Raynaud's phenomenon (secondary)

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ABSTRACT

INTRODUCTION: Raynaud's phenomenon is episodic vasospasm of the peripheral vessels, causing pallor followed by cyanosis and redness with pain and sometimes paraesthesia, and, rarely, ulceration of the fingers and toes. It presents as episodic colour changes of the digits, usually in response to cold exposure or stress. The classic triphasic colour change is white (ischaemia), then blue (deoxygenation), then red (reperfusion). Raynaud's phenomenon can be primary (idiopathic) or secondary to several different conditions and causes. This review deals with secondary Raynaud's phenomenon. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of self-help measures for secondary Raynaud's phenomenon? What are the effects of drug treatments for secondary Raynaud's phenomenon? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 25 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: alpha-blockers; angiotensin-converting enzyme (ACE) inhibitors; angiotensin II receptor antagonists; antithrombotics/inhibitors of platelet aggregation; biofeedback; calcium channel blockers; endothelin-1 receptor antagonists; glyceryl trinitrate (transdermal); hand exercises; inositol nicotinate; moxisylyte; naftidrofuryl oxylate; phosphodiesterase inhibitors; prostaglandins (oral, intravenous); relaxation therapy; serotonin reuptake inhibitors (SRIs); smoking cessation; and warming hands and feet.

QUESTIONS

INTERVENTIONS

Key points

- Raynaud's phenomenon is episodic vasospasm of the peripheral vessels, causing pallor followed by cyanosis and redness with pain and sometimes paraesthesia, and, rarely, ulceration of the fingers and toes.
- It presents as episodic colour changes of the digits, usually in response to cold exposure or stress. The classic change is white (ischaemia), then blue (deoxygenation), then red (reperfusion).

Raynaud's phenomenon (secondary)

- Raynaud's phenomenon can be primary (idiopathic) or secondary to several different conditions and causes. This review deals with secondary Raynaud's phenomenon.
- Most trials we found were in people with Raynaud's phenomenon secondary to systemic sclerosis.
- We don't know whether biofeedback, hand exercises, relaxation therapy, smoking cessation, or warming hands and feet or keeping warm work, as we found no evidence.

  Although we found no evidence, given the adverse effects of smoking on the vasculature, it is reasonable to encourage people with secondary Raynaud's to stop smoking.

  Similarly, although we found no evidence, given that many people report exacerbation of symptoms in the cold, it is reasonable to avoid cold exposure and to keep the hands and feet warm if an attack develops.
- Intravenous iloprost (a prostaglandin) reduces the frequency and severity of attacks compared with placebo in people with Raynaud's phenomenon secondary to systemic sclerosis.

  Intravenous prostaglandins other than iloprost have been less well studied.
- Calcium channel blockers (mainly nifedipine) may decrease the frequency and severity of vasospastic attacks over 2 weeks compared with placebo in people with Raynaud's phenomenon secondary to systemic sclerosis. However, evidence is limited.
- Bosentan (a dual endothelin-1 receptor antagonist) may reduce new digital ulcer formation compared with placebo in people with Raynaud's phenomenon secondary to systemic sclerosis and with previous digital ulcers in the last 12 months. However, we found no evidence on bosentan in people with secondary Raynaud's without previous digital ulceration, so the results are not generalisable to all people with secondary Raynaud's.
- We don't know whether naftidrofuryl oxalate, alpha-blockers, angiotensin II receptor antagonists, ACE inhibitors, antithrombotics/inhibitors of platelet aggregation, glyceryl trinitrate (transdermal), inositol nicotinate, moxisylyte, phosphodiesterase inhibitors, or SRIs work, as we found no evidence.
- Oral prostaglandins are unlikely to be beneficial in people with secondary Raynaud's phenomenon.

DEFINITION

Raynaud's phenomenon is episodic vasospasm of the peripheral vessels, causing pallor followed by cyanosis and redness with pain and sometimes paraesthesia, and, rarely, ulceration of the fingers and toes. It presents as episodic colour changes of the digits, usually in response to cold exposure or stress. The classic triphasic colour change is white (ischaemia), then blue (deoxygenation), then red (reperfusion). Raynaud's phenomenon can be primary (idiopathic) or secondary to several different conditions or causes, including connective tissue diseases such as systemic sclerosis, extrinsic vascular obstruction (e.g., in thoracic outlet syndrome), certain drugs/chemicals (e.g., ergotamine, vinyl chloride), vibration exposure (hand-arm vibration syndrome), and hyperviscosity states. [1] This review excludes primary (idiopathic) Raynaud's phenomenon, and concerns the management of secondary Raynaud's phenomenon. Most of the evidence we found on secondary Raynaud's phenomenon was in people with systemic sclerosis.

INCIDENCE/ PREVALENCE

See Raynaud's phenomenon (primary). The prevalence of secondary Raynaud's depends on the associated disease or condition. For example, the prevalence of Raynaud's phenomenon in people with systemic sclerosis is almost 100%.

AETIOLOGY/ RISK FACTORS

Many different conditions can be associated with secondary Raynaud's phenomenon, and the pathogenesis and pathophysiology of Raynaud's phenomenon vary depending upon these underlying conditions. Abnormalities of the blood vessel wall, of the neural control of vascular tone, and intravascular factors may all have a role. [2] Other factors have also been implicated, including smoking (in people with systemic sclerosis, smoking is associated with severity of digital ischaemia), hormonal factors (Raynaud's is more common in women than in men), and genetic factors. [2]

PROGNOSIS

Secondary Raynaud's phenomenon can be severe, and may progress to ulceration, scarring, and sometimes gangrene necessitating amputation. [3] Therefore, prognosis depends, at least to some extent, on the underlying cause of Raynaud's phenomenon. Prognosis has been studied best in people with systemic sclerosis who develop underlying structural vascular abnormalities affecting both the microcirculation and the digital arteries. One study found that, of 1168 people with systemic sclerosis, 203 people (17.4%) had severe digital vasculopathy (Raynaud's phenomenon complicated by digital ulceration, critical digital ischaemia, gangrene, or requiring digital sympathectomy). [3]

AIMS OF INTERVENTION

To relieve or reduce the frequency and severity of Raynaud s attacks, prevent tissue damage, preserve hand function, and improve quality of life, with minimal adverse effects of treatment.

OUTCOMES

Raynaud's attacks: frequency and duration of symptoms as assessed by patient diary; severity of symptoms assessed by patient diary or by visual analogue scales, Likert scales, or the Raynaud's

Condition Score; **Digital ulceration:** rates, size and healing of digital ulceration; **Hand function; Quality of life;** and **Adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal May 2007. The following databases were used to identify studies for this systematic review: Medline 1987 to May 2007 for systematic reviews and 1987 to July 2007 for RCTs and cohort studies, Embase 1987 to May 2007 for systematic reviews and 1987 to July 2007 for RCTs and cohort studies, and The Cochrane Database of Systematic Reviews Issue 2, 2007 and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches used these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the reviews. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for evaluation in this review were: published systematic reviews and RCTs in any language, at least single blinded for drug interventions but including open studies for non-drug interventions, and containing 20 or more people, of whom more than 65% were followed up. In addition, we searched for prospective cohort studies for non-drug interventions. We included studies of people with primary Raynaud's if a subset of people with secondary Raynaud's could be separately identified and outcomes independently assessed, or if over 75% of people in the RCT had secondary Raynaud's. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. Most studies we found of treatment for secondary Raynaud's phenomenon were in people with systemic sclerosis. Difficulties in undertaking and interpreting clinical trials in people with Raynaud's phenomenon include the need to account for other extrinsic factors (e.g., symptoms may be worse over winter) and the need for an adequate comparison group (due to high rates of placebo response and the fluctuating nature of the disease). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 34). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of self-help measures for secondary Raynaud's phenomenon?

OPTION WARMING HANDS AND FEET OR KEEPING WARM New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether warming hands and feet or keeping warm work, as we found no evidence.
- Although we found no evidence, given that many people report exacerbation of symptoms in the cold, it is reasonable to avoid cold exposure and to keep the hands and feet warm if an attack develops.

Benefits and harms

Warming hands and feet or keeping warm versus no treatment:

We found no systematic reviews, RCTs, or cohort studies.

Warming hands and feet or keeping warm versus other self-help interventions covered in this review:

We found no systematic reviews, RCTs, or cohort studies.

Further information on studies

Comment: **Clinical guide:**
Although there have been no clinical trials of warming of the hands and feet in people with secondary Raynaud's phenomenon, people almost invariably report exacerbation of their symptoms in the cold, and so it seems sensible to, firstly, avoid cold exposure whenever possible and, secondly, to keep the hands and feet warm and if an attack does develop, to rewarm them as soon as possible to expedite reperfusion.

OPTION RELAXATION THERAPY New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether relaxation therapy works as we found no evidence.

Benefits and harms

Relaxation therapy versus no treatment:

We found one systematic review (search date 1999), [4] which identified one RCT that did not meet *Clinical Evidence* reporting criteria.

Relaxation therapy versus other self-help interventions covered in this review:

We found no systematic reviews, RCTs, or cohort studies.

Further information on studies

Comment: **Clinical guide:**
Relaxation therapy has been little studied in people with secondary Raynaud's phenomenon. However, many people report that stress exacerbates their symptoms, and so avoiding stress through relaxation therapy may confer benefit in some people.

OPTION BIOFEEDBACK New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether biofeedback works, as we found no evidence.

Benefits and harms

Biofeedback versus no treatment:

We found no systematic reviews, RCTs, or cohort studies.

Biofeedback versus other self-help interventions covered in this review:

We found no systematic reviews, RCTs, or cohort studies.

Further information on studies

Comment: **Clinical guide:**
Temperature biofeedback has been more studied in primary than in secondary Raynaud's phenomenon. One controlled trial in 2000 did not demonstrate any efficacy of temperature biofeedback in primary Raynaud's, and this treatment is not widely recommended for either primary or secondary Raynaud's phenomenon. [5]

OPTION SMOKING CESSATION New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether smoking cessation works as we found no evidence.
- Although we found no evidence, given the adverse effects of smoking on the vasculature, it is reasonable to encourage people with secondary Raynaud's to stop smoking.

Benefits and harms

Smoking cessation versus no treatment:

We found no systematic reviews, RCTs, or cohort studies.

Smoking cessation versus other self-help interventions covered in this review:

We found no systematic reviews, RCTs, or cohort studies.

Further information on studies

Comment: **Clinical guide:**
Although smoking cessation has not been studied in secondary Raynaud's phenomenon, the adverse effects of smoking on the vasculature suggest that it is appropriate for clinicians to encourage people to stop smoking.

OPTION HAND EXERCISES New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether hand exercises work, as we found no evidence.

Benefits and harms

Hand exercises versus no treatment:

We found no systematic reviews, RCTs, or cohort studies.

Hand exercises versus other self-help interventions covered in this review:

We found no systematic reviews, RCTs, or cohort studies.

Further information on studies

Comment: **Clinical guide:**
The effects of hand exercises have not been studied in secondary Raynaud's phenomenon. Where the Raynaud's phenomenon is associated with reduced finger movements — for example, in systemic sclerosis — then it seems sensible to recommend exercises to retain as great a range of mobility as possible.

QUESTION What are the effects of drug treatments for secondary Raynaud's phenomenon?

OPTION GLYCERYL TRINITRATE (TRANSDERMAL) New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether glyceryl trinitrate (transdermal) works.
- Transdermal glyceryl trinitrate has been associated with headaches, which limits its use in people with Raynaud's phenomenon.

Benefits and harms

Glyceryl trinitrate (transdermal) versus placebo:
We found one crossover RCT. [6]

Raynaud's attacks

Transdermal glyceryl trinitrate compared with placebo Transdermal glyceryl trinitrate may be more effective at reducing the mean number and severity of Raynaud's attacks over 7 days (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of attack					
[6] RCT **Crossover design**	21 people with Raynaud's phenomenon secondary to systemic sclerosis Subgroup analysis Total population was 42 people with Raynaud's phenomenon (primary and secondary)	**Mean difference of frequency of attacks (post-crossover) , 7 days** with transdermal glyceryl trinitrate (0.2 mg/hour for 12 hours/day) with placebo Absolute results not reported	P = 0.046 Result is of borderline significance Result should be interpreted with caution; see further information on studies for full details	○○○	transdermal glyceryl trinitrate
Severity of attack					
[6] RCT **Crossover design**	21 people with Raynaud's phenomenon secondary to systemic sclerosis Subgroup analysis Total population was 42 people with Raynaud's phenomenon (primary and secondary)	**Mean difference in overall severity score (post-crossover) , 7 days** with transdermal glyceryl trinitrate (0.2 mg/hour for 12 hours/day) with placebo Absolute results not reported	P = 0.036 Result should be interpreted with caution; see further information on studies for full details	○○○	transdermal glyceryl trinitrate
[6] RCT **Crossover design**	21 people with Raynaud's phenomenon secondary to systemic sclerosis Subgroup analysis Total population was 42 people with Raynaud's phe-	**Mean difference in numbness score (post-crossover) , 7 days** with transdermal glyceryl trinitrate (0.2 mg/hour for 12 hours/day) with placebo Absolute results not reported Numbness measured on a 4-point scale, increasing severity with increased score.	P = 0.009 Result should be interpreted with caution; see further information on studies for full details	○○○	transdermal glyceryl trinitrate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	nomenon (primary and secondary)				
[6] RCT **Crossover design**	21 people with Raynaud's phenomenon secondary to systemic sclerosis Subgroup analysis Total population was 42 people with Raynaud's phenomenon (primary and secondary)	**Mean difference in pain score (post-crossover) , 7 days** with transdermal glyceryl trinitrate (0.2 mg/hour for 12 hours/day) with placebo Absolute results not reported	P = 0.034 Result should be interpreted with caution; see further information on studies for full details	○○○	transdermal glyceryl trinitrate

Digital ulceration

No data from the following reference on this outcome. [6]

Hand function

No data from the following reference on this outcome. [6]

Quality of life

No data from the following reference on this outcome. [6]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache					
[6] RCT **Crossover design**	42 people with primary (17 people) and secondary (15 people) Raynaud's phenomenon	**Headache** 26/32 (81%) with glyceryl trinitrate 10/32 (31%) with placebo	P <0.001 Result should be interpreted with caution; see further information on studies for full details	○○○	placebo
Withdrawals					
[6] RCT **Crossover design**	42 people with primary (17 people) and secondary (15 people) Raynaud's phenomenon	**Withdrawals** with glyceryl trinitrate with placebo Eight people withdrew from the study during treatment with glyceryl trinitrate All eight people had headaches, and two also had nausea	Significance not assessed		

Glyceryl trinitrate (transdermal) versus other drug treatments covered in this review:

We found no systematic review or RCTs.

Further information on studies

[6] The RCT did not include a washout period and did not report pre-crossover results or methods of randomisation. Results based on 15/21 (71%) people with secondary Raynaud's who completed the trial.

Comment: **Clinical guide:**
Although topical glyceryl trinitrate, a nitric oxide donor, administered by "patch", has been shown in one small study to be effective in systemic sclerosis-related Raynaud's phenomenon, this is at the expense of adverse effects (mainly headaches) due to its systemic absorption. Therefore, local delivery systems (applying glyceryl trinitrate directly to the fingers) are being researched with the aim of achieving local but not systemic increases in blood flow.

OPTION CALCIUM CHANNEL BLOCKERS New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- Calcium channel blockers (mainly nifedipine) may decrease the frequency and severity of vasospastic attacks over 2 weeks compared with placebo in people with Raynaud's phenomenon secondary to systemic sclerosis. However, evidence is limited.

Benefits and harms

Calcium channel blockers versus placebo:

We found two systematic reviews (search date 2000, [7] 8 RCTs, 187 people, 109 with Raynaud's phenomenon secondary to systemic sclerosis) and (search date 2005), [8] comparing calcium channel blockers versus placebo. The first review identified seven RCTs assessing nifedipine and one RCT assessing nicardipine. The second systematic review was narrative in character, and did not meta-analyse data or identify any further RCTs not identified by the first review. [8]

Raynaud's attacks

Calcium channel blockers compared with placebo Calcium channel blockers (mainly nifedipine) may be more effective at reducing the frequency and severity of vasospastic attacks at 2 weeks in people with Raynaud's secondary to systemic sclerosis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of attack					
[7] Systematic review	59 people with Raynaud's phenomenon secondary to systemic sclerosis 6 RCTs in this analysis All RCTs were of crossover design	**Mean reduction in frequency of attack , 2 weeks** with calcium channel blockers with placebo Absolute results not reported	WMD –8.31 attacks 95% CI –15.71 attacks to –0.91 attacks P = 0.03 Methodological limitations; see further information on studies for full details	◌◌◌	calcium channel blockers
[7] Systematic review	44 people with Raynaud's phenomenon secondary to systemic sclerosis	**Mean reduction in frequency of attack , 2 to 12 weeks** with nifedipine (10–20 mg three times daily) with placebo	WMD –10.21 attacks 95% CI –20.09 attacks to –0.34 attacks P = 0.04	◌◌◌	nifedipine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	5 RCTs in this analysis All RCTs were of crossover design		Methodological limitations; see further information on studies for full details		
Severity of attack					
[7] Systematic review	31 people with Raynaud's phenomenon secondary to systemic sclerosis 3 RCTs in this analysis All RCTs were of crossover design	**Severity of attack , 2 weeks** with calcium channel blockers with placebo	SMD –0.69 95% CI –1.21 to –0.17 P = 0.01 Methodological limitations; see further information on studies for full details	○○○	calcium channel blockers

Digital ulceration

No data from the following reference on this outcome. [7]

Hand function

No data from the following reference on this outcome. [7]

Quality of life

No data from the following reference on this outcome. [7]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[9] RCT	15 people in total, 9 with systemic sclerosis In review [7]	**headache** 80% with nifedipine 20% with placebo Absolute numbers not reported	P = 0.003	○○○	placebo
[9] RCT	15 people in total, 9 with systemic sclerosis In review [7]	**Lightheadedness** 33% with nifedipine 7% with placebo Absolute numbers not reported	P = 0.17	⟷	Not significant
[10] RCT	22 people in total, 8 with systemic sclerosis In review [7]	**Adverse effects** 12/22 (55%) with nifedipine 2/22 (9%) with placebo	P <0.005	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Adverse effects with nifedipine included flushing, headache, and orthostatic hypotension			
[11] RCT	15 people in total, 7 people with systemic sclerosis In review [7]	**Adverse effects** 6/15 (40%) with nifedipine 2/15 (13%) with placebo Adverse effects with nifedipine included headache, flushing, dizziness, nausea, and ankle oedema	Significance not assessed		
[12] RCT	30 people in total, 10 people with systemic sclerosis In review [7]	**Headache** 4 people with nifedipine 0 people with placebo	Significance not assessed		
[12] RCT	30 people in total, 10 people with systemic sclerosis In review [7]	**Nausea** 5 people with nifedipine 2 people with placebo	Significance not assessed		
[12] RCT	30 people in total, 10 people with systemic sclerosis In review [7]	**Ankle oedema** 7 people with nifedipine 0 people with placebo	Significance not assessed		
[12] RCT	30 people in total, 10 people with systemic sclerosis In review [7]	**Facial flushing** 5 people with nifedipine 0 people with placebo	Significance not assessed		
[12] RCT	30 people in total, 10 people with systemic sclerosis In review [7]	**Faintness** 0 people with nifedipine 1 person with placebo	Significance not assessed		
[12] RCT	30 people in total, 10 people with systemic sclerosis In review [7]	**Palpitations** 0 people with nifedipine 1 person with placebo	Significance not assessed		

Calcium channel blockers versus intravenous prostaglandins:

We found two systematic reviews (search date 2000 [7] and search date 2005), [8] and one subsequent RCT. [13] The first systematic review [7] identified one RCT, comparing oral nifedipine versus intravenous iloprost. [14] The RCT reported only baseline changes for the number, duration, or severity of attacks, and did not report a direct statistical comparison between nifedipine and iloprost for these outcomes, so we have not reported data on our outcomes of interest. We have reported general adverse effects from this RCT. [14] The second systematic review (search date 2005) reported the findings of the first systematic review, but did not pool data or identify any further RCTs. [8] The subsequent RCT compared oral nifedipine versus intravenous iloprost for 12 months. [13] However, the RCT reported only baseline changes for severity of attacks, and did not report a direct statistical comparison between nifedipine and iloprost for this outcomes, so we have not reported data on our outcomes of interest. We have reported general adverse effects from this RCT. [13]

Raynaud's attacks

No data from the following reference on this outcome. [7] [8] [13]

Digital ulceration

No data from the following reference on this outcome. [7] [8] [13]

Hand function

No data from the following reference on this outcome. [7] [8] [13]

Quality of life

No data from the following reference on this outcome. [7] [8] [13]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] RCT	23 people with Raynaud's phenomenon and systemic sclerosis In review [7]	**Withdrawals** with oral nifedipine with intravenous iloprost The RCT found that 5/11 (45%) people given nifedipine could not tolerate the maximum dose. In total, 3/11 (27%) people withdrew from the study on lower-dose nifedipine; 2/11 (18%) because of headache, and 1/11 (9%) because of peripheral oedema More than 50% of people given intravenous iloprost reported transient headache, nausea, and vomiting, which resolved with completion of the infusion No comparative data reported			
[13] RCT	46 people with Raynaud's phenomenon and systemic sclerosis	**Headache** 100% with intravenous iloprost (given initially by infusion over 8 hours on 5 consecutive days plus one 8-hour infusion every 6 weeks) 18% with oral nifedipine (twice daily) Absolute numbers not reported See further information on studies for additional adverse effects associated with intravenous iloprost and oral nifedipine	Significance not assessed		
[13] RCT	46 people with Raynaud's phenomenon and systemic sclerosis	**Hypotension** 14% with intravenous iloprost (given initially by infusion over 8 hours on 5 consecutive days plus	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		one 8-hour infusion every 6 weeks) 29% with oral nifedipine (twice daily) Absolute numbers not reported See further information on studies for additional adverse effects associated with intravenous iloprost and oral nifedipine			
[13] RCT	46 people with Raynaud's phenomenon and systemic sclerosis	**Withdrawals** 6 people with (given initially by infusion over 8 hours on 5 consecutive days plus one 8-hour infusion every 6 weeks) 5 people with oral nifedipine (twice daily) Reason for withdrawal from the iloprost group were lack of compliance (3 people), scleroderma renal crisis (1 person), interstitial pneumonia (1 person), MI (1 person) All five withdrawals from the nifedipine group were due to intolerance See further information on studies for additional adverse effects associated with intravenous iloprost and oral nifedipine	Significance not assessed		

Calcium channel blockers versus angiotensin II receptor antagonists:

We found three systematic reviews. [7] [8] [15] The first and third systematic review (search date 2000, [7] and search date 2006) [15] identified one RCT comparing slow-release nifedipine versus losartan. [16] The RCT did not satisfy *Clinical Evidence* inclusion criteria as it is an open study, and is therefore not discussed further. The second systematic review (search date 2005) reported the findings of the first systematic review, but identified no additional RCTs. [8]

Calcium channel blockers versus SRIs:

We found one crossover RCT (53 people, 27 with secondary Raynaud's phenomenon) comparing oral nifedipine versus fluoxetine for 6 weeks. [17] The RCT did not meet *Clinical Evidence* reporting criteria as it is an open study, and is therefore not discussed further.

Calcium channel blockers versus glyceryl trinitrate (transdermal), alpha-blockers, naftidrofuryl oxylate, moxisylyte, inositol nicotinate, ACE inhibitors, endothelin-1 receptor antagonists, phosphodiesterase inhibitors, antithrombotics/inhibitors of platelet aggregation, or prostaglandins (oral):

We found no systematic review or RCTs.

Further information on studies

[7] Of the eight RCTs included in the review, seven RCTs were of crossover design. The review noted that results prior to crossover were not reported in many studies, which may have led to a smaller than expected treatment effect. It noted that, because many of the studies included people with primary and secondary Raynaud's phenomenon, the subgroup analysis could be biased if randomisation was not stratified within the groups of people with secondary Raynaud's. The review also noted that treatment duration was often short, and the eight RCTs had small sample sizes (109 people in total with systemic sclerosis).

[13] Additional adverse effects reported with iloprost included nausea/vomiting (83%), jaw pain (69%), myalgia (34%), diarrhoea (28%), and chills (17%). Additional adverse effects reported with nifedipine included tachycardia (6%).

Comment: **Clinical guide:**
Many clinicians believe that calcium channel blockers should be used as first-line drug treatment for secondary Raynaud's phenomenon, although not all people benefit, and a large proportion of people have adverse effects, including headache, flushing, hypotension, peripheral oedema, and nausea.

OPTION ALPHA-BLOCKERS (ORAL) New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether alpha-blockers work.

Benefits and harms

Alpha-blockers versus placebo:

We found two systematic reviews (search date 1996 [18] and search date 2005). [8] The first review (2 RCTs, 26 people with Raynaud's phenomenon and systemic sclerosis) compared alpha-blockers versus placebo in people with Raynaud's and systemic sclerosis. [18] The review included RCTs of people with primary Raynaud's phenomenon and Raynaud's phenomenon secondary to systemic sclerosis if results from people with scleroderma could be separately identified and their outcome independently assessed. [18] The analysis of the second RCT in the review included less than 20 people — which does not meet *Clinical Evidence* reporting criteria, and so is not reported further. [18] The second systematic review identified the same RCTs as the first systematic review, but did not pool data or identify any further RCTs. [8]

Raynaud's attacks

Alpha-blockers compared with placebo The alpha-blocker prazosin may be more effective at reducing the frequency of vasospastic attacks at 12 weeks in people with Raynaud's phenomenon secondary to systemic sclerosis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of attack					
[18] Systematic review	20 people with Raynaud's phenomenon and systemic sclerosis Data from 1 RCT RCT is of crossover design	**Frequency of vasospastic attack , 12 weeks** with oral prazosin (3–9 mg/day) with placebo Absolute results not reported	WMD –3.50 attacks 95% CI –5.85 attacks to –1.15 attacks P = 0.003	○○○	oral prazosin

Digital ulceration

No data from the following reference on this outcome. [18]

Hand function

No data from the following reference on this outcome. [18]

Quality of life

No data from the following reference on this outcome. [18]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] Systematic review	20 people with Raynaud's phenomenon and systemic sclerosis Data from 1 RCT RCT is of crossover design	**Adverse effects** 2/11 people (18%) with prazosin 0/9 people (0%) with placebo	OR 6.82 95% CI 0.39 to 119.26 P = 0.2	⟷	Not significant

Alpha-blockers versus other drug treatments covered in this review:
We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
There is weak evidence supporting the use of alpha-blockers in secondary Raynaud's. Further RCTs are necessary to establish the role of alpha-blockers for secondary Raynaud's phenomenon.

OPTION NAFTIDROFURYL OXYLATE New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether naftidrofuryl oxylate works as we found no evidence.

Benefits and harms

Naftidrofuryl oxylate versus placebo:
We found no systematic review or RCTs.

Naftidrofuryl oxylate versus other drug treatments covered in this review:
We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although naftidrofuryl oxalate is occasionally prescribed for people with secondary Raynaud's phenomenon, at present there is no evidence to support its use. RCTs are needed to establish whether naftidrofuryl oxalate is of benefit for people with Raynaud's phenomenon.

OPTION MOXISYLYTE New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don’t know whether moxisylyte works as we found no evidence.

Benefits and harms

Moxisylyte versus placebo:
We found systematic review or RCTs.

Moxisylyte versus other drug treatments covered in this review:
We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although moxisylyte is occasionally prescribed for people with secondary Raynaud's phenomenon, at present there is no evidence to support its use. RCTs are needed to establish whether moxisylyte is of benefit for people with Raynaud's phenomenon.

OPTION INOSITOL NICOTINATE New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don’t know whether inositol nicotinate works as we found no evidence.

Benefits and harms

Inositol nicotinate versus placebo:
We found no systematic review or RCTs.

Inositol nicotinate versus other drug treatments covered in this review:
We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although inositol nicotinate is occasionally prescribed for people with secondary Raynaud's phenomenon, at present there is no evidence to support its use. RCTs are required to establish whether inositol nicotinate is of benefit for people with Raynaud's phenomenon.

OPTION ACE INHIBITORS New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether ACE inhibitors work as we found no evidence.

Benefits and harms

ACE inhibitors versus placebo:

We found one systematic review (search date 2006), [15] which identified no RCTs that met *Clinical Evidence* reporting criteria. The searches in the review were restricted to English language studies. We found no subsequent RCTs.

ACE inhibitors versus other drug treatments covered in this review:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
There is no good evidence in favour of ACE inhibitors for the treatment of secondary Raynaud's phenomenon. Further RCTs are required to establish the role of ACE inhibitors for secondary Raynaud's phenomenon.

OPTION ANGIOTENSIN II RECEPTOR ANTAGONISTS (ORAL) New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether angiotensin II receptor antagonists work as we found no evidence.

Benefits and harms

Angiotensin II receptor antagonists versus placebo:

We found no systematic review or RCTs.

Angiotensin II receptor antagonists versus calcium channel blockers:

See option on calcium channel blockers, p 8 .

Angiotensin II receptor antagonists versus glyceryl trinitrate (transdermal), alpha-blockers, naftidrofuryl oxylate, moxisylyte, inositol nicotinate, ACE inhibitors, SRIs, endothelin-1 receptor antagonists, phosphodi-

esterase inhibitors, antithrombotics/inhibitors of platelet aggregation, prostaglandins (oral), or prostaglandins (intravenous):

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Some clinicians prescribe angiotensin II receptor antagonists for people with secondary Raynaud's phenomenon, although at present there is only weak evidence for this from an open study comparing losartan to nifedipine. [16] Further RCTs are needed to establish the role of angiotensin II receptor antagonists for secondary Raynaud's phenomenon.

OPTION SRIS (SEROTONIN REUPTAKE INHIBITORS) New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don’t know whether SRIs work as we found no evidence.

Benefits and harms

SRI versus placebo:

We found no systematic review or RCTs.

SRI versus calcium channel blockers:

See option on calcium channel blockers, p 8 .

SRI versus glyceryl trinitrate (transdermal), alpha-blockers, naftidrofuryl oxylate, moxisylyte, inositol nicotinate, ACE inhibitors, angiotensin II receptor antagonists, endothelin-1 receptor antagonists, phospho-diesterase inhibitors, antithrombotics/inhibitors of platelet aggregation, prostaglandins (oral), or prostaglandins (intravenous):

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Some clinicians prescribe SRIs for people with secondary Raynaud's phenomenon, although at present there is only weak evidence for this from an open study comparing fluoxetine versus nifedipine. [17] Further RCTs are required to establish the role of SRIs for secondary Raynaud's phenomenon.

OPTION ENDOTHELIN-1 RECEPTOR ANTAGONISTS New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .

- Bosentan (a dual endothelin-1 receptor antagonist) may reduce new digital ulcer formation compared with placebo in people with Raynaud's phenomenon secondary to systemic sclerosis and with previous digital ulcers in the last 12 months. However, we found no evidence on bosentan in people with secondary Raynaud's without previous digital ulceration, so the results are not generalisable to all people with secondary Raynaud's.
- Bosentan has been associated with abnormal liver function tests.

Benefits and harms

Bosentan versus placebo:

We found one RCT comparing oral bosentan versus placebo for 16 weeks. [19]

Digital ulceration

Bosentan compared with placebo Bosentan (a dual endothelin-1 receptor antagonist) may be more effective at reducing the number of new digital ulcers in people with systemic sclerosis and a history of digital ulceration in the previous 12 months, but not at improving ulcer healing rates. We found no evidence in people with secondary Raynaud's without previous digital ulceration (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of digital ulcers					
[19] RCT	122 people with systemic sclerosis and a history of a documented digital ulcer within the previous 12 months	**Mean number of new digital ulcers , 16 weeks** 1.4 with bosentan (125 mg twice daily) 2.7 with placebo People could continue treatment with other vasodilating drugs during the RCT, but treatment with parenteral prostanoids within the previous 3 months was not allowed	P = 0.0083	○○○	bosentan
[19] RCT	76 people with existing digital ulcers at baseline Subgroup analysis Total population was 122 people with systemic sclerosis and a history of a documented digital ulcer within the previous 12 months	**Mean number of new digital ulcers , 16 weeks** 1.8 with bosentan (125 mg twice daily) 3.6 with placebo People could continue treatment with other vasodilating drugs during the RCT, but treatment with parenteral prostanoids within the previous 3 months was not allowed	P = 0.0075	○○○	bosentan
Time to ulcer healing					
[19] RCT	122 people with systemic sclerosis and a history of a documented digital ulcer within the previous 12 months	**Time to complete or partial ulcer healing , 16 weeks** with bosentan (125 mg twice daily) with placebo Absolute results reported graphically People could continue treatment with other vasodilating drugs during the RCT, but treatment with parenteral prostanoids within the previous 3 months was not allowed	Reported as not significant P value not reported	⟷	Not significant

Hand function

Bosentan compared with placebo Bosentan may be more effective at improving hand function (as measured by modified Scleroderma Health Assessment Questionnaire [SHAQ]) at 16 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hand function					
[19] RCT	122 people with systemic sclerosis and a history of a documented digital ulcer within the previous 12 months	**Hand function (measured by modified Scleroderma Health Assessment Questionnaire [SHAQ]) , 6 weeks** with bosentan (125 mg twice daily) with placebo Absolute results reported graphically People could continue treatment with other vasodilating drugs during the RCT, but treatment with parenteral prostanoids within the previous 3 months was not allowed	P <0.005	○○○	bosentan

Raynaud's attacks

No data from the following reference on this outcome. [19]

Quality of life

No data from the following reference on this outcome. [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT	122 people with systemic sclerosis and a history of a documented digital ulcer within the previous 12 months	**Serious adverse effects** 2/79 (3%) with bosentan (125 mg twice daily) 3/43 (7%) with placebo People could continue treatment with other vasodilating drugs during the RCT, but treatment with parenteral prostanoids within the previous 3 months was not allowed See further details on studies for details of serious adverse effects in each group and for abnormal liver function tests associated with bosentan	Significance not assessed		

Endothelin-1 receptor antagonists other than bosentan versus placebo:

We found no systematic review or RCTs.

Endothelin-1 receptor antagonists versus other drug treatments covered in this review:

We found no systematic review or RCTs.

Further information on studies

[19] **Serious adverse effects** Serious adverse effects in the bosentan group were palpitations (1/79 [1.3%]), and dyspnoea (1/79 [1.3%]). Serious adverse effects in the placebo group were dyspnoea (1/43 [2.3%]), oesophagitis and vomiting (1/43 [2.3%]), and digital ischaemia (1/43 [2.3%]) **Liver function tests:** In total, 11/89 (14%) people given bosentan developed abnormal liver function tests, specifically elevated transaminases. Abnormalities of liver function tests led to five people discontinuing bosentan. In all people who stopped treatment, transaminase values returned to normal.

Comment: **Clinical guide:**
There is some evidence to support the use of bosentan in people with systemic sclerosis-related digital ulceration, particularly those with multiple or recurrent ulcers. Liver function must be closely monitored, because a significant proportion of people develop raised transaminases.

OPTION PHOSPHODIESTERASE INHIBITORS New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether phosphodiesterase inhibitors work.

Benefits and harms

Phosphodiesterase inhibitors versus placebo:

We found one systematic review (search date 2006), [20] which identified one RCT that did not meet *Clinical Evidence* reporting criteria. The searches in the review were restricted to English language studies. We found one additional RCT. [21]

Raynaud's attacks

Phosphodiesterase inhibitors compared with placebo Phosphodiesterase type III inhibitors (oral cilostazol) may be no more effective at reducing the frequency and severity of vasospastic attacks at 6 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of attack					
[21] RCT	21 people with Raynaud's phenomenon (secondary to connective tissue disorder) Subgroup analysis Total population in RCT of 43 people with primary or secondary Raynaud's phenomenon	**mean number of vasospastic attacks , 6 weeks** 46 with oral cilostazol (100 mg twice daily) 45 with placebo Number of people with secondary Raynaud's phenomenon in each group not clear	P = 0.96 Method of randomisation not clear	⟷	Not significant
[21] RCT	21 people with Raynaud's phenomenon (secondary to connective tissue disorder)	**mean attack incidence , number of attacks/day** 1 with oral cilostazol (100 mg twice daily) 1 with placebo	P = 0.99 Method of randomisation unclear	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Subgroup analysis Total population in RCT of 43 people with primary or secondary Raynaud's phenomenon	Number of people with secondary Raynaud's phenomenon in each group not clear			
Severity of attack					
[21] RCT	21 people with Raynaud's phenomenon (secondary to connective tissue disorder) Subgroup analysis Total population in RCT of 43 people with primary or secondary Raynaud's phenomenon	**mean severity score [scale of 0–9] , 6 weeks** 3.0 with oral cilostazol (100 mg twice daily) 2.6 with placebo Number of people with secondary Raynaud's phenomenon in each group not clear	P = 0.64 Method of randomisation unclear	⟷	Not significant

Digital ulceration

No data from the following reference on this outcome. [21]

Hand function

No data from the following reference on this outcome. [21]

Quality of life

No data from the following reference on this outcome. [21]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache					
[21] RCT	21 people with Raynaud's phenomenon (secondary to connective tissue disorder) Subgroup analysis Total population in RCT of 43 people with primary or secondary Ray-	**Headache** 35% with oral cilostazol (100 mg twice daily) 0% with placebo Absolute numbers not reported Number of people with secondary Raynaud's phenomenon in each group not clear	Significance not assessed Method of randomisation unclear		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	naud's phenomenon				
Palpitations					
[21] RCT	21 people with Raynaud's phenomenon (secondary to connective tissue disorder) Total population in RCT of 43 people with primary or secondary Raynaud's phenomenon	**Palpitations** 2 people with oral cilostazol (100 mg twice daily) 0 people with placebo Number of people with secondary Raynaud's phenomenon in each group not clear	Significance not assessed Method of randomisation unclear		

Phosphodiesterase inhibitors versus other drug treatments covered in this review:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
At present, there is no good evidence for using phosphodiesterase inhibitors for secondary Raynaud's phenomenon — although there is anecdotal evidence for benefit in some people, and a good therapeutic rationale for their use. Some clinicians prescribe these drugs in people refractory to other treatments. Further RCTs are needed to establish the role of phosphodiesterase inhibitors for secondary Raynaud's phenomenon.

OPTION ANTITHROMBOTICS/INHIBITORS OF PLATELET AGGREGATION New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- We don't know whether antithrombotics/inhibitors of platelet aggregation work as we found no evidence.

Benefits and harms

Antithrombotics/inhibitors of platelet aggregation versus placebo:

We found no systematic review or RCTs.

Antithrombotics/inhibitors of platelet aggregation versus other drug treatments covered in this review:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although there is a therapeutic rationale for using antithrombotics and inhibitors of platelet aggregation in some people with secondary Raynaud s phenomenon — for example in people with systemic sclerosis, a disorder in which platelet activation is well recognised — at present there is no good evidence base for this approach. Further RCTs are needed to establish the role of these drugs for secondary Raynaud's phenomenon.

OPTION PROSTAGLANDINS (ORAL) New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- Oral prostaglandins are unlikely to be beneficial in people with secondary Raynaud's phenomenon.

Benefits and harms

Oral prostaglandins versus placebo:

We found one systematic review (search date 1996, 2 RCTs, 112 people with Raynaud's phenomenon and systemic sclerosis) comparing oral prostaglandins versus placebo. [22] The review included RCTs of people with primary and secondary Raynaud's phenomenon if results from people with secondary Raynaud's phenomenon were reported separately, or if at least 80% of people in the RCT had systemic sclerosis. We found three subsequent RCTs. [23] [24] [25]

Raynaud's attacks

Oral prostaglandins compared with placebo Oral prostaglandins may be no more effective at reducing the severity, duration, and pain of Raynaud's attacks at 6 to 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[22] Systematic review	63 people with Raynaud's phenomenon and systemic sclerosis Data from 1 RCT	**Proportion of people who improved** 20/32 (63%) with iloprost (50–150 micrograms twice daily for 10 days) 12/31 (31%) with placebo Improvement in severity, duration, and pain of Raynaud's attack, as assessed by patient global assessment	OR 2.55 95% CI 0.96 to 6.80 P = 0.06	⟷	Not significant
[22] Systematic review	49 people with Raynaud's phenomenon and systemic sclerosis Data from 1 RCT	**Proportion of people who improved** 8/16 (50%) with cisaprost (2.5 or 5.0 micrograms three times daily for 10 days) 7/16 (44%) with placebo measured by patient global assessment	OR 1.28 95% CI 0.33 to 5.00 P = 0.7	⟷	Not significant
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Proportion of people with >50% improvement in frequency of attacks , 5 to 6 weeks** 24.8% with iloprost (50 micrograms twice daily) 24.5% with placebo Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Reduction in Raynaud's condition score from baseline** 1.32 with iloprost (50 micrograms twice daily) 1.00 with placebo	adjusted mean difference: –0.24 P = 0.323	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Proportion of people with >50% reduction in the Raynaud's score , 5 to 6 weeks** 35% with iloprost (50 micrograms twice daily) 25% with placebo Absolute numbers not reported	P = 0.043	○○○	iloprost
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Duration of Raynaud's attacks , 5 to 6 weeks** with iloprost (50 micrograms twice daily) with placebo Absolute results not reported	Adjusted mean difference: 5.74 mins P = 0.569	⟷	Not significant
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Proportion of people with >50% improvement in duration of attacks** 46% with oral iloprost (50 micrograms twice daily) 42% with placebo Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Proportion of people who improved (physician global assessment) , 6 weeks** 57% with iloprost (50 micrograms twice daily) 64% with iloprost (100 micrograms twice daily) 44% with placebo Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Proportion of people who improved (physician global assessment) , 12 weeks** 50% with iloprost (100 micrograms twice daily) 50% with iloprost (50 micrograms twice daily) 50% with placebo Absolute numbers not reported	Significance not assessed		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Patient-assessed Raynaud's condition mean score , 5 to 6 weeks** 3.0 with iloprost (50 micrograms twice daily) 2.6 with iloprost (100 micrograms twice daily) 3.9 with placebo	Significance not assessed		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Patient-assessed Raynaud's condition % change from baseline , 5 to 6 weeks** –29% with iloprost (50 micrograms twice daily) –47% with iloprost (100 micrograms twice daily) –14% with placebo	P = 0.07 for among-group difference	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Patient-assessed Raynaud's mean condition score , 11 to 12 weeks** 2.8 with iloprost (50 micrograms twice daily) 1.8 with iloprost (100 micrograms twice daily) 3.7 with placebo	Significance not assessed		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Patient-assessed Raynaud's condition score; % change from baseline , 11 to 12 weeks** –38% with iloprost (50 micrograms twice daily) –60% with iloprost (100 micrograms twice daily) –15% with placebo	P = 0.007 for among-group difference		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Mean frequency of daily Raynaud's attacks , 5 to 6 weeks** 2.5 with iloprost (50 micrograms twice daily) 2.9 with iloprost (100 micrograms twice daily) 3 with placebo	Significance not assessed		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Frequency of daily Raynaud's attacks; % change from baseline , 5 to 6 weeks** –31% with iloprost (50 micrograms twice daily) –34% with iloprost (100 micrograms twice daily) –13% with placebo	P = 0.37 for among-group difference	⟷	Not significant
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Mean frequency of daily Raynaud's attacks , 11 to 12 weeks** 2.1 with iloprost (50 micrograms twice daily) 2.3 with iloprost (100 micrograms twice daily) 3 with placebo	Significance not assessed		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Mean frequency of daily Raynaud's attacks; % change from baseline , 11 to 12 weeks** –46% with iloprost (50 micrograms twice daily) –50% with iloprost (100 micrograms twice daily) –15% with placebo	P = 0.07 for among-group difference	⟷	Not significant
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Mean change in duration of Raynaud's attacks (from baseline) , 5 to 6 weeks** From 83 mins to 46 minutes with iloprost (50 micrograms twice daily) From 95 minutes to 51 minutes with iloprost (100 micrograms twice daily)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		From 69 minutes to 81 minutes with placebo			
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Mean duration of Raynaud's attacks; % change from baseline , 5 to 6 weeks** –40% with iloprost (50 micrograms twice daily) –35% with iloprost (100 micrograms twice daily) +10% with placebo	P = 0.03 for among-group difference		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Mean change in duration of Raynaud's attacks (from baseline) , 11 to 12 weeks** From 83 minutes to 32 minutes with iloprost (50 micrograms twice daily) From 95 minutes to 27 minutes with iloprost (100 micrograms twice daily) From 69 minutes to 70 minutes with placebo	Significance not assessed		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Mean duration of Raynaud's attacks; % change from baseline , 11 to 12 weeks** –60% with iloprost (50 micrograms twice daily) –60% with iloprost (100 micrograms twice daily) –9% with placebo	P = 0.001 for among-group difference		

Digital ulceration

Oral prostaglandins compared with placebo Oral prostaglandins seem no more effective at reducing the proportion of people with new digital ulcerations at 5 weeks to 12 months, or the mean time to appearance of digital ulceration (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Digital ulcer status					
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Frequency of Raynaud's attacks (digital ulcer status) , 5 to 6 weeks** with iloprost (50 micrograms twice daily) with placebo Absolute results not reported	Adjusted mean difference: –0.15 P = 0.459	⟷	Not significant
[25] RCT	107 people with a history of previous healed digital ulceration	**New digital ulceration , 6 to 12 months** 25/52 (48%) with beraprost sodium (60 micrograms three times daily) 30/51 (59%) with placebo	OR 0.65 95% CI 0.3 to 1.4 P = 0.33	⟷	Not significant
[25] RCT	107 people with a history of previous healed digital ulceration	**Mean time to appearance of digital ulceration** 160 days with beraprost sodium (60 micrograms three times daily)	P = 0.23	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		105 days with placebo			

No data from the following reference on this outcome. [22] [24]

Hand function

No data from the following reference on this outcome. [22] [23] [24] [25]

Quality of life

No data from the following reference on this outcome. [22] [23] [24] [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] Systematic review	63 people with Raynaud's phenomenon and systemic sclerosis Data from 1 RCT	**Adverse effects** 31/32 (97%) with iloprost (50–150 micrograms twice daily for 10 days) 19/31 (61%) with placebo	OR 8.49 95% CI 2.53 to 28.48	●●●	placebo
[22] Systematic review	49 people with Raynaud's phenomenon and systemic sclerosis Data from 1 RCT	**Adverse effects** 12/16 (75%) with cisaprost (2.5 or 5.0 micrograms three times daily for 10 days) 10/16 (63%) with placebo	OR 1.76 95% CI 0.40 to 7.65 P = 0.5	⟷	Not significant
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Headache** 67% with iloprost (50 micrograms twice daily) 29% with placebo Absolute numbers not reported	P <0.0001	○○○	placebo
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Flushing** 31% with iloprost (50 micrograms twice daily) 6% with placebo Absolute numbers not reported	P <0.0001	○○○	placebo
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Nausea** 22% with iloprost (50 micrograms twice daily) 11% with placebo Absolute numbers not reported	P = 0.009	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Dizziness** 19% with iloprost (50 micrograms twice daily) 9% with placebo Absolute numbers not reported	P = 0.019	○○○	placebo
[23] RCT	308 people with Raynaud's phenomenon and systemic sclerosis	**Discontinued treatment** 9% with iloprost (50 micrograms twice daily) 5% with placebo Absolute numbers not reported	Significance not assessed		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Headache** 26/33 (79%) with iloprost (50 micrograms twice daily) 30/35 (86%) with iloprost (100 micrograms twice daily) 14/35 (40%) with placebo	P <0.001 for among-group difference		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Flushing** 9/33 (27%) with iloprost (50 micrograms twice daily) 16/35 (46%) with iloprost (100 micrograms twice daily) 6/35 (17%) with placebo	P = 0.03 for among-group difference		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Nausea** 10/33 (30%) with iloprost (50 micrograms twice daily) 13/35 (37%) with iloprost (100 micrograms twice daily) 1/35 (3%) with placebo	P = 0.001 for among-group difference		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Flu syndrome** 3/33 (9%) with iloprost (50 micrograms twice daily) 5/35 (14%) with iloprost (100 micrograms twice daily) 11/35 (31%) with placebo	P = 0.02 for among-group difference		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Trismus** 2/33 (6%) with iloprost (50 micrograms twice daily) 6/35 (17%) with iloprost (100 micrograms twice daily) 0/35 (0%) with placebo	P = 0.03 for among-group difference		
[24] RCT **3-armed trial**	103 people with Raynaud's phenomenon and systemic sclerosis	**Discontinuing treatment** 9/33 (27%) with iloprost (50 micrograms twice daily) 18/35 (51%) with iloprost (100 micrograms twice daily) 2/35 (6%) with placebo	P <0.001 for among-group difference		
[25] RCT	107 people with a history of previous healed digital ulceration	**Adverse effects** 42/55 (76%) with beraprost sodium 23/52 (44%) with placebo	P = 0.0008	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Most frequently reported adverse effects were mild transient headache and/or vasodilation			
[25] RCT	107 people with a history of previous healed digital ulceration	**Withdrawals** 13/55 (24%) with beraprost sodium 16/52 (31%) with placebo	Significance not assessed		

Oral prostaglandins versus other drug treatments covered in this review:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although one RCT suggested some benefit from oral prostanoid therapy, taken together, the results from all RCTs do not show good evidence of efficacy, and people experienced more adverse events with prostanoids than with placebo. Oral prostaglandins/prostanoids are not generally available for prescription in the UK, Europe, and the US.

OPTION PROSTAGLANDINS (INTRAVENOUS) New

- For GRADE evaluation of interventions for Raynaud's phenomenon (secondary), see table, p 34 .
- Intravenous iloprost (a prostaglandin) reduces the frequency and severity of attacks compared with placebo in people with Raynaud's phenomenon secondary to systemic sclerosis.
- Intravenous prostaglandins other than iloprost have been less well studied.

Benefits and harms

Intravenous prostaglandins versus placebo:

We found one systematic review (search date 1996, 7 RCTs in total [5 RCTs of intravenous iloprost, 1 RCT of oral iloprost, 1 RCT of oral cisaprost], 332 people with Raynaud's phenomenon and systemic sclerosis). [22] The review included RCTs of people with primary and secondary Raynaud's phenomenon if results from people with secondary Raynaud's phenomenon were reported separately, or if at least 80% of people in the RCT had systemic sclerosis.

Raynaud's attacks

Intravenous prostaglandins compared with placebo Intravenous iloprost may be more effective at reducing the frequency and severity of Raynaud's attacks in people with Raynaud's phenomenon (secondary to systemic sclerosis) (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of attacks					
[22] Systematic review	217 people with Raynaud's phenomenon and systemic sclerosis 4 RCTs in this analysis	**Reduction in frequency of attacks** with intravenous iloprost with placebo	WMD –17.6 attacks 95% CI –19.19 attacks to –15.73 attacks P <0.0001	○○○	intravenous iloprost

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported	Significant statistical heterogeneity among the RCTs, and significance was sensitive to the method of analysis used (fixed or random effects) One RCT (63 people) in the meta-analysis assessed oral rather than intravenous iloprost See further information on studies for separate reporting of largest RCT included in meta-analysis		
Severity scores					
[22] Systematic review	238 people with Raynaud's phenomenon and systemic sclerosis 4 RCTs in this analysis	**Reduction in severity scores (measured by Likert scale or visual analogue scale)** with intravenous iloprost with placebo Absolute results not reported	WMD –0.69 (units not reported) 95% CI –1.12 to –0.26 P = 0.002 Significant statistical heterogeneity among the RCTs, and significance was sensitive to the method of analysis used (fixed or random effects) One RCT (63 people) in the meta-analysis assessed oral rather than intravenous iloprost See further information on studies for separate reporting of largest RCT included in meta-analysis	○○○	intravenous iloprost

Digital ulceration

No data from the following reference on this outcome. [22]

Hand function

No data from the following reference on this outcome. [22]

Quality of life

No data from the following reference on this outcome. [22]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] Systematic review	166 people 2 RCTs in this analysis	**Adverse effects** 72/82 (88%) with intravenous iloprost 29/84 (35%) with placebo	OR 9.44 95% CI 5.05 to 17.67 P <0.0001	●●●	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Common adverse effects included headache, flushing, nausea, vomiting, and jaw pain			

Intravenous prostaglandins versus calcium channel blockers:

See option on calcium channel blockers, p 8 .

Prostaglandins (intravenous) versus glyceryl trinitrate (transdermal), alpha-blockers, naftidrofuryl oxylate, moxisylyte, inositol nicotinate, ACE inhibitors, angiotensin II receptor antagonists, SRIs, endothelin-1 receptor antagonists, phosphodiesterase inhibitors, antithrombotics/inhibitors of platelet aggregation, or prostaglandins (oral):

We found no systematic review or RCTs.

Further information on studies

[22] Of the five RCTs comparing intravenous iloprost versus placebo included in the review, the largest and most robust multicentre double-blind RCT (131 people) found that intravenous iloprost significantly increased the proportion of people who improved at 6 and 9 weeks compared with placebo (measured by physician global assessment, % "improved" or "greatly improved": 6 weeks, 32/61 [52%] with intravenous iloprost *v* 17/62 [27%] with placebo; P = 0.008; 9 weeks, 39/64 [61%] with intravenous iloprost *v* 18/67 [27%] with placebo; P <0.001). [26] The RCT found that intravenous iloprost significantly reduced the mean weekly number of Raynaud's attacks at 9 weeks compared with placebo (mean decrease in attack frequency weeks 1–9: 39.1% with intravenous iloprost *v* 22.2% with placebo; P = 0.005). It also found that intravenous iloprost significantly improved disease severity at 9 weeks compared with placebo (mean decrease in severity measured by Raynaud severity score weeks 1–9: 34.8% with intravenous iloprost *v* 19.7% with placebo; P = 0.01). [26]

Comment:

Clinical guide:
There is some evidence that intravenous iloprost is effective in Raynaud's phenomenon (secondary to systemic sclerosis). Other intravenous prostanoids have been less well studied. This treatment requires hospitalisation and has a role in those people not responding to, or intolerant of, oral treatments.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Warming hands and feet or keeping warm New option. No systematic reviews, RCTs, or cohort studies identified. Categorised as Unknown effectiveness.

Relaxation therapy New option. No systematic reviews, RCTs, or cohort studies identified. Categorised as Unknown effectiveness.

Biofeedback New option. No systematic reviews, RCTs, or cohort studies identified. Categorised as Unknown effectiveness.

Smoking cessation New option. No systematic reviews, RCTs, or cohort studies identified. Categorised as Unknown effectiveness.

Hand exercises New option. No systematic reviews, RCTs, or cohort studies identified. Categorised as Unknown effectiveness.

Glyceryl trinitrate (transdermal) New option. One small crossover RCT (42 people in total, of whom 21 people had secondary Raynaud's phenomenon) included, which compares transdermal glyceryl trinitrate versus placebo. [6] Categorised as Unknown effectiveness.

Calcium channel blockers New option. Three systematic reviews [7] [8] [15] and two RCTs identified. [13] [17] One systematic review, which included eight RCTs (109 people with secondary Raynaud's phenomenon [secondary to systemic sclerosis]), pooled data and compared calcium channel blockers versus placebo, and also nifedipine alone versus placebo. [7] Categorised as Likely to be beneficial.

Alpha-blockers (oral) New option. Two systematic reviews identified, [8] [18] both of which identified one RCT of sufficient quality [18] comparing oral prazosin versus placebo. Categorised as Unknown effectiveness.

Naftidrofuryl oxylate New option. No systematic reviews or RCTs identified. Categorised as Unknown effectiveness.

Moxisylyte New option. No systematic reviews or RCTs identified. Categorised as Unknown effectiveness.

Inositol nicotinate New option. No systematic reviews or RCTs identified. Categorised as Unknown effectiveness.

ACE inhibitors New option. One systematic review identified, [15] which identified no RCTs that satisfy *Clinical Evidence* inclusion criteria, and no subsequent RCTs identified. Categorised as Unknown effectiveness.

Angiotensin II receptor antagonists (oral) New option. Three systematic reviews identified, [7] [8] [15] which found no RCTs that satisfied *Clinical Evidence* inclusion criteria. Categorised as Unknown effectiveness.

SRIs New option. No systematic reviews or RCTs that satisfied *Clinical Evidence* inclusion criteria identified. Categorised as Unknown effectiveness.

Endothelin-1 receptor antagonists New option. One RCT (122 people with systemic sclerosis and a history of a documented digital ulcer within the previous 12 months) added comparing oral bosentan versus placebo. [19] "Bosentan (an endothelin-1 receptor antagonist) (reduced new digital ulcers compared with placebo in people with systemic sclerosis and previous digital ulceration in the last 12 months; however, no evidence in people with secondary Raynaud's without previous digital ulceration)" categorised as Likely to be beneficial.

Phosphodiesterase inhibitors New option. One systematic review [20] identified, which found no RCTs that met *Clinical Evidence* inclusion criteria. One small additional RCT (43 people in total, of whom 21 people has secondary Raynaud's) added, [21] comparing cilostazol versus placebo. Categorised as Unknown effectiveness.

Antithrombotics/inhibitors of platelet aggregation New option. No systematic reviews or RCTs identified. Categorised as Unknown effectiveness.

Prostaglandins (oral) New option. One systematic review, which includes two RCTs identified, [22] and three subsequent RCTs identified, [23] [24] [25] comparing various oral prostaglandins (including oral iloprost, oral cisaprost, and oral beraprost sodium) versus placebo. Categorised as Unlikely to be beneficial.

Prostaglandins (intravenous) New option. One systematic review identified, [22] which includes five RCTs comparing intravenous prostaglandins versus placebo, and which pools data. Categorised as beneficial.

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GRADE **Evaluation of interventions for Raynaud's phenomenon (secondary).**

Important outcomes	Digital ulceration, Hand function, Quality of life, Raynaud's attacks								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of drug treatments for secondary Raynaud's phenomenon?									
1 (15) [6]	Raynaud's attacks	Glyceryl trinitrate (transdermal) versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and methodological weaknesses
8 (109) [7]	Raynaud's attacks	Calcium channel blockers versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and short follow-up. Directness point deducted for inclusion of people with primary Raynaud's phenomenon
1 (20) [18]	Raynaud's attacks	Alpha-blockers versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (122) [19]	Digital ulceration	Bosentan versus placebo	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness points deducted for uncertainty about generalisability of results in people without a history of digital ulceration and for co-intervention (vasodilators)
22 (1) [19]	Hand function	Bosentan versus placebo	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness points deducted for uncertainty about generalisability of results in people without a history of digital ulceration, and for co-intervention (vasodilators)
1 (43) [21]	Raynaud's attacks	Phosphodiesterase inhibitors versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and for not specifying method of randomisation. Directness point deducted for inclusion of people with primary Raynaud's disease
5 (630) [22] [23] [24] [25]	Raynaud's attacks	Oral prostaglandins versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
2 (415) [23] [25]	Digital ulceration	Oral prostaglandins versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
At least 4 (At least 238) [22]	Raynaud's attacks	Intravenous prostaglandins versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for heterogeneity among RCTs in analysis (one RCT assessed oral iloprost)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.