comment: This was probably done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 964): "...area of the wart was measured by a dermatologist unaware of treatment allocation." Comment: This was adequate.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts were given at each stage of the trial. The dropouts were balanced across the groups
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Togsverd-Bo 2010

Methods	This study was carried out in a secondary care setting, and it was multicentre Outcome assessors were blinded, but it was unclear whether participants were blinded Intention-to-treat analysis was carried out. This study was conducted in Denmark.
Participants	89 participants were recruited: 11 dropped out. **Inclusion criteria of the trial** • Adults or children not specified, median ages ranged from 40 to 46 • Refractory warts • Warts on the hands or feet
Interventions	• Paring versus • Paring with intense pulse light with 3 treatments at 3-weekly intervals
Outcomes	**Outcomes of the trial** 1. Clearance of warts and adverse effects at 6 weeks
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 180): "Central treatment allocation was carried out blindly by an independent telephone randomisation system (Copenhagen Trial Unit) that was based on a computer-generated randomisation list."
Allocation concealment (selection bias)	Low risk	Quote (page 180): "The allocation was concealed until immediately before an included patient was to receive the first treatment." Comment: This was probably done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants and the doctor that performed the IPL were not blinded to the intervention as this was not possible. Nurses performed paring of the warts were blinded to whether patients received paring or paring + IPL. Additional information was supplied by the trial investigator
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 181): "Treatment response and adverse effects were evaluated 6 weeks after the last of three treatments by blinded, photographic evaluations on a semi-quantitative clinical assessment and were compared with pre-treatment photos. One

		blinded assessor evaluated all photographs (KT)." Comment: All treatment effect evaluations were carried out blinded (additional information was supplied by the trial investigator)
Incomplete outcome data (attrition bias) All outcomes	Low risk	83/89 participants completed. Quote (page 181): "Clinical photos were missing (accidentally deleted) from five patients, who were excluded from treatment response analysis. In total, data from 78 patients was included in the treatment response intention-to-treat analysis." Figure 1 shows 1 patient was missing from paring + IPL and 4 participants from paring alone Comment: Although the report of the study describes an intention-to-treat analysis, the missing participants suggest that the analysis is not in fact ITT
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Vali 2007

Methods	This study was carried out in a secondary care setting. This study was blinded. It was unclear if ITT analysis was carried out This was a left-right study. This study was conducted in India.
Participants	78 participants were recruited: 3 dropped out. **Inclusion criteria of the trial** • Aged 10 to 50 years old • Plane warts • The site was not specified
Interventions	• 0.05% tretinoin lotion versus • 50% citric acid solution Treatment was applied twice daily on the wart for 6 weeks.
Outcomes	**Outcomes of the trial** 1. Number of warts at 3-week and 6-week intervals
Notes	The unit of analysis was individual warts.
Risk of bias	

Vali 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 97): "The side that was treated was randomly selected by a fair coin flipped manner."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 97): "Both drugs were inside identical tubes, had similar appearance and were marked with a recognition code." However, it was unclear how the personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear; no details were given about the blinding of the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "75 out of 78 patients participated in the entire study. Two patients were excluded because of irregular use of drugs and another did not complete to the follow-up visits." Comment: This was unlikely to introduce bias.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Vance 1986

Methods	This study was carried out in a secondary care setting, and it was multicentre This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in the USA.
Participants	111 participants were recruited: 11 dropped out. **Inclusion criteria of the trial** • Adults • Ordinary or refractory warts not specified • Warts on the feet only
Interventions	• IFN-alpha: high-dose 10 millionU/ml versus • Low-dose 1 millionU/ml versus • Placebo Warts were injected intralesionally with 0.1 mL of 1 of the 3 solutions 3 times weekly for 3 weeks

Vance 1986 (*Continued*)

Outcomes	**Outcomes of the trial** 1. Cure at 12 weeks
Notes	1 wart per participant was injected. McEwen 1983 was a conference abstract of an RCT of interferon subsequently published in 1986 with Vance as first author (Vance 1986).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details were given.
Allocation concealment (selection bias)	Unclear risk	There was no information about the how the randomisation sequence was concealed (sealed envelopes etc) Comment: Vials were sequentially numbered; therefore, it was unclear if the allocation order was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The content of the vials were prepared by the manufacturers and were not revealed to participants or personnel. (page 273)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear who did the outcome assessment and if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	100/111 participants completed and were analysed. 5 participants in the 10 IFN group discontinued because of adverse reactions; 6 participants terminated for extraneous reasons, as well as 2 in each treatment group Comment: Withdrawals because of adverse events in the intervention arm were likely to introduce bias
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Varnavides 1997

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This study was conducted in the UK.
Participants	51 participants were recruited: 9 dropped out. **Inclusion criteria of the trial** • Adults • Refractory warts • Warts on the hands or feet
Interventions	• IFN-alpha (10 IU/ml weekly X 12) • Placebo Intralesional injections were given once weekly for 12 weeks
Outcomes	**Outcomes of the trial** 1. Cure at 24 weeks
Notes	1 wart per participant was injected.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 170): "...assigned either interferon alpha or placebo according to a computer-generated randomised code."
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: This was probably done, but while trial or placebo medication was supplied in 'identical 1 ml vials' (page 170) and the trial was stated to be double-blind, it was not clear how blinding was achieved. However, both participants and personnel were probably blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 170): "Objective assessment was made by a photographic record on slide film at entry..." Comment: This was probably done.
Incomplete outcome data (attrition bias) All outcomes	High risk	9/51 participants did not complete the trial because of adverse effects, attendance, or worsening: 3/9 participants in the intervention group and 6/9 participants in the placebo group. 7/9 participants withdrew because of painful injections/adverse ef-

		fects; however, groups were not stated. It was unbalanced between the groups
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Veien 1977

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This was a left-right study. This study was conducted in Denmark.
Participants	56 participants were recruited: 6 dropped out. **Inclusion criteria of the trial** • Adults and children • Refractory warts • Warts on the hands or feet
Interventions	• PDT with proflavine/DMSO versus • Neutral red/DMSO PDT • Placebo dye plus PDT 8 weekly treatments were given in total.
Outcomes	**Outcomes of the trial** 1. Cure at 8 weeks
Notes	The placebo half of the body was also cured in all those who responded. In those who did not respond to treatment, the placebo half of the body was unaffected (i.e. no warts were cured)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 445): "...following randomisation." The method was not stated
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 445): "A double-blind, paired comparison treatment schedule was initiated." It was not stated whether participants or personnel were blinded Quote (page 445): "The dyes were freshly prepared for each patient", so it was unlikely that the personnel were blinded; however, 'all the bottles were identical ap-

Veien 1977 (*Continued*)

		pearance, and the active dyes were indistinguishable from the corresponding placebos.' (page 445)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not stated whether the outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/56 participants withdrew. The reasons for withdrawal were not stated Comment: It was unlikely to introduce high risk of bias.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Veien 1991

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was carried out. This study was conducted in Denmark.
Participants	250 participants were recruited: 80 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary or refractory warts not specified • Feet (simple plantar)
Interventions	• SA/LA with occlusion • SA/LA Applied twice daily for up to 17 weeks.
Outcomes	**Outcomes of the trial** 1. Cure at 17 weeks
Notes	Results were expressed as percentage only. Higher cure rates in children were noted.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 59): "Groups of ten patients were allocated to one of the two treatments by balanced block randomisation." Comment: This was probably done.
Allocation concealment (selection bias)	Unclear risk	This was unclear

Veien 1991 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	This was described as open.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was described as open.
Incomplete outcome data (attrition bias) All outcomes	High risk	170/250 participants completed. There was a high dropout rate (n = 80). Dropout related to therapy was more common among participants treated with the keratolytic agent and occlusion (n = 18) than among participants treated with the keratolytic agent alone (n = 9) The results were presented using an intention-to-treat analysis, but percentages were given rather than participant numbers
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Wang 2002

Methods	This study was carried out in a secondary care setting. The blinding within this study was unclear. It was unclear if ITT analysis was carried out This study was conducted in China.
Participants	126 participants were recruited: The number of dropouts was unclear **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the hands and face
Interventions	• Topical Chinese herbal medicines + 1% retinoic acid • Retinoic acid alone Either therapy was applied 3 times daily for up to 3 7-day courses of treatment
Outcomes	**Outcomes of the trial** 1. Cure after 3 courses of treatment
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Wang 2002 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	It was stated that participants were randomly divided into 2 groups. No details were given
Allocation concealment (selection bias)	Unclear risk	This was unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was unclear if blinding was used. The 2 treatment modalities were different; therefore, the study was probably not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear if blinding was used.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts were reported.
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported. Comment: It was unclear how the per cent improvement was judged

Wenner 2007

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was carried out. This study was conducted in the USA.
Participants	90 participants were recruited: 10 dropped out. **Inclusion criteria of the trial** • Adults • Ordinary or refractory warts not specified • Non-genital warts
Interventions	• Transparent duct tape versus • moleskin pad worn for 7 days with debridement Treatment was continued for up to 2 months
Outcomes	**Outcomes of the trial** 1. Cure at 1 month or 2 months
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote (page 310): "Allocation to these 2 groups was determined by computer-generated randomisation."
Allocation concealment (selection bias)	Low risk	Quote (page 310): "Allocation to these 2 groups was determined by computer-generated randomisation log accessible only to a research pharmacist" Comment: This was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 310): "The investigators and participants were blinded to the randomisation status." Participants and personnel were blinded to the intervention as they appeared identical (appeared to be a flesh-coloured pad). Additional information came from the trial investigator
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded as the treatment group was not revealed until all data were recorded. Additional information came from the trial investigator
Incomplete outcome data (attrition bias) All outcomes	Low risk	80/90 participants completed; 5 in each group withdrew. Reasons for discontinuation were reported. Withdrawals were distributed evenly between the groups
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Wilson 1983

Methods	This study was carried out in a secondary care setting, and it was open Intention-to-treat analysis was applicable. This study was conducted in the UK.
Participants	60 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults • Ordinary warts • Warts on the hands
Interventions	• DNCB • Cryotherapy • No treatment No details were given regarding duration or repeat treatments

Wilson 1983 (*Continued*)

Outcomes	**Outcomes of the trial** 1. Cure at 4 months
Notes	This was published as an abstract only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was described, but no details were given.
Allocation concealment (selection bias)	Unclear risk	Quote (page 191): "...using sealed envelopes". It was unclear if they were sequentially numbered and opaque Comment: This was adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no apparent attempt at blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	There was no apparent attempt at blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 60 participants completed the study.
Selective reporting (reporting bias)	Unclear risk	This was unclear; all outcomes were apparently reported, but there was no indication of adverse effects

Wolff 1980

Methods	This study was carried out in a secondary care setting. This study was blinded. Intention-to-treat analysis was not carried out. This was a left-right study. This study was conducted in Germany.
Participants	30 participants were recruited: 7 dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • Warts on the hands or feet
Interventions	• 5-FU/SA • Placebo

Wolff 1980 (*Continued*)

Outcomes	**Outcomes of the trial** 1. Cure at a mean of 4.4 weeks
Notes	This was an unpublished study. The follow-up period was not clear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was described as double-blind, and the code was broken only at the end of the study Comment: This was probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	7/30 participants were not used in the analysis. 6/7 participants in the 5-FU group and 1/7 in the placebo group applied treatment incorrectly. This 1 participant was excluded from the analysis. Only 21 were wart participants; 2 were molluscum contagiosum participants (data excluded) Comment: It was unclear how dropouts were distributed between the groups
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Wu 2005

Methods	This study was carried out in a secondary care setting. The blinding within this study was unclear. It was unclear if ITT analysis was carried out This study was conducted in China.
Participants	60 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults • Ordinary or refractory warts not specified • Warts on the hands and face

Wu 2005 (*Continued*)

Interventions	• Chinese tradition herbal medicine (Qu You Ding) • Peptide butylamine lineament in the control group Both groups underwent a 2-week course of daily treatment.
Outcomes	**Outcomes of the trial** 1. Cure at 8 weeks
Notes	The article was in Chinese; full translation was obtained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was unclear.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details were given about blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details were given about blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	6/60 participants were not included in the analysis because of incomplete data: 2/30 participants were in the treatment group; 4/30 participants were in the control group It was unclear why the participants discontinued.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Yazar 1994

Methods	This study was carried out in a secondary care setting. The blinding within this study was unclear. It was unclear if ITT analysis was carried out This study was conducted in Turkey.
Participants	70 participants were recruited: None dropped out. **Inclusion criteria of the trial** • Adults and children • Ordinary warts • The site was not specified

Yazar 1994 (*Continued*)

Interventions	• Silver nitrate • Placebo (black ink) Treatment was applied by a physician 3 times at intervals of 3 days
Outcomes	**Outcomes of the trial** 1. Cure at 1 month
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised; no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	An attempt was made to disguise the appearance of the placebo solution Quote (page 330): "The patients were warned that the colour of their warts would change to black later". Also, black ink was applied, which suggest that there was some attempt at blinding participants Comment: It was unclear if blinding strategies were used or whether they were adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/70 participants dropped out.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Yazdanfar 2008

Methods	This study was carried out in a secondary care setting. This study was blinded. It was unclear if ITT analysis was carried out This was a left-right study. This study was conducted in Iran.

Participants	40 participants were recruited: 6 dropped out. **Inclusion criteria of the trial** • Adults • Ordinary or refractory warts not specified • Not feet or periungual
Interventions	• Normal saline versus • 4 ml/50 mg/ml 5-FU, 1 mg/20 mg/ml lignocaine, and 0.0125 mg/ml epinephrine The interventions were injected intradermally into the base of the wart, weekly, up to 4 times
Outcomes	**Outcomes of the trial** 1. Cure at 1 month and 6 months
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was unclear.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described as double-blind. Quote (page 657): "Patients, physicians, and nurses who participated in this study were blinded to the exact nature of the medications being injected throughout the study." Comment: This was probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not stated whether the outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote (page 657): "6 patients [who] withdrew did so for reasons unrelated to treatment, such as job relocation and scheduling conflicts." It was unclear if these were equally balanced across the intervention and control groups
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Zhang 1999

Methods	This study was carried out in a secondary care setting. The blinding within this study was unclear. It was unclear if ITT analysis was carried out This study was conducted in China.
Participants	107 participants were recruited: The number of dropouts was unclear **Inclusion criteria of the trial** • Children or adults not specified • Ordinary warts • Warts on the feet
Interventions	• Chinese herbal medicine decoction (soak foot once daily for 30 minutes for up to 10 days) • Electrocautery knife
Outcomes	**Outcomes of the trial** 1. Recovery after 3 courses of treatment
Notes	The data were obtained from a brief translation of the paper - see correspondence from Taixiang Wu

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was unclear.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear if there were dropouts.
Selective reporting (reporting bias)	Unclear risk	It was unclear if all outcomes were reported.

5-FU = topical 5-fluorouracil
ALA = aminolaevulinic acid
BCG = bacille Calmette-Guérin (BCG is a vaccine against tuberculosis)
Cg = cryogun
Cwb = cotton wool bud

DMSO = dimethyl sulphoxide
DNCB = dinitrochlorobenzene
GM-CSF = granulocyte-macrophage colony stimulating factor
IFN-alpha = interferon-alpha
Intralesional MMR = measles, mumps, and rubella vaccine (MMR)
IPL = intense pulsed light
LA = lactic acid
LFU = lost to follow up
MCAA = monochloroacetic acid
SA = salicylic acid
PDL = pulsed dye laser
PDT = photodynamic therapy
PP = per-protocol
OTC = over-the-counter medication
VIS = visible light
wIRA = water-filtered infrared-A

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

Study	Reason for exclusion
Ahmed 2001	This was a controlled clinical trial of cryogun versus cotton-bud cryotherapy. Treatment was allocated by a consultant in charge (there was no randomisation)
Amer 1988	This was a within-participant, open controlled clinical trial of intralesional bleomycin. There was no randomisation
Anderson 1963	This was a controlled clinical trial of formalin soaks versus oral and topical placebos. Allocation to treatment was alternate
Androphy 1984	This was a controlled clinical trial of intralesional and systemic interferon-alpha in participants with an abnormal immune response to HPV. There was no randomisation
Baggish 1985	This was a randomised controlled trial of laser treatments on genital and perianal warts, i.e. in the genital area and not 'common warts'
Benton 1991	This was a RCT of systemic inosine pranobex.
Blancas 2002	There was no mention of randomisation. It was not clear whether treatment was local or systemic
Bleiker 1997	This was a controlled clinical trial of cryogun versus cotton-bud cryotherapy. It was not randomised
Braatz 1974	This was a RCT of ultrasound therapy, which was not an intervention used in this review
Breitbart 1979	This was a double-blind, within-participant controlled clinical trial of topical 5-fluorouracil. There was no mention of randomisation
Canpolat 2008	This was a quasi-randomised study.

(*Continued*)

Ebrahimi 2007	The study used alternate allocation as method of 'randomisation'
El-Tonsy 1999	This was a probable randomised trial of carbon dioxide laser, but no clinical outcomes were measured
Erbagci 2005	No results were available.
Fabbrocini 2001	This was a quasi-randomised trial.
Gach 2005	This study did not evaluate cure rate.
Goihman-Yahr 1978	This was a controlled clinical trial of topical DNCB. This was an open, left-right study with no randomisation
Gupta 2006	No results were available.
Johnson 2001	This was a quasi-randomised study of intralesional mumps or Candida antigens versus cryotherapy
Jung 1971	This was a controlled clinical trial of caustic and surgical removal of warts with and without oral amantadine. There was no mention of randomisation
Kainz 1996	This was a randomised controlled trial of a systemic homeopathic treatment rather than a local treatment (prior publication as a poster presentation and data subsequently published formally (duplicate publications))
Kang 1999	This assessed systemic treatment.
Kassis 1989	This was a RCT of ultrasound therapy, which was not an intervention used in this review
Khan 1998	This was a small case series of 30 participants treated with topical Thuja
Kim 2010	This was a phase 1 clinical trial of intralesional injection of Candida antigen for the treatment of warts
Kubeyinje 1996	This was a randomised controlled trial of 0.05% tretinoin cream, which was not a focus of this review
Labecque 1992	This was a RCT of 3 systemic homeopathic treatments (Thuja, antimony, and nitric acid)
Lahti 1982	This was a controlled clinical trial of topical tuberculin jelly. There was no mention of randomisation
Locke 1970	Description of the treatment was with intralesional sodium tetradecyl sulfate. Percentage success was reported, but no numbers were. This was obviously not an RCT
Lyell 1951	This was a histological study of a case series of 102 participants
Ma 2000	This was a controlled clinical trial.
Manchanda 1997	This was a RCT of various systemic homeopathic treatments.

(*Continued*)

Marchant 1974	This was an open clinical trial of various topical treatments, including 70% SA for plantar warts. There was no mention of randomisation
Peng 2001	This was a randomised trial of systemic treatment (intramuscular fractionated BCG)
Penny 2005	This study did not report cure rate as an outcome.
Pueyo 1990	This was a within-participant clinical trial of intralesional interferon-alpha. Only 3 of 9 participants received placebo. There was no mention of randomisation or blinding
Schreiner 1995	This was a possible randomised trial of topical 0.025% tretinoin gel, topical 100,000 IU/g interferon-beta gel, and both treatments combined. A letter addressed to the authors requesting clarification of the randomisation procedure was not answered
Shumer 1983	This was a double-blind controlled clinical trial of intralesional bleomycin with alternate allocation of treatment
Stender 2006	This did not evaluate efficacy of treatment.
Stern 1992	This was a randomised controlled trial of localised heat therapy, which was not a focus of this review
Stevens 1975	This was a randomised controlled trial of transfer factor (systemic rather than local treatment)
Takigawa 1985	This was a controlled clinical trial of placebo tape versus tape impregnated with bleomycin
Xhao 2000	This was a controlled clinical trial.
Xia 2001	This was a controlled clinical trial.
Yaghoobi 2009	The study looked at oral treatment not topical treatment.
Yu 2000	The study assessed a mixture of systemic and local treatments - oral Chinese herbal medicine + topical aciclovir versus intramuscular vitamin B and oral and topical aciclovir
Zedan 2009	This was a RCT of oral therapy (propilis).

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bastuji-Garin 2001

Methods	This was a randomised double-blind trial.
Participants	**Inclusion criteria of the trial** • Recalcitrant foot warts
Interventions	• Photodynamic therapy with 5-aminolevulinic acid or placebo

Bastuji-Garin 2001 (*Continued*)

Outcomes	**Outcomes of the trial** These were unclear.
Notes	A full text copy of this study was unavailable at the time of review preparation

Dall'oglio 2012

Methods	This was a systematic review.
Participants	Information about participants was unclear.
Interventions	• Salicylic acid • Silver nitrate • Glutaraldehyde • Cryotherapy • Alternative therapeutic options (topical, intralesional, systemic, and physical destruction)
Outcomes	**Outcomes of the trial** • Remission rates - "significantly higher remission rates may be expected only with cryotherapy and salicylic acid used in combination"
Notes	A full text copy of this study was unavailable at the time of review preparation

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

ISRCTN78267267

Trial name or title	Cryotherapy versus Salicylic Acid with Monochloracetic Acid for the Treatment of Verrucae: A Randomised Controlled Trial
Methods	This was a randomised controlled trial.
Participants	There were 133 participants in each treatment group. **Inclusion criteria of the trial** • Plantar warts
Interventions	• Cryotherapy (alone) versus • Salicylic acid with monochloroacetic acid
Outcomes	**Outcomes of the trial** • Effectiveness of the 2 treatments in cleaning up the warts • Cost-effectiveness of the 2 treatments compared to one another • Acceptability of participants' treatment and possible side-effects, such as pain
Starting date	2003

ISRCTN78267267 (*Continued*)

Contact information	Miss Julie C Day Podiatry Department First Floor East Wing St Pancras Hospital 4 St Pancras Way UK jules.day@virgin.net
Notes	This trial was stopped in 2006 because of staffing problems.

NCT00155584

Trial name or title	Topical 5-Aminolevulinic Acid Photodynamic Therapy for the Treatment of Verruca Vulgaris: Comparison of Red and Green Light-Emitting Diode Array
Methods	This is using a random-sample observational model: natural history Time perspective: longitudinal Time perspective: prospective
Participants	**Inclusion criteria of the trial** • 10 to 80 years of age with warts
Interventions	• ALA-PDT and red versus green LED light source A topical ALA formulation and LED array will be specifically designed and developed for the skin lesions
Outcomes	**Outcomes of the trial** • The efficacy of the ALA formulation designed for wart treatment will be evaluated with in vivo fluorescence imaging system • The therapeutic efficacy of ALA-PDT will be evaluated by using a LED array designed for skin irradiation • The unwanted side-effects of pain and burning will be further compared between red and green LED array
Starting date	December 1994
Contact information	National Taiwan University Hospital Taipei Taiwan Contact: Hsiung-Fei Chien, MD, PhD Tel: 886223123456 ext.: 5594 hfchien@ha.mc.ntu.edu.tw Investigator: Chin-Tin Chen, PhD, Sub-Investigator Investigator: Hisung-Fei Chien, MD, PhD, Principal Investigator
Notes	This trial is apparently recruiting, but its status has not been verified recently

NCT00254280

Trial name or title	Treatment of Recalcitrant Hand and Foot Warts With Intense Pulsed Light and Paring Versus Paring Alone - a Randomized Controlled Trial With Blinded Response Evaluation
Methods	This is a single-blind, parallel-assignment, randomised efficacy study
Participants	**Inclusion criteria of the trial** • 18 years or older • Recalcitrant warts • No previous IPL treatment of warts
Interventions	• Intense pulsed light + paring versus paring alone
Outcomes	**Outcomes of the trial** • Efficiacy
Starting date	November 2005
Contact information	Merete Haedersdal, MD, PhD, DrMedSci, Principal Investigator Bispebjerg Hospital Copenhagen NV, Denmark 2400
Notes	This is active but not recruiting.

NCT00973856

Trial name or title	Evaluation of the Effectiveness of an Alcohol Based Hand Gel for the Reduction of Warts on the Hands
Methods	This is a double-blind, single-group assignment, randomised efficacy study
Participants	**Inclusion criteria of the trial** • 18 to 65 years of age • Participants with 2+ warts being seen at a dermatologist's office • 2 or more warts on the hands that are located at least 1 cm apart or on separate fingers • Warts must have been present for at least 2 months • Wart size must be between 2 mm to 15 mm in diameter • Participants must be in good general health • Participants must be able to speak and read in English • Participants must be able to read and sign the participant instruction sheet, and informed consent and authorisation • Participants must be able to understand and execute the instructions presented in pictorial form
Interventions	• PURELL® VF481 (alcohol-based gel)
Outcomes	**Outcomes of the trial** • Difference in per cent clearance between Product A and Product B at each time point: 4, 8, and 12 weeks • Change in size of warts treated by each product at each time point: 4, 8, and 12 weeks

NCT00973856 (*Continued*)

Starting date	September 2009
Contact information	Akron Dermatology Akron Ohio, USA 44307 Contact: Nairmeen Haller, PhD Tel: 330-344-6001 nhaller@agmc.org
Notes	This trial is recruiting.

NCT01059110

Trial name or title	Comparison of Occlusive Dressings, Salicylate Ointment, Cryotherapy, Topical 5-fluoro-uracil and Imiquimod in Immunocompetent Patients Presenting Plantar Warts in Office-based Settings: a Randomized Clinical Trial
Methods	This is a parallel-assignment, open-label randomised efficacy study
Participants	**Inclusion criteria of the trial** • Male or female participants aged > 18 years
Interventions	• Salicylate ointment • Imiquimod • 5-fluorouracil • Cryotherapy • Occlusive dressings
Outcomes	**Outcomes of the trial** • Complete clinical remission of the warts assessed by the dermatologist at 90 days • Time remission at 30, 60, and 90 days • Number of warts in remission versus baseline at 30, 60, and 90 days • Time to first relapse at 30, 60, 90, 120, 180, 360, and 720 days • Percentage of relapse (phone call assessment) at 360 days and 720 days • Safety at 90 days • Evaluation of distress (visual analogue scale) at 90 days • Compliance at 90 days
Starting date	February 2010
Contact information	Medical center Athis-Mons, France 91200 Contact: Dr Yolaine Farcet Tel: +33 01 60 48 15 29 yo19@wanadoo.fr

NCT01059110 (*Continued*)

Notes	This is recruiting.

NCT01084824

Trial name or title	A Randomized Clinical Trial Examining the Efficacy of Treatment of Cutaneous Verruca Vulgaris in Adult Patients With Combined Liquid Nitrogen Cryotherapy and Topically Applied Cantharidin
Methods	This is a parallel-assignment, double-blind randomised study
Participants	**Inclusion criteria of the trial** • Common warts on non-genital and non-facial skin • Otherwise healthy • Aged between 18 to 65 and able to give informed consent • Capable of tolerating treatment
Interventions	• Liquid nitrogen and cantharidin • Liquid nitrogen and topical placebo
Outcomes	**Outcomes of the trial** • Percentage of common warts cleared at 12 weeks • Percentage of treated warts cleared with treatment, as measured with dermatoscopic examination, after 12 weeks
Starting date	June 2007
Contact information	Richard A Flygare, PhD, Principal Investigator TUI University North Idaho Dermatology Coeur D'Alene Idaho, USA 83814
Notes	This trial has completed.

NCT01286441

Trial name or title	A Randomized, Double-blind, Parallel-group, Multicenter, Vehicle-controlled Phase 2 Dose-Ranging Trial of the Safety and Efficacy of East Indian Sandalwood Oil in the Treatment of Common Warts (Verruca Vulgaris)
Methods	The primary objective of this study is to evaluate the efficacy and safety of 10%, 20%, and 30% East Indian Sandalwood Oil (EISO) ointment compared with the ointment placebo administered twice daily (bid) for 12 weeks for the treatment of common warts (verruca vulgaris)
Participants	**Inclusion criteria of the trial** • Male or female • 18 years of age or older at enrolment

NCT01286441 (*Continued*)

Interventions	• East Indian Sandalwood Oil (EISO) ointment compared with the ointment placebo administered twice daily (bid) for 12 weeks
Outcomes	**Outcomes of the trial** • Efficacy and safety • Complete resolution (Clinical evaluations, including wart counts, wart measurements, and recording of adverse events and concomitant medications, will be performed. Photographs of the treatment area will be taken at all study visits.) • Recurrence of common warts and to obtain an estimate of systemic exposure to alpha-santalol at steady state
Starting date	May 2011
Contact information	Howard L Sofen, MD, Principal Investigator
Notes	This trial is not yet recruiting.

DATA AND ANALYSES

Comparison 1. Topical salicylic acid (SA/LA) vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate all studies all sites	6	486	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.20, 2.03]
2 Cure rate hands and feet	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Hands only	2	120	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.43, 5.01]
2.2 Feet only	2	239	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.07, 1.55]
2.3 Combined hands and feet	3	114	Risk Ratio (M-H, Random, 95% CI)	1.62 [1.15, 2.30]

Comparison 2. Cryotherapy vs placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate all studies all sites	3	227	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.65, 3.23]
2 Cure rate hands and feet	3	214	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.66, 3.39]
2.1 Hands only	2	104	Risk Ratio (M-H, Random, 95% CI)	2.63 [0.43, 15.94]
2.2 Feet only	2	110	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.26, 3.07]

Comparison 3. Cryotherapy vs salicylic acid (SA/LA) acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate all sites	4	707	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.88, 1.71]
2 Cure rate hands and feet	4	699	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.89, 1.35]
2.1 Hands only	3	342	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.80, 1.70]
2.2 Feet only	3	357	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.76, 1.57]

Comparison 4. Cryotherapy treatment intervals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cryotherapy at 2- vs 3-week intervals	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Cure rate	3	313	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.77, 1.37]
2 Cryotherapy at 3- vs 4-week intervals	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Cure rate	2	161	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.76, 2.63]
3 Cryotherapy at 2- vs 4-week intervals	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Cure rate	2	167	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.70, 2.38]

Comparison 5. Aggressive vs gentle cryotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	4	592	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.15, 3.15]
2 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Blistering	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Cryotherapy + salicylic acid (SA/LA) vs salicylic acid (SA/LA) alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	318	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.07, 1.43]
1.1 Hands only	2	271	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.02, 1.53]
1.2 Feet alone	1	47	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.74, 2.52]

Comparison 7. Cryotherapy + salicylic acid (SA/LA) vs cryotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	328	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.99, 1.45]
1.1 Hands only	2	277	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.99, 1.57]
1.2 Feet only	1	51	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.60, 1.57]

Comparison 8. Intralesional interferon vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	3	150	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.56, 1.33]

Comparison 9. Topical DNCB vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	80	Risk Ratio (M-H, Random, 95% CI)	2.12 [1.38, 3.26]

Comparison 10. Duct tape vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	193	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.51, 4.05]

Comparison 11. Duct tape vs cryotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	1	61	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.99, 2.31]

Comparison 12. Intralesional bleomycin vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	1	31	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.92, 1.78]

Comparison 13. Additional data tables

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Trials of topicals containing salicylic acid			Other data	No numeric data
2 Trials of cryotherapy			Other data	No numeric data
3 Trials of intralesional bleomycin			Other data	No numeric data
4 Trials of intralesional interferons			Other data	No numeric data
5 Trials of dinitrochlorobenzene			Other data	No numeric data
6 Trials of photodynamic therapy			Other data	No numeric data
7 Trials of duct tape			Other data	No numeric data
8 Trials of pulsed dye laser			Other data	No numeric data
9 Trials of topical zinc			Other data	No numeric data
10 Trials of topical 5-fluorouracil			Other data	No numeric data
11 Trials of intralesional 5-fluorouracil			Other data	No numeric data
12 Trials of other interventions			Other data	No numeric data

Analysis 1.1. Comparison 1 Topical salicylic acid (SA/LA) vs placebo, Outcome 1 Cure rate all studies all sites.

Review: Topical treatments for cutaneous warts

Comparison: 1 Topical salicylic acid (SA/LA) vs placebo

Outcome: 1 Cure rate all studies all sites

Study or subgroup	SA/LA n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Spanos 1990	0/10	1/10		0.7 %	0.33 [0.02, 7.32]
Felt 1998	10/17	5/20		8.0 %	2.35 [1.00, 5.54]
Bart 1989	19/28	7/28		11.4 %	2.71 [1.36, 5.41]
Bruggink 2010	20/82	13/82		13.2 %	1.54 [0.82, 2.88]
Steele 1988b	24/29	15/28		25.0 %	1.54 [1.05, 2.27]
Bunney 1971	64/76	50/76		41.6 %	1.28 [1.06, 1.55]
Total (95% CI)	**242**	**244**		**100.0 %**	**1.56 [1.20, 2.03]**

Total events: 137 (SA/LA), 91 (Placebo)

Heterogeneity: Tau^2 = 0.03; Chi^2 = 7.66, df = 5 (P = 0.18); I^2 =35%

Test for overall effect: Z = 3.30 (P = 0.00097)

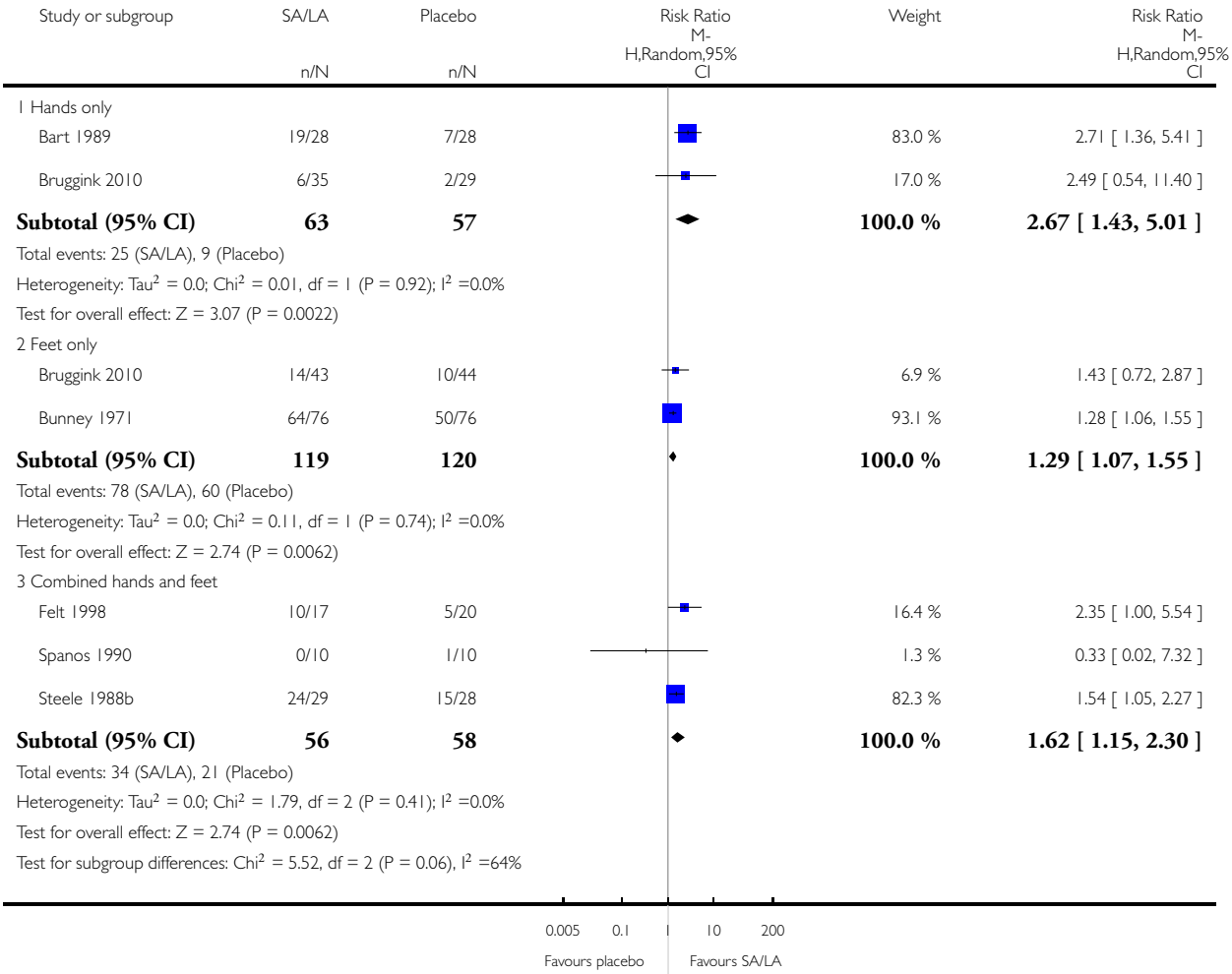
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Topical salicylic acid (SA/LA) vs placebo, Outcome 2 Cure rate hands and feet.

Review: Topical treatments for cutaneous warts

Comparison: 1 Topical salicylic acid (SA/LA) vs placebo

Outcome: 2 Cure rate hands and feet



Analysis 2.1. Comparison 2 Cryotherapy vs placebo/no treatment, Outcome 1 Cure rate all studies all sites.

Review: Topical treatments for cutaneous warts

Comparison: 2 Cryotherapy vs placebo/no treatment

Outcome: 1 Cure rate all studies all sites

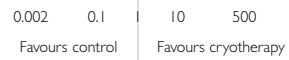
Study or subgroup	Cryotherapy n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Gibson 1984	1/11	5/18		12.6 %	0.33 [0.04, 2.45]
Wilson 1983	10/20	8/20		41.4 %	1.25 [0.63, 2.50]
Bruggink 2010	30/76	13/82		46.0 %	2.49 [1.41, 4.41]
Total (95% CI)	**107**	**120**		**100.0 %**	**1.45 [0.65, 3.23]**

Total events: 41 (Cryotherapy), 26 (Placebo/no treatment)

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 5.04$, df = 2 (P = 0.08); $I^2 = 60\%$

Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Cryotherapy vs placebo/no treatment, Outcome 2 Cure rate hands and feet.

Review: Topical treatments for cutaneous warts

Comparison: 2 Cryotherapy vs placebo/no treatment

Outcome: 2 Cure rate hands and feet

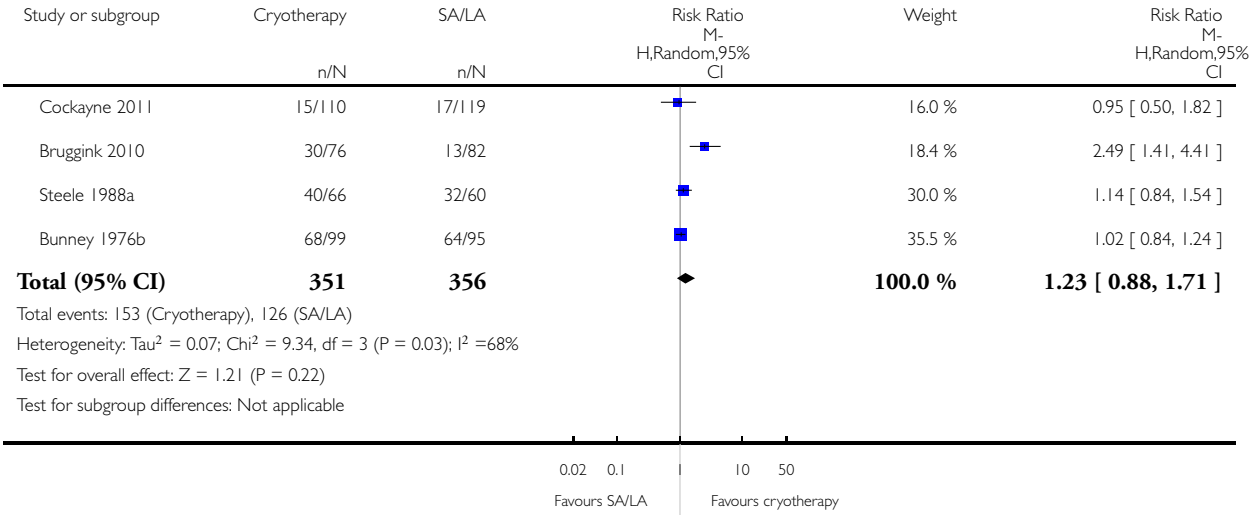
Study or subgroup	Cryotherapy n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Hands only					
Bruggink 2010	16/35	2/29		19.8 %	6.63 [1.66, 26.48]
Wilson 1983	10/20	8/20		34.6 %	1.25 [0.63, 2.50]
Subtotal (95% CI)	**55**	**49**		**54.4 %**	**2.63 [0.43, 15.94]**
Total events: 26 (Cryotherapy), 10 (Placebo/no treatment)					
Heterogeneity: Tau^2 = 1.40; Chi^2 = 5.48, df = 1 (P = 0.02); I^2 =82%					
Test for overall effect: Z = 1.05 (P = 0.29)					
2 Feet only					
Gibson 1984	1/11	5/18		12.1 %	0.33 [0.04, 2.45]
Bruggink 2010	11/37	10/44		33.5 %	1.31 [0.63, 2.73]
Subtotal (95% CI)	**48**	**62**		**45.6 %**	**0.90 [0.26, 3.07]**
Total events: 12 (Cryotherapy), 15 (Placebo/no treatment)					
Heterogeneity: Tau^2 = 0.40; Chi^2 = 1.66, df = 1 (P = 0.20); I^2 =40%					
Test for overall effect: Z = 0.17 (P = 0.87)					
Total (95% CI)	**103**	**111**		**100.0 %**	**1.50 [0.66, 3.39]**
Total events: 38 (Cryotherapy), 25 (Placebo/no treatment)					
Heterogeneity: Tau^2 = 0.38; Chi^2 = 7.29, df = 3 (P = 0.06); I^2 =59%					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Chi^2 = 0.93, df = 1 (P = 0.34), I^2 =0.0%					

Analysis 3.1. Comparison 3 Cryotherapy vs salicylic acid (SA/LA) acid, Outcome 1 Cure rate all sites.

Review: Topical treatments for cutaneous warts

Comparison: 3 Cryotherapy vs salicylic acid (SA/LA) acid

Outcome: 1 Cure rate all sites

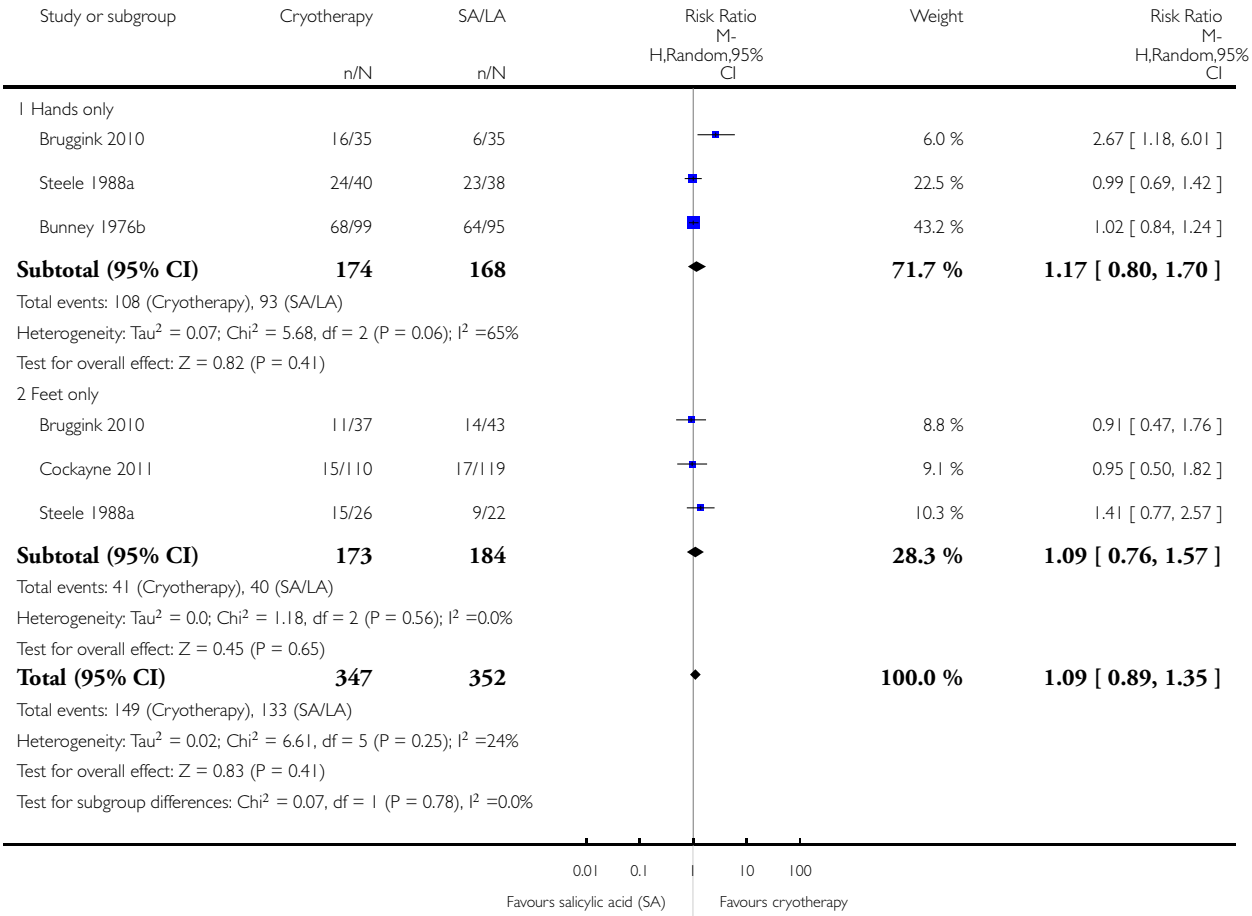


Analysis 3.2. Comparison 3 Cryotherapy vs salicylic acid (SA/LA) acid, Outcome 2 Cure rate hands and feet.

Review: Topical treatments for cutaneous warts

Comparison: 3 Cryotherapy vs salicylic acid (SA/LA) acid

Outcome: 2 Cure rate hands and feet

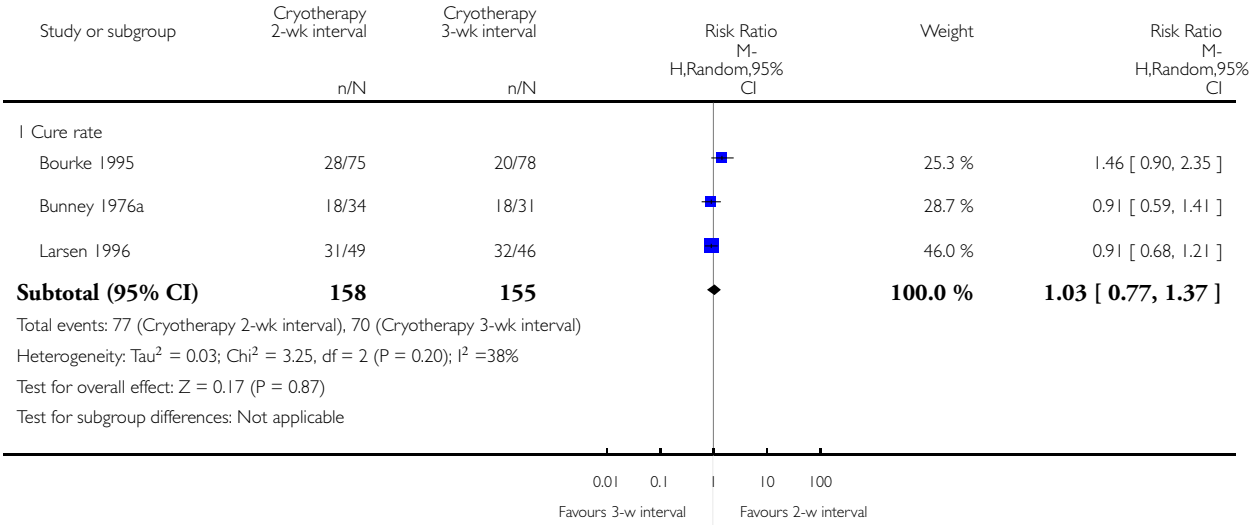


Analysis 4.1. Comparison 4 Cryotherapy treatment intervals, Outcome 1 Cryotherapy at 2- vs 3-week intervals.

Review: Topical treatments for cutaneous warts

Comparison: 4 Cryotherapy treatment intervals

Outcome: 1 Cryotherapy at 2- vs 3-week intervals

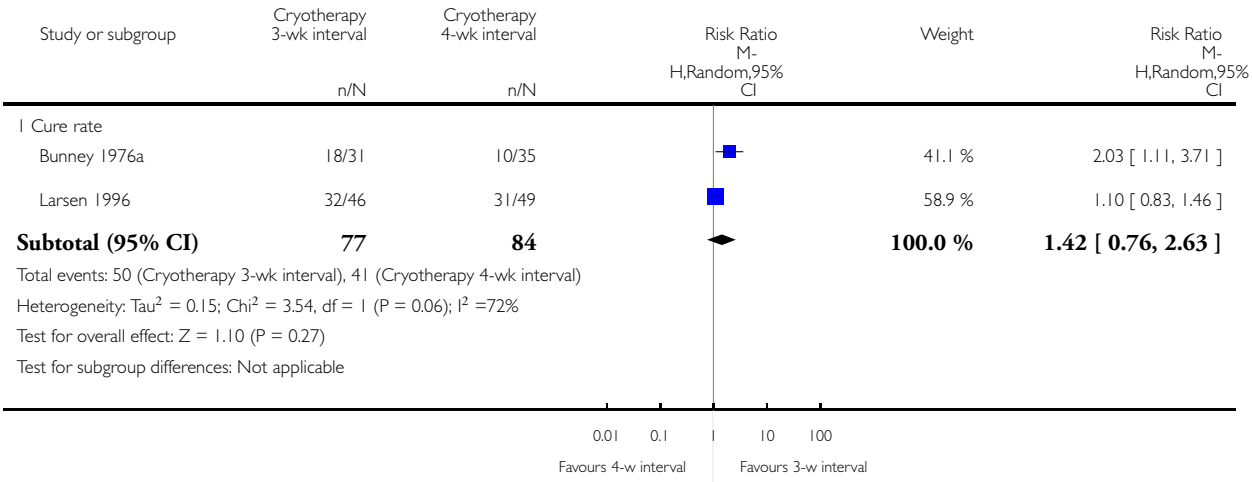


Analysis 4.2. Comparison 4 Cryotherapy treatment intervals, Outcome 2 Cryotherapy at 3- vs 4-week intervals.

Review: Topical treatments for cutaneous warts

Comparison: 4 Cryotherapy treatment intervals

Outcome: 2 Cryotherapy at 3- vs 4-week intervals

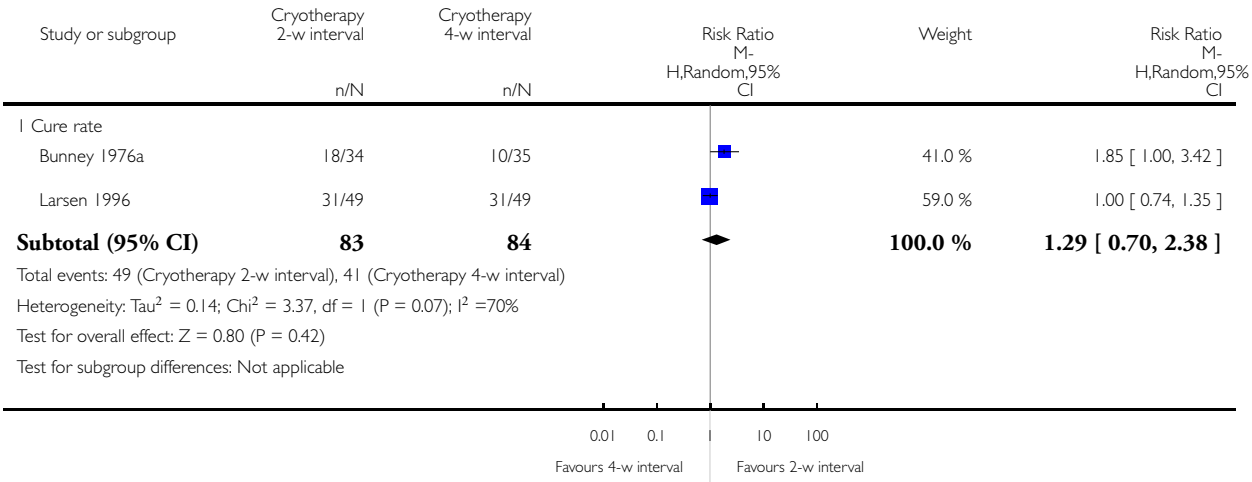


Analysis 4.3. Comparison 4 Cryotherapy treatment intervals, Outcome 3 Cryotherapy at 2- vs 4-week intervals.

Review: Topical treatments for cutaneous warts

Comparison: 4 Cryotherapy treatment intervals

Outcome: 3 Cryotherapy at 2- vs 4-week intervals



Analysis 5.1. Comparison 5 Aggressive vs gentle cryotherapy, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 5 Aggressive vs gentle cryotherapy

Outcome: 1 Cure rate

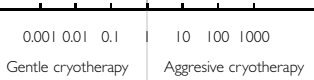
Study or subgroup	Aggresive cryotherapy n/N	Gentle cryotherapy n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Sonnex 1988	14/31	0/31		3.1 %	29.00 [1.81, 465.72]
Hansen 1986	24/33	7/27		24.3 %	2.81 [1.43, 5.49]
Connolly 1999	42/71	25/75		34.5 %	1.77 [1.22, 2.58]
Berth-Jones 1994	79/169	57/155		38.2 %	1.27 [0.98, 1.65]
Total (95% CI)	**304**	**288**		**100.0 %**	**1.90 [1.15, 3.15]**

Total events: 159 (Aggresive cryotherapy), 89 (Gentle cryotherapy)

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 10.76$, df = 3 (P = 0.01); $I^2 = 72\%$

Test for overall effect: Z = 2.50 (P = 0.013)

Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5 Aggressive vs gentle cryotherapy, Outcome 2 Adverse events.

Review: Topical treatments for cutaneous warts

Comparison: 5 Aggressive vs gentle cryotherapy

Outcome: 2 Adverse events

Study or subgroup	Aggresive cryotherapy n/N	Gentle cryotherapy n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Pain				
Connolly 1999	33/64	22/62		1.45 [0.96, 2.19]
2 Blistering				
Connolly 1999	31/64	24/62		1.25 [0.84, 1.87]

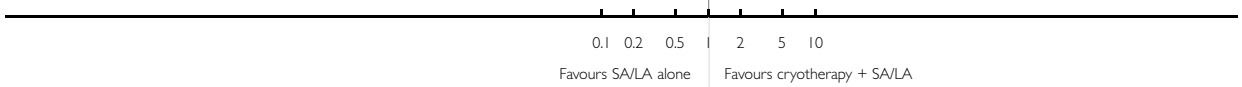
Analysis 6.1. Comparison 6 Cryotherapy + salicylic acid (SA/LA) vs salicylic acid (SA/LA) alone, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 6 Cryotherapy + salicylic acid (SA/LA) vs salicylic acid (SA/LA) alone

Outcome: 1 Cure rate

Study or subgroup	Cryotherapy + SA/LA n/N	SA/LA alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Hands only					
Steele 1988a	33/38	23/38		25.7 %	1.43 [1.08, 1.91]
Bunney 1976b	78/100	64/95		68.7 %	1.16 [0.97, 1.38]
Subtotal (95% CI)	**138**	**133**		**94.4 %**	**1.25 [1.02, 1.53]**
Total events: 111 (Cryotherapy + SA/LA), 87 (SA/LA alone)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.58$, df = 1 (P = 0.21); $I^2 = 37\%$					
Test for overall effect: Z = 2.17 (P = 0.030)					
2 Feet alone					
Steele 1988a	14/25	9/22		5.6 %	1.37 [0.74, 2.52]
Subtotal (95% CI)	**25**	**22**		**5.6 %**	**1.37 [0.74, 2.52]**
Total events: 14 (Cryotherapy + SA/LA), 9 (SA/LA alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
Total (95% CI)	**163**	**155**		**100.0 %**	**1.24 [1.07, 1.43]**
Total events: 125 (Cryotherapy + SA/LA), 96 (SA/LA alone)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.71$, df = 2 (P = 0.43); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.86 (P = 0.0042)					
Test for subgroup differences: $Chi^2 = 0.08$, df = 1 (P = 0.78), $I^2 = 0.0\%$					

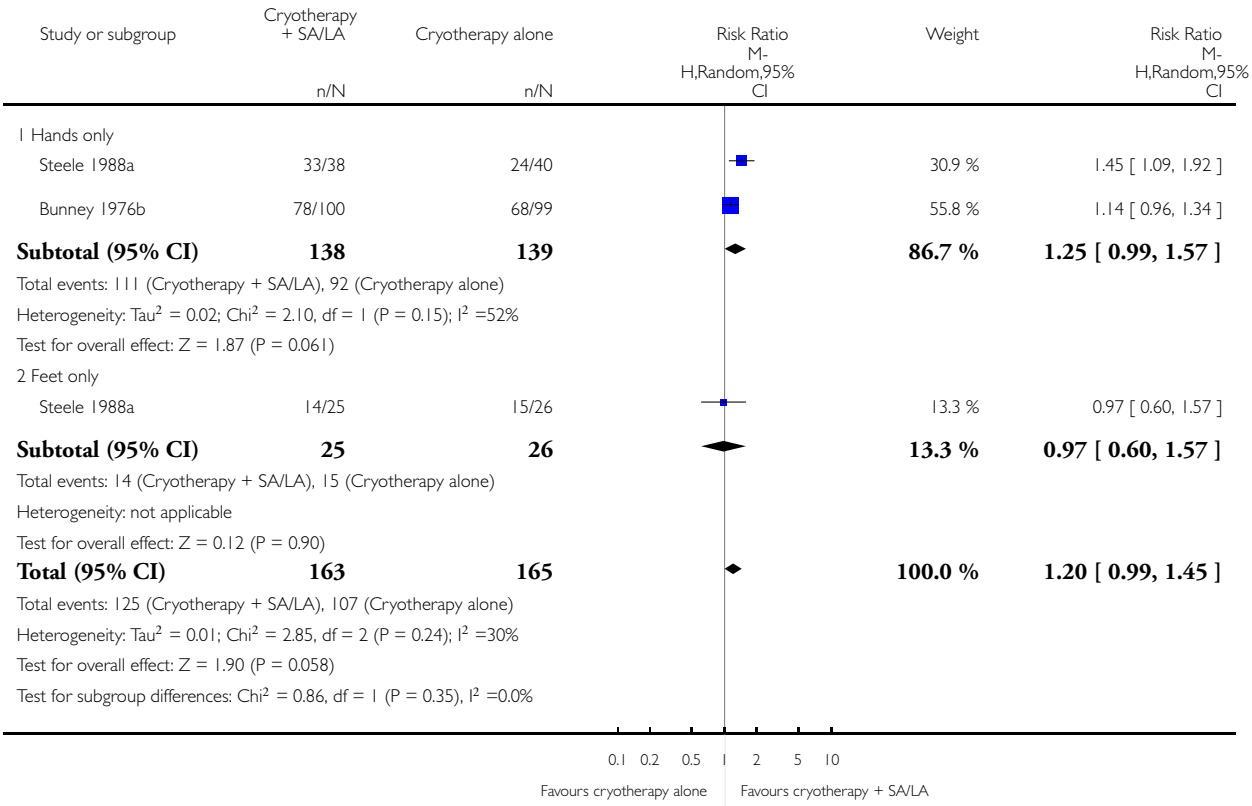


Analysis 7.1. Comparison 7 Cryotherapy + salicylic acid (SA/LA) vs cryotherapy alone, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 7 Cryotherapy + salicylic acid (SA/LA) vs cryotherapy alone

Outcome: 1 Cure rate



Analysis 8.1. Comparison 8 Intralesional interferon vs placebo, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 8 Intralesional interferon vs placebo

Outcome: 1 Cure rate

Study or subgroup	Intralesional interferon n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Berman 1986	2/4	1/4		4.8 %	2.00 [0.28, 14.20]
Vance 1986	11/62	8/38		27.5 %	0.84 [0.37, 1.91]
Varnavides 1997	12/23	12/19		67.7 %	0.83 [0.49, 1.39]
Total (95% CI)	**89**	**61**		**100.0 %**	**0.87 [0.56, 1.33]**

Total events: 25 (Intralesional interferon), 21 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.74$, df = 2 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 0.66 (P = 0.51)

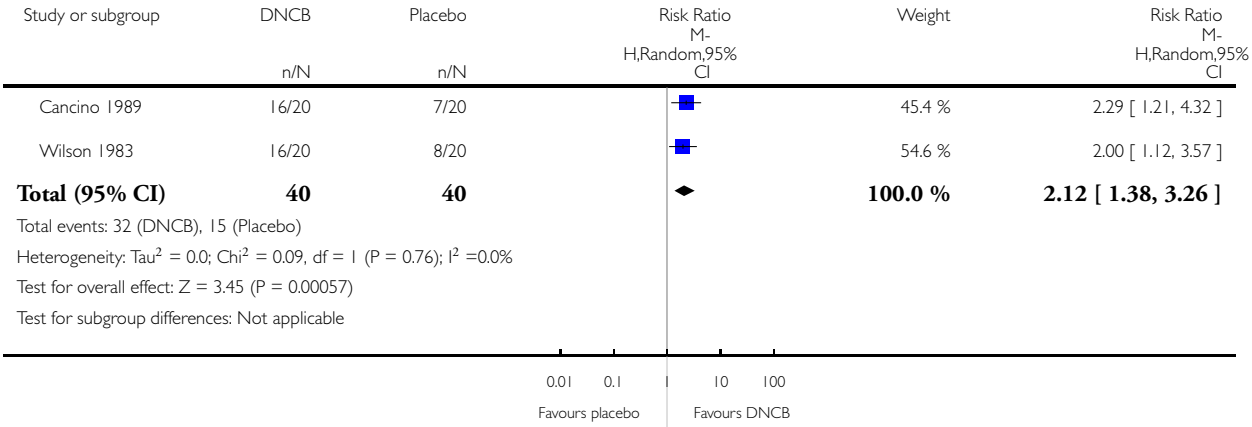
Test for subgroup differences: Not applicable

Analysis 9.1. Comparison 9 Topical DNCB vs placebo, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 9 Topical DNCB vs placebo

Outcome: 1 Cure rate

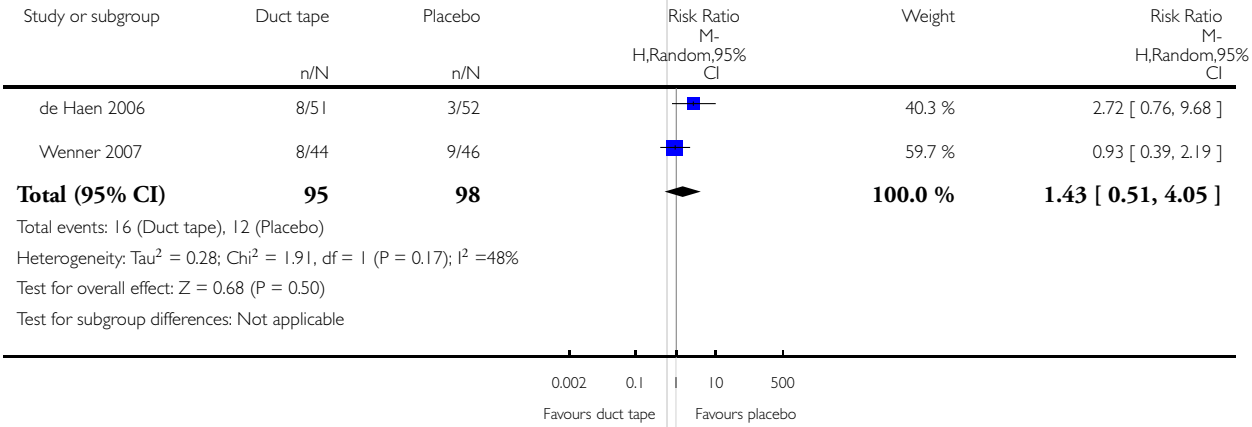


Analysis 10.1. Comparison 10 Duct tape vs placebo, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 10 Duct tape vs placebo

Outcome: 1 Cure rate



Analysis 11.1. Comparison 11 Duct tape vs cryotherapy, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 11 Duct tape vs cryotherapy

Outcome: 1 Cure rate

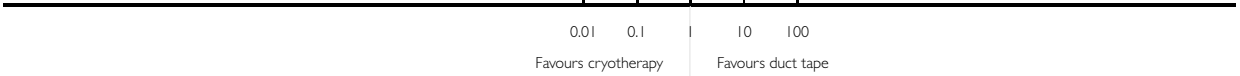
Study or subgroup	Duct tape n/N	Cryotherapy n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Focht 2002	22/30	15/31		100.0 %	1.52 [0.99, 2.31]
Total (95% CI)	**30**	**31**		**100.0 %**	**1.52 [0.99, 2.31]**

Total events: 22 (Duct tape), 15 (Cryotherapy)

Heterogeneity: not applicable

Test for overall effect: Z = 1.93 (P = 0.054)

Test for subgroup differences: Not applicable

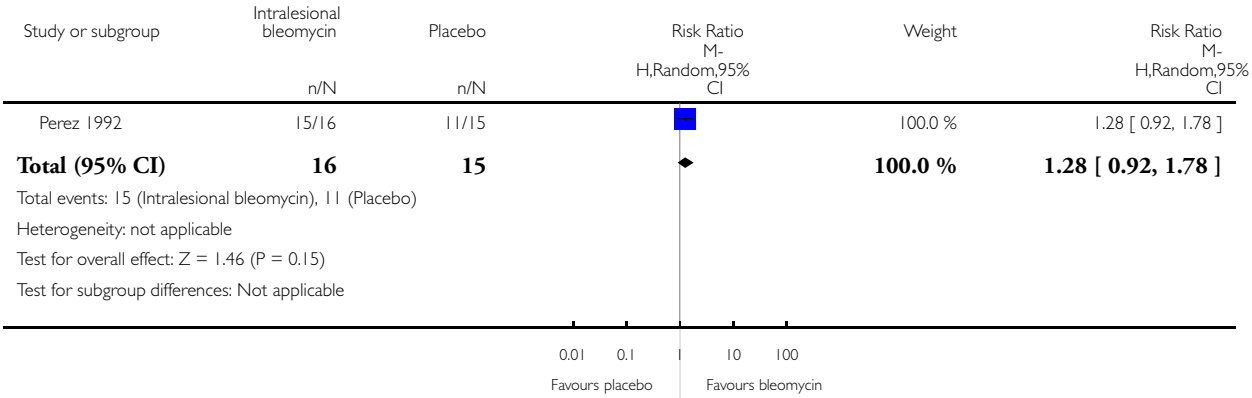


Analysis 12.1. Comparison 12 Intralesional bleomycin vs placebo, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 12 Intralesional bleomycin vs placebo

Outcome: 1 Cure rate



Analysis 13.1. Comparison 13 Additional data tables, Outcome 1 Trials of topicals containing salicylic acid.

Trials of topicals containing salicylic acid

Study	Interventions	Results	Outcomes
Abou-Auda 1987	15% SA patch vs placebo patch	SA better than placebo	'Successful treatment' in 27/31 (87%) vs 11/23 (48%) at 12 weeks
Auken 1975	SA/LA vs 'conventional treatment' (anything else or no treatment)	No advantage of either approach	Cure in 43/84 (51%) vs 54/101 (54%) at 3 months
Bart 1989	SA vs placebo	SA better than placebo	Cure in 19/28 (68%) vs 7/25 (28%) at 12 weeks
Bruggink 2010	Cryotherapy vs SA vs 'wait and see'	Cryotherapy was the most effective treatment, especially for non-plantar warts	Cure in 39%, 24%, and 16% in all warts and 49%, 15%, and 8% in all non-plantar warts
Bunney 1971	SA vs collodion alone vs callusolve vs 50% podophyllin	No significant difference between any of the treatments. Lower cure rate for mosaic as opposed to simple plantar warts	Cure in 64/76 (84%) vs 50/76 (66%) vs 47/70 (67%) vs 60/74 (81%) at 12 weeks
Bunney 1976c	SA vs SA + polyoxyethylene	No difference	Cure in 55/71 (77%) vs 50/67 (75%) at 12 weeks

Trials of topicals containing salicylic acid (*Continued*)

Bunney 1976d	10% glutaraldehyde vs SA	No difference	Cure in 18/38 (47%) vs 19/43 (44%) at 12 weeks
Bunney 1976e	40% SA vs ordinary SA/LA	No significant difference	Cure in 15/50 (30%) vs 17/43 (40%) at 12 weeks
Felt 1998	Anthralin vs SA/LA	Anthralin significantly better than conventional SA/LA	Cure in 15/27 (56%) vs 8/31 (26%) at 2 months
Flindt-Hansen 1984	Anthralin vs SA/LA	Anthralin significantly better than conventional SA/LA	Cure in 15/27 (56%) vs 8/31 (26%) at 2 months
Parton 1994	Abrasion vs SA	Faster cure with abrasion	Mean time to cure of 2.1 weeks (2 to 4) vs 18.2 weeks (8 to 38). Itching in 93% of abrasion group (100% cure rate with both treatments implied by text)
Spanos 1990	Hypnosis vs SA vs placebo vs no treatment	Hypnosis significantly better than all other 3 groups	'Loss of warts' in 6/10 (60%) vs 0/10 (0%) vs 1/10 (10%) vs 3/10 (30%) at 6 weeks
Steele 1988b	MCAA + SA vs placebo	MCAA/SA more effective than placebo	Cure in 19/29 (66%) vs 5/28 (18%) at 6 weeks
Veien 1991	SA/LA with vs without occlusion	No difference between the 2 groups. No advantage of occlusions	Cure in 48% and 47% at 17 weeks

Analysis 13.2. Comparison 13 Additional data tables, Outcome 2 Trials of cryotherapy.

Trials of cryotherapy

Study	**Intervention**	**Results**	**Outcome**
Banihashemi 2008	Cryotherapy vs 80% phenol	No significant difference between cryotherapy and phenol treatment Both treatments had side-effects, but more were experienced in the phenol group	Cure in 20/30 (67%) for the cryotherapy group and 19/30 (63%) for the phenol group at 6 weeks 9/30 in the cryotherapy group experienced pain, hyperpigmentation, or hypopigmentation, while 15/30 experienced pain, erythema, and hypopigmentation in the phenol group (with ITT)

Trials of cryotherapy (*Continued*)

Berth-Jones 1992a	Cryotherapy + SA/LA with vs without paring	Paring improves cure rate in plantar warts only. Chance of cure inversely related to duration of warts. Low cure rate compared to Bunney's work in the 1970s may reflect higher proportion of refractory warts in secondary care	Cure in 46% vs 50% of hands and 75% vs 39% of feet at 3 months
Berth-Jones 1992b	Cryotherapy continued after 3 months for refractory warts vs discontinuing	No significant increase in cure rate by prolonging treatment	Cure in 43% and 38% after a further 3 months
Berth-Jones 1994	Cryotherapy + SA/LA: double vs single freeze	Results suggest that a double freeze (aggressive cryotherapy) improves cure rate for plantar warts only No comment on side-effects	Cure in 46/103 (45%) vs 41/100 (41%) with hand warts and 33/66 (50%) vs 16/55 (29%) with feet warts at 3 months
Bourke 1995	Cryotherapy + SA/LA: weekly vs 2-weekly vs 3-weekly	Faster cure with more frequent treatments, but no significant difference in long-term cure rate. Pain and blistering seen more frequently with short treatment intervals	43%, 48%, and 44% cured after 12 treatments. Faster cure in more frequent treatments Blistering in 29%, 7%, and 0%
Bruggink 2010	Cryotherapy vs SA vs 'wait and see'	Cryotherapy was the most effective treatment, especially for non-plantar warts	Cure in 39%, 24%, and 16% (all warts) and 49%, 15%, and 8% (in all non-plantar warts)
Bunney 1976a	Cryotherapy: 2- vs 3- vs 4-weekly	70% to 80% cure rate achievable within 12 weeks as long as treatment interval was not longer than 3 weeks. Cure unlikely with less than 3 treatments. No comments on side-effects	87%, 78%, and 64% cured after 6 treatments. Cure in 18/34 (53%) vs 18/31 (58%) vs 10/35 (29%) at 12 weeks (with ITT)
Bunney 1976b	Cryotherapy vs SA/LA vs both	Topical SA/LA as good as cryotherapy for effecting cure at 12 weeks. Addition of topicals to cryotherapy may improve the cure rate	Cure in 68/99 (69%), 64/95 (67%) and 78/100 (78%) at 12 weeks
Cockayne 2011	Cryotherapy vs 50% SA (plantar warts only)	No significant difference between the 2 treatments	Cure in 15/110 (14%) vs 17/119 (14%)
Connolly 1999	Aggressive vs gentle cryotherapy	Significantly higher cure rate with aggressive cryotherapy but also higher rate of pain and blistering	Cure in 42/71 (59%) vs 25/75 (33%) at 8 weeks. Pain/blistering in 64 (64%) vs 44 (44%)

Trials of cryotherapy (*Continued*)

Erkens 1992	Cryotherapy vs 2-weekly histofreezer	Significantly higher cure rate with cryotherapy. More severe pain during treatment reported in cryotherapy group	Cure in 25/43 (58%) vs 14/50 (28%) at 2.5 months
Focht 2002	Cryotherapy vs duct tape occlusion	Duct tape more effective with fewer side-effects	Cure in 22/26 (85%) vs 15/25 (60%) at 2 months
Gibson 1984	Topical aciclovir vs placebo vs cryotherapy/gluterol	No statistically significant difference between any of the 3 treatments. Trend suggests the creams were superior to cryotherapy	Cure in 7/18 (39%), 5/18 (28%), and 1/11 (9%) at 8 weeks
Hansen 1986	Cryoprobe: 2 minutes vs 15 seconds	Significantly higher cure rate in 2 minute (aggressive cryotherapy)-group but higher rate of pain and blistering	Cure in 24/33 (73%) and 7/27 (26%) at 9 weeks. Pain in 19% of 2-minutes group
Larsen 1996	Cryotherapy: 2- vs 3- vs 4-weekly	No significant difference between the 3 groups after 6 months. No comment on side-effects	Cure in 31/49 (63%), 32/46 (70%) , and 31/49 (63%) index warts at 6 months
Marroquin 1997	*Jatropha* sap vs cryotherapy (X1 only) vs placebo	100% cure rate with *Jatropha* sap	100%, 85%, and 0% of warts cured at 30 days
Martinez 1996	Dimethyl ether propane Cryotherapy vs liquid nitrogen cryotherapy	No significant difference between the 2 treatments	Cure in 65/68 (96%) vs 80/86 (93%) 15 days after last treatment
Rahimi 2008	Cryotherapy vs smoke from *Populus euphratica* leaves	No significant difference between burnt leaves compared to cryotherapy	Cure in 13/30 (43%) and 16/30 (53%) at 22 weeks. Cryotherapy treatment caused 11 cases of pain and 6 cases of blistering, while burnt leaves caused 3 cases of pruritis (with ITT)
Sonnex 1988	Aggressive vs gentle cryotherapy for refractory warts	Only aggressive cryotherapy was effective. No comment on side-effects	Cure in 11/16 (69%) vs 0/16 (0%) hands and 3/15 (20%) vs 0/15 (0%) feet at 4 weeks
Steele 1988a	Cryotherapy vs SA/LA vs both	Both treatments together were significantly better than either alone for hand warts. No significant difference for plantar warts	Cure in 24/40 (60%), 23/38 (61%) , and 33/38 (87%) hands; and 15/26 (58%), 9/22 (41%), and 14/25 (56%) feet at 6 months
Wilson 1983	DNCB vs cryotherapy vs placebo	DNCB more effective than conventional cryotherapy	Cure in 16/20 (80%), 10/20 (50%) , and 8/20 (40%) at 4 months

Analysis 13.3. Comparison 13 Additional data tables, Outcome 3 Trials of intralesional bleomycin.

Trials of intralesional bleomycin

Study	Intervention	Results	Outcomes
Adalatkhah 2007	Bleomycin vs cryotherapy	Cure rate for bleomycin was statistically better than cryotherapy	Cure in 38/44 (86%) vs 30/44 (68%) at 6 weeks
Bunney 1984	Bleomycin vs placebo	Higher cure rate with bleomycin	Cure in 34/59 (58%) vs 6/59 (10%) warts at 6 weeks. 1 withdrawal with pain
Dhar 2009	Bleomycin vs cryotherapy	Bleomycin more effective	Cure in 37/39 (94.9%) vs 26/34 (76.5%) 8 weeks after last treatment
Hayes 1986	3 different doses of bleomycin used (0.25, 0.5, & 1.0 IU)	No significant difference between treatments. Trend towards higher concentrations being more effective	Cure in 11/15 (73%) vs 21/24 (88%) vs 9/10 (90%) warts at 3 months. Most participants experienced pain irrespective of dose
Munkvad 1983	Bleomycin vs placebo	No difference between treatments. (In fact, significantly higher cure rates with placebo.) Bleomycin not recommended	Cure in 4/22 (bleomycin + saline) (18%) vs 5/36 (bleomycin in oil) (14%) vs 8/19 (saline placebo) (42%) vs 10/22 (oil placebo) (45%) warts at 3 months
Perez 1992	Bleomycin vs placebo	No difference between treatments. Saline cheaper and as effective as a treatment	Cure in 15/16 (94%) and 11/15 (73%) participants at 30 days
Rossi 1981	Bleomycin vs placebo	Bleomycin significantly better	Cure in 31/38 (82%) vs 16/46 (35%) warts at 1 month

Analysis 13.4. Comparison 13 Additional data tables, Outcome 4 Trials of intralesional interferons.

Trials of intralesional interferons

Study	Intervention	Results	Outcome
Berman 1986	IFN-alpha vs placebo	Results suggest that IFN-alpha is an effective treatment	Cure in 2/4 (50%) vs 1/4 (25%) at 8 weeks
Horn 2005	Intralesional skin test antigen vs antigen + IFN-alpha vs IFN-alpha vs saline	Intralesional immunotherapy is an effective treatment for warts. Interferon did not significantly enhance the response rate and did not differ from normal saline	57/95 (60%) antigen vs 25/106 (24%), saline, or IFN had resolution of at least 1 wart
Lee 1990	IFN-gamma: high-dose vs low-dose vs placebo	Significantly higher response rate with high-dose interferon but also a	Cure in 20/36 (56%) vs 16/53 (30%) vs 6/36 (17%) at 4 weeks.

Trials of intralesional interferons (*Continued*)

		higher rate of systemic side-effects	Fever in 71% and 25% of high-dose and low-dose groups
Niimura 1990	IFN-beta vs placebo	IFN-beta significantly better than placebo. No adverse effects	Cure in 42/64 (66%) vs 7/64 (11%) at 10 weeks
Pazin 1982	IFN-alpha vs placebo	IFN-alpha significantly better than placebo	Cure in 5/12 (42%) vs 0/4 (0%) warts at 15.5 weeks
Vance 1986	IFN-alpha: high-dose vs low-dose vs placebo	No significant difference between any of the groups	Cure in 4/30 (13%) vs 7/32 (22%) vs 8/38 (21%) at 12 weeks
Varnavides 1997	IFN-alpha vs placebo	No significant differences	Cure in 12/23 (52%) vs 12/19 (63%) at 24 weeks

Analysis 13.5. Comparison 13 Additional data tables, Outcome 5 Trials of dinitrochlorobenzene.

Trials of dinitrochlorobenzene

Study	**Intervention**	**Results**	**Outcomes**
Cancino 1989	DNCB vs placebo	Significantly higher cure rate with DNCB	Cure in 16/20 (80%) and 7/20 (35%)
Wilson 1983	DNCB vs cryotherapy vs placebo	DNCB more effective than conventional cryotherapy	Cure in 16/20 (80%), 10/20 (50%), and 8/20 (40%) at 4 months

Analysis 13.6. Comparison 13 Additional data tables, Outcome 6 Trials of photodynamic therapy.

Trials of photodynamic therapy

Study	**Intervention**	**Results**	**Outcomes**
Fuchs 2004	PDT with methylene blue/DMSO X 8 vs SA/creosote	Neither treatment very effective	Cure in 5/65 (6%) vs 8/56 (15%) at 8 weeks
Stahl 1979	PDT with methylene blue/DMSO X 8 vs SA/creosote	Neither treatment very effective	Cure in 5/65 (6%) vs 8/56 (15%) at 8 weeks
Stender 1999	ALA-PDT with white light X 1 vs white X 3 vs red X 3 vs blue light X 3 vs cryotherapy (X 4)	White light superior to blue or red for ALA-PDT	Cure at 73%, 71%, 42%, 28%, and 20% of warts at 4 to 6 weeks
Stender 2000	ALA-PDT vs placebo PDT with red light source (X 3 to 6)	ALA-PDT a safe and effective treatment	Cure in 64/114 (56%) vs 47/113 (42%) of warts at 18 weeks

Trials of photodynamic therapy (*Continued*)

Veien 1977	PDT with proflavine or neutral red (both in DMSO) vs placebo PDT with picric acid or color rubor (both in DMSO)	PDT moderately effective. Simultaneous clearing of the placebo-treated half could be due to part of the placebo treatment having a therapeutic effect possibly DMSO	Cure in 10/27 (37%) proflavin vs 110/23 (43%) neutral red at 8 weeks

Analysis 13.7. Comparison 13 Additional data tables, Outcome 7 Trials of duct tape.

Trials of duct tape

Study	**Intervention**	**Results**	**Outcomes**
de Haen 2006	Duct tape vs clavi ring (corn pad without medication used as placebo)	No statistical difference between the 2 treatments	Cure rate in 8/51 (16%) vs 3/52 (6%) at 6 weeks. Both treatments had side-effects, but there were more in the duct tape group: pain (11 vs 9), bleeding (8 vs 4), erythema, itching, and eczema
Focht 2002	Duct tape vs cryotherapy	Duct tape more effective with fewer side-effects	Cure in 22/26 (85%) vs 15/25 (60%) at 2 months
Wenner 2007	Duct tape vs moleskin pads (placebo)	There was no statistical difference between the 2 treatments	Cure rate was 8/44 vs 9/46 at 6 months. Both treatments had side-effects of numbness of fingers and bleeding

Analysis 13.8. Comparison 13 Additional data tables, Outcome 8 Trials of pulsed dye laser.

Trials of pulsed dye laser

Study	**Intervention**	**Results**	**Outcomes**
Aum 2006	Pulsed dye laser + bleomycin vs bleomycin	There was no statistical difference between the 2 treatments	12/12 (100%) cure rate in both groups, but there was more pain and blistering in the pulsed bleomycin-only group
Passeron 2007	Pulsed dye laser + cryotherapy vs cryotherapy	There was no statistical difference between the 2 treatments	6/19 (32%) vs 3/16 (19%), but there was more pain in the pulsed dye laser group
Robson 2000	Pulsed dye laser (585 nm) vs conventional treatment	Pulsed dye laser as effective as conventional treatment	Complete response in 70% vs 66% of warts approximately 16 weeks

Analysis 13.9. Comparison 13 Additional data tables, Outcome 9 Trials of topical zinc.

Trials of topical zinc

Study	Intervention	Results	Outcomes
Khattar 2007	20% zinc oxide vs 15% SA/LA	There were similar cure rates for zinc oxide and SA/LA	Cure rate in 8/22 vs 8/22 at 3 months. Adverse events included erythema (10 vs 17), swelling (12 vs 5), scaling (7 vs 14), blackening (4 vs 2) , and the SA/LA group also had itching and tenderness
Sharquie 2007	10% zinc sulphate vs 5% zinc sulphate vs placebo	There were higher cure rates for zinc sulphate compared to placebo	Cure in 7/16 (44%) vs 4/29 (14%) vs 1/22 (5%) at 6 months. Adverse events were only experienced in the zinc sulphate group, and this included 7 cases of itching or pain and 6 cases of postinflammatory hypopigmentation

Analysis 13.10. Comparison 13 Additional data tables, Outcome 10 Trials of topical 5-fluorouracil.

Trials of topical 5-fluorouracil

Study	Intervention	Results	Outcomes
Artese 1994	5-FU + SA vs cautery	5-FU better than cautery	Cure in 127/150 (85%) vs 99/150 (66%) at 75 days
Bunney 1973	2% 5-FU vs 5% 5-FU vs SA/LA vs idoxuridine	No significant difference between any of these	Cure at 13/28 (46%), 8/15 (53%), 8/16 (50%), and 9/36 (25%) at 12 weeks
Hursthouse 1975	5-FU vs placebo	5-FU significantly better	Cure in 29/64 (45%) vs 8/64 (13%) at 4 weeks
Luk 2006	5-FU + cryotherapy vs cryotherapy	5-FU treatment added no additional benefit to cryotherapy	Cure in 5-FU + cryotherapy group was 12/40 vs 17/40, while cure in cryotherapy + 5-FU treatment group was associated with more blistering (21 vs 14) and pain (19 vs 11)
Salk 2006	5-FU vs tape	Highly significantly better treatment with 5-FU compared to tape occlusion	Cure in 17/20 vs 2/20 at 6 months. 5-FU treatment was associated with more pain (12 vs 9)
Schmidt 1981	5-FU/SA vs placebo	5-FU/SA significantly better	Cure in 13/28 (46%) vs 5/27 (19%) at 6 weeks

Trials of topical 5-fluorouracil (*Continued*)

Wolff 1980	5-FU/SA vs placebo	5-FU/SA significantly better	Success in 12/21 (57%) vs 9/21 (43%)

Analysis 13.11. Comparison 13 Additional data tables, Outcome 11 Trials of intralesional 5-fluorouracil.

Trials of intralesional 5-fluorouracil

Study	**Intervention**	**Results**	**Outcome**
Iscimen 2004	Intralesional 5-FU/lidocaine/ epinephrine vs saline	5-FU + LE mixture was safe and effective	118/169 (70%) vs 43/146 (29%) warts showed complete response
Yazdanfar 2008	Intralesional 5-FU/lidocaine/ epinephrine vs saline	Significantly higher cure rate with intralesional 5-FU compared to saline	22/34 (65%) vs 12/34 (35%) showed complete response. 5-FU caused 6 cases of pain, erythema, and oedema vs 3 in saline group, and there was 1 case of hypopigmentation in each group. The 5-FU group also had 4 cases of ulceration and necrosis and 2 cases of scarring

Analysis 13.12. Comparison 13 Additional data tables, Outcome 12 Trials of other interventions.

Trials of other interventions

Study	**Interventions**	**Results**	**Outcomes**
Aldara 3M 2000a	Topical 5% imiquimod cream (different vehicles) vs placebo for plantar warts	ITT: no significant difference in clearance of warts between Aldara cream any delivery methods or vehicle control	Cure in 10.0% to 12.8% in active treatment groups; 2.9% in vehicle control group
Aldara 3M 2000b	Topical 5% imiquimod cream (different vehicles) vs placebo for common warts	ITT: no significant difference in clearance of warts between Aldara cream any delivery methods or vehicle control	Cure in 9.5% vs 10.0%
Faghihi 2010	Inoculation of 85% formic acid vs distilled water	Formic acid more effective	Cure in 91.3% vs 10.7%
Gustafsson 2004	Alpha-lactalbumin-oleic acid (ALOA) vs saline	'ALOA has beneficial and lasting effect'	9/20 (45%) vs 3/20 (15%) with at least 1 wart resolved
Huo 2010	Hyperthermia from infrared device vs placebo	Hyperthermia more effective	Cure in 15/30 (50%) vs 3/30 (10%)
Khan 1999	Topical Thuja vs placebo	Efficacy of Thuja demonstrated	12/15 (80%) vs 5/15 (33%) showed resolution

Trials of other interventions (*Continued*)

Khan 2000	Hexane vs chloroform vs ethyl acetate fractions of Thuja	Chloroform fraction superior	0/10 vs 10/10 vs 4/10 cases, respectively
Nofal 2010	Intralesional MMR vs intralesional saline	MMR more effective than saline	Cure in 57/85 (67%) vs 11/50 (22%)
Togsverd-Bo 2010	Paring and intense pulsed light (IPL) vs paring alone	No significant difference between the 2 treatments	Cure in 9/45 (20%) vs 5/44 (11%)
Wang 2002	Chinese herbal medicine + 0.1% retinoic acid vs retinoic acid alone	Chinese herbal medicine + retinoic has a relatively good efficacy	Cure in 57/70 (81%) vs 29/56 (52%)
Wu 2005	Qu You Ding vs peptide butylamine liniment	Qu You Ding has a higher cure rate than Peptide butylamine liniment	Cure in 21/30 (70%) vs 17/30 (57%). In the Qu You Ding group, there were 2 cases of erythema, which cleared at 4 days
Yazar 1994	Silver nitrate vs placebo	Silver nitrate has a higher cure rate than placebo	Cure in 15/35 (43%) vs 4/35 (11%)
Zhang 1999	Chinese herbal medicine decoction vs electrocautery knife	Chinese herbal medicine was more effective than cautery	Recovery in 58/89 (65%) vs 7/18 (39%)

ADDITIONAL TABLES

Table 1. Glossary of Medical Terms

Medical term	Explanation
Corneocytes	Cells found in the outer skin layer
Cryotherapy	The use of cold as a surgical treatment, commonly with either carbon dioxide snow or liquid nitrogen
Distal	Away from, or far from, a point of reference in the anatomy
Epithelium	The cellular layer that forms the epidermis of the skin and lines the hollow organs and all passages of the respiratory, alimentary, and genitourinary systems
Hapten	A small molecule that can bind to a larger protein molecule to induce an immune response
Keratinocytes	The cells that make up most of the epidermis (the outermost layer of the skin) and produce keratin
Keratolytic	Breaking down the keratin component (outer layer) of skin
Lysis	Breaking down or destruction of cellular matter

Table 1. Glossary of Medical Terms (*Continued*)

Papule	A solid circumscribed elevation of the skin no bigger than 1 cm in diameter
Periungual	Next to the fingernail or toenail
Phase II clinical trial	A clinical trial of a new drug or therapy. Phase I trials are conducted in small groups of participants; phase II studies are conducted in a larger group of participants
Plantar warts	Warts on the soles of the feet
Plaque	A superficial, solid, elevated skin lesion greater than 1 cm in diameter
Primary care	Health care provided at the principal point of consultation for patients within a healthcare system, e.g. GP practices
Secondary care	Health care provided by medical specialists and other health professionals, including dermatologists, who generally do not have first contact with patients. Secondary care may be hospital or out-patient based
Topical	Pertaining to a certain surface area (usually the skin) and in the case of a treatment, only affecting the area to which it is applied

Table 2. Pharmaceutical companies contacted

Name	Response	Additional RCTs
Smith & Nephew	No	No
Stiefel	Yes	No
Dermal	Yes	No
William Ransom & Son plc	Yes	No
Norgine	No	No
Typharm	No	No
Bray Healthcare	No	No
Alliance Pharma	No	No
Brymill	Yes	No
Crymedica	No	No
Meda pharmaceuticals (3M)	No	No

Table 3. Clinicians and researchers contacted

Name	Country	Response	Additional RCTs
Claire Benton	UK	Yes	No
Tanya Bleiker	UK	Yes	No
John Bourke	Eire	Yes	No
Deirdre Buckley	UK	Yes	No
Alvin Chong	Australia	Yes	No
Australasian College of Dermatologists	Australia	No	No
Kiyofumi Egawa	Japan	No	No
Merete Haedersdal	Denmark	Yes	No
Thomas Horn	USA	Yes	No
Sandra Johnson	USA	No	No
Martin Keefe	New Zealand	Yes	No
M Ramam	India	Yes	No
Indian Association of Dermatologists	India	Yes	No
Ida Marie Stender	Germany	No	No
Stephen Tyring	USA	Yes	No
Gita Faghihi	Iran	Yes	No
Sabuj Baran Dhar	Bangladesh	Yes	No
Sjoerd Bruggink	Netherlands	Yes	No
Burhan Engin	Turkey	Yes	No
Feliz Canpolat	Turkey	Yes	No
Luk Nai Ming	Hong Long, China	Yes	No
Katrine Togsverd-Bo	Denmark	Yes	No

Table 3. Clinicians and researchers contacted (*Continued*)

Thierry Passeron	France	Yes	No
Rachel Wenner	USA	Yes	No
Ahmad Nofal	Egypt	Yes	No
Mahnaz Banihashemi	Iran	Yes	No
Khalifa Sharquie	Iraq	Yes	No
Xing-Hua (Barry) Gao	China	Yes	No
Gabriella Fabroccini	Italy	Yes	No

APPENDICES

Appendix 1. Skin Group Specialised Register search strategy

((PLANTAR AND WART*) OR VERRUCA* OR (VERRUCA* AND VULGARIS) OR (PAPILLOMAVIRUS AND HUMAN) OR (HPV) OR (MOSAIC AND WART*) OR (PLANE AND WART*) OR (COMMON AND WART*) OR (FOOT AND DERMATOS*) OR (HAND AND DERMATOS*) OR (SKIN AND DISEASE* AND VIRAL) OR (PAPOVAVIRIDAE AND INFECTION*)) AND NOT (genital and (ulcer* or wart*))

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 ((plantar or plane or common or mosaic or cutaneous or resistant or recalcitrant) near wart*) or verruca* or (papilloma near vir* near human)
#2 (skin near disease* near vir*)
#3 (papovaviridae near infection*)
#4 MeSH descriptor Epidermodysplasia Verruciformis explode all trees in MeSH products
#5 MeSH descriptor Warts, this term only in MeSH products
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 (genital* or vagina* or anogenital or cervical or condylomata):ti
#8 (#6 AND NOT #7)
#9 SR-SKIN
#10 (#8 AND NOT #9)

Appendix 3. MEDLINE (OVID) search strategy

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomised.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animals not (human and animals)).sh.
10. 8 not 9
11. wart$.mp. or exp WARTS/
12. (plant$ adj5 wart$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. (mosaic adj5 wart$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. (common adj5 wart$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
15. (cutaneous adj5 wart$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
16. (plan$ adj wart$).mp.
17. (flat adj wart$).mp.
18. verruca$.mp.
19. or/11-18
20. (papilloma adj5 vir$ adj5 human).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. papilloma virus.mp.
22. papovavirus.mp.
23. human papillomavirus.mp.
24. human papilloma virus.mp.
25. hpv.mp.
26. or/20-25
27. (hand$ or foot or feet or skin).mp.
28. 26 and 27
29. 19 or 28
30. genital wart.mp.
31. exp Condylomata Acuminata/
32. venereal wart$.mp.
33. verruca acuminata.mp.
34. 30 or 31 or 32 or 33
35. 29 not 34
36. 10 and 35

Appendix 4. EMBASE (OVID) search strategy

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
6. (singl$ adj blind$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
7. (assign$ or allocat$).mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. randomised Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. wart$.mp. or exp Verruca Vulgaris/
15. exp Wart virus/
16. (plant$ adj5 wart$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
17. (mosaic adj5 wart$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
18. (common adj5 wart$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
19. (cutaneous adj5 wart$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. (plan$ adj wart$).mp.
21. (flat adj wart$).mp.
22. verruca$.mp.
23. or/14-22
24. (papilloma adj5 vir$ adj5 human).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
25. exp papilloma virus/
26. exp papovavirus/
27. human papilloma virus.mp.
28. human papillomavirus.mp.
29. hpv.mp.
30. or/24-29
31. (hand$ or foot or feet or skin).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
32. 30 and 31
33. 23 or 32
34. genital wart$.mp. or exp condyloma acuminatum/
35. venereal wart$.mp.
36. Verruca acuminata.mp.
37. 34 or 35 or 36
38. 33 not 37
39. 13 and 38

Appendix 5. AMED (OVID) search strategy

1. randomised controlled trial$/
2. random allocation/
3. double blind method/
4. single blind method.mp.
5. exp Clinical trials/
6. (clin$ adj25 trial$).mp. [mp=abstract, heading words, title]
7. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$ or dummy)).mp. [mp=abstract, heading words, title]
8. (placebo$ or random$).mp. [mp=abstract, heading words, title]
9. research design/ or clinical trials/ or comparative study/ or double blind method/ or random allocation/
10. prospective studies.mp.
11. cross over studies.mp.
12. Follow up studies/
13. control$.mp.
14. (multicent$ or multi-cent$).mp. [mp=abstract, heading words, title]
15. ((stud or design$) adj25 (factorial or prospective or intervention or crossver or cross-over or quasi-experiment$)).mp. [mp=abstract, heading words, title]
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. wart$.mp. or exp WARTS/
18. (plant$ adj5 wart$).mp. [mp=abstract, heading words, title]
19. (mosaic adj5 wart$).mp. [mp=abstract, heading words, title]
20. (common adj5 wart$).mp. [mp=abstract, heading words, title]
21. (cutaneous adj5 wart$).mp. [mp=abstract, heading words, title]
22. (plan$ adj wart$).mp.
23. (flat adj wart$).mp.
24. verruca$.mp.
25. or/17-24
26. (papilloma adj5 vir$ adj5 human).mp. [mp=abstract, heading words, title]
27. papilloma virus.mp.
28. papovavirus.mp.
29. human papillomavirus.mp.
30. human papilloma virus.mp.
31. hpv.mp.
32. or/26-31
33. (hand$ or foot or feet or skin).mp.
34. 32 and 33
35. 25 or 34

Appendix 6. LILACS search strategy

((Pt randomised CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh randomised CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control$ or tw aleat$ or tw random$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Words] and verruga or verruca or wart or warts [Words]

Appendix 7. CINAHL (EBSCO) search strategy

S19 S16 and S18
S18 s4 not s17
S17 TX genital or venereal or "verruca acuminata" or "condylomata acuminata"
S16 S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15
S15 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S14 "randomi#ed control* trial*"
S13 TX allocat* random*
S12 (MH "Quantitative Studies")
S11 (MH "Placebos")
S10 TX placebo*
S9 TX random* allocat*
S8 (MH "Random Assignment")
S7 TX (clinic* n1 trial*)
S6 PT clinical trial
S5 (MH "Clinical Trials+")
S4 S1 or S2 or S3
S3 TX wart or warts
S2 TX verruca*
S1 (MH "Warts+") OR (MH "Warts, Plantar")

Appendix 8. Personal experience

Personal story received 3 December 2002

Summary - Verruca history

I suffered from verrucas for 5 years, having picked them up in a swimming pool abroad when I was 40 and ignored them until I moved back to England the following year. I finally went for treatment about a year after I had contracted them. On the doctor's advice, I filed my warts down with a foot file every night and tried all the wart paints on the market, both over-the-counter and on prescription, to no avail. I had the warts frozen with liquid nitrogen every fortnight at a wart clinic, which was painful and had no result - they quickly grew back. Finally, after a year's unsuccessful treatment, the doctor gave up and recommended me to the local hospital, where I saw a dermatologist after about a year's wait.

While I was waiting to see the specialist, the doctor suggested that I try homeopathy, since although it might not work, it should do me no harm. I duly went along to a homeopath, who (on payment of £25) listened to me sympathetically, drew pictures of my verruca-covered feet, and made notes about everything else that had recently happened in my life. He then gave me a few pills to take over a week, with the instruction to report back on any changes. There were no changes for either better or worse, so he made me some more pills for another £25, and then another batch for a further £25...eventually, after sampling quite a number of these tailor-made remedies, I was no better off and, indeed, somewhat poorer. I had no adverse side-effects, but my verrucas had not improved at all. The homeopath agreed that homeopathic treatment did not work for everyone, and gave up. By this time, both feet and the backs of my heels, were completely covered in verrucas.

As I was starting to think about being involved in an evidence-based education project, I looked up the Cochrane review on the web to discover what evidence there was for any treatment being effective, and I found that the evidence was inconclusive. I mentioned this to the dermatologist at the hospital, and he agreed with me, but thought he could try and laser one or two of my warts (both underneath my big toe). When he did this, my foot bled quite a lot, since the roots of one large verruca went down further than he had expected. It was also initially extremely painful, since the local anaesthetic had not worked properly, and I could feel that I was being burnt. (I was given more anaesthetic at this point, so at the end I could just smell the burning flesh but not actually feel it). The wound was dressed by a nurse at the hospital, and I was told to come back to the hospital for it to be redressed in a few days. However, the next night, when I had a shower with my foot encased in a plastic bag to avoid getting the wound wet, water unfortunately got into the bag, which I'd tied rather inexpertly round my leg, and the wound started bleeding and wouldn't stop. So I hobbled to the phone and phoned the NHS Helpline, and a nurse eventually rang me back about 45 minutes later and suggested that if it was still bleeding (which it was), I should tie a tea towel around it, which I did, and it eventually stopped.

The next day I went to see a nurse at my GP's practice, but although she redressed the wound for me, she didn't want to use the special blue pack filled with water, which I'd been told by the hospital to put onto the wound directly before dressing it, because she was unfamiliar with this material (as indeed I was). I should have insisted, but I didn't and put it back in my bag. When I went back to the hospital a few days later, the dressing had stuck inside the rather cavernous hole in my foot, and had to be soaked out. I then learnt how to dress the wound properly myself, so at least I learnt something from the experience. After this, I did not want to have any more warts lasered, and at the time, I suspected that my foot would be scarred for life (although this was not the case). On the advice of the dermatologist, I tried one more remedy - soaking my heel in a formaldehyde solution - another unpleasant procedure, which caused oedema and left me with the problem of disposing of the toxic solution (I poured it outside on the flowerbed, and it killed a primula). I finally decided that since there wasn't any evidence that anything worked, I would stop treating my verrucas and, indeed, ignore them. I did this for a couple of months, and then, by chance, saw that the verrucas were disappearing from my foot - a wave of clear skin was appearing. The doctor was astonished on my next visit, and thought that perhaps the wound from my laser treatment had meant the virus had got into my blood stream and caused my immune system to finally kick back. At the time, I thought that it could also mean that doing nothing was just as effective as doing anything, since treatment does not necessarily work. However, I now think he was right. Wounding my foot seemed a rather drastic treatment at the time, but perhaps that was what was needed.

Anyway, the laser wound has now completely healed, and I only have one (rather large and painful) wart on the sole of my foot instead of having both feet completely covered with warts. (I also still have two warts on my right hand, but at one time I had a lot more.) So it is not a complete success story, and at 45 I still have some warts, but at least my feet don't hurt all the time, as they used to even when I was lying in bed.

From my own experience, I would agree with the Cochrane review that there is not much evidence for anything being a fool-proof way of curing warts - the one good thing about reading the evidence meant that I had information that was previously only accessible to doctors, and if there had been any treatment which had been proved to be effective, I would have found out about it. It also put me in a better position when discussing my problem with them. It is only a pity that no evidence has been found of an effective treatment, but perhaps if more people report their experiences, more comparative tests can be carried out in the future to see if what works for one person will work for others.

DJM 2002

Reply

We have decided to use the comments and criticism facility occasionally, to publish personal experiences, relevant to particular reviews, and will withhold the senders name if requested.

Contributors

Comment forwarded to us by: Andrew Herxheimer, DIPEx, Emeritus Fellow, UK Cochrane Centre

Processed by: Tina Leonard, former Review Group Co-ordinator for the Cochrane Skin Group

WHAT'S NEW

Last assessed as up-to-date: 31 May 2011.

Date	Event	Description
23 August 2012	Amended	Cathy Bennett's affiliation was updated.

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 2, 2001

Date	Event	Description
14 August 2012	New search has been performed	New search for studies.
14 August 2012	New citation required and conclusions have changed	Updated with new studies. New authors added. Conclusions updated with new evidence for the efficacy of salicylic acid and cryotherapy from two large studies

CONTRIBUTIONS OF AUTHORS

Jane Sterling and Rosie Stark were involved in the original version of this review.

SG was the contact person with the editorial base.

SG and CB co-ordinated contributions from the co-authors and wrote the final draft of the review.

CSK, RH, and SG screened papers against eligibility criteria.

CSK, RH, and SG obtained data on ongoing and unpublished studies.

CB, RH, CSK, RA, and SG appraised the quality of papers.

CSK, RH, and SG with CB extracted data for the review and sought additional information about papers.

CSK, SG, and CB entered data into RevMan.

CSK, RH, CB, and SG analysed and interpreted data.

CSK, RH, CB, and SG worked on the methods sections.

SG drafted the clinical sections of the background and responded to the clinical comments of the referees.

CB and SG responded to the methodology and statistics comments of the referees.

CB was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.

SG is the guarantor of the update.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- Cochrane Skin Group, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the protocol and review include the searching of additional databases (LILACs and AMED) that were not searched in the previous published review.

We specifically excluded trials relating to molluscum contagiosum.

We updated the Background section in the light of emerging information from new trials and studies.

We revised the working of the Objectives section according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 4), which advises a single precise sentence. The Objectives remain unchanged.

We included plans to investigate heterogeneity by sensitivity analyses and stated that we would use random-effects models in our analyses. We clarified thresholds for the interpretation of I^2 statistic in the Methods section.

We had stated that we intended to conduct subgroup analyses of hand compared to plantar warts, but the small number of trials for many treatments and small sample sizes for each trial made subgroup analyses of limited value. We did conduct some subgroup analyses comparing hand versus feet warts.

Previous versions of the review included economic analyses, which we have not included in this update.

Consistent with Cochrane guideline changes since the publishing of the previous review, additional elements have been added to the 'Risk of bias' tables that were not present in the previous published review.

NOTES

Several studies that were previously on the excluded studies list were removed from this updated review because they did not meet the inclusion criteria of randomised controlled trials. Many of these removed studies were non-randomised studies and case reports.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Topical; Bleomycin [administration & dosage]; Cryotherapy [*methods]; Dermatologic Agents [*therapeutic use]; Dinitrochlorobenzene [administration & dosage]; Fluorouracil [administration & dosage]; Interferons [administration & dosage]; Photochemotherapy [*methods]; Randomized Controlled Trials as Topic; Salicylic Acids [administration & dosage]; Surgical Tape; Warts [*therapy]

MeSH check words

Adult; Child; Humans