Leg cramps

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ABSTRACT

INTRODUCTION: Involuntary, localised leg cramps are common and typically affect the calf muscles at night. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for idiopathic leg cramps? What are the effects of treatments for leg cramps in pregnancy? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2014 (BMJ 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 16 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: analgesics; anti-epileptic drugs; calcium salts; diltiazem; magnesium salts; multivitamin and mineral supplements; quinine; sodium chloride; stretching exercises; verapamil; vitamin B6 (pyridoxine); and vitamin E.

QUESTIONS

INTERVENTIONS

IDIOPATHIC LEG CRAMPS

Trade off between benefits and harms

Unknown effectiveness

LEG CRAMPS IN PREGNANCY

Unknown effectiveness

Covered elsewhere in Clinical Evidence

Compression hosiery for venous leg ulcers

Key points

- Involuntary, localised leg cramps are common and typically affect the calf muscles at night.

  The causes of leg cramps are unclear, but risk factors include pregnancy, exercise, salt and electrolyte imbalances, disorders affecting peripheral nerves or blood vessels, renal dialysis, and some drugs.

- This review examined RCTs on the effects of interventions on idiopathic leg cramps and leg cramps in pregnancy. Overall, many of the RCTs were small and had weak methods.
- Idiopathic leg cramps:
- Quinine reduces the frequency of idiopathic leg cramps at night compared with placebo.

  CAUTION: quinine may be associated with cardiac arrhythmias, thrombocytopenia, and severe hypersensitivity reactions. It is a known teratogen and the risks are not outweighed by any potential benefits of its use in pregnancy. It may also be associated with fatal adverse effects.

- We don't know whether analgesics, anti-epileptic drugs, diltiazem, magnesium salts, stretching exercises, verapamil, vitamin B6, or vitamin E reduce idiopathic leg cramps.
- Leg cramps in pregnancy:
- We don't know whether magnesium is more effective than placebo at reducing leg cramps in pregnancy.

  The RCT evidence was weak and contradictory. Further well-conducted RCTs are needed.

- We don't know whether calcium salts, multivitamins and mineral supplements, sodium chloride, vitamin B6, or vitamin E reduce leg cramps in pregnant women.

Leg cramps

DEFINITION

Leg cramps are involuntary, localised, and usually painful skeletal muscle contractions, which commonly affect calf muscles but can occur anywhere in the leg from foot up to the thigh. Leg cramps typically occur at night and usually last only seconds to minutes. Leg cramps may be idiopathic (of unknown cause) or may be associated with a definable process or condition such as pregnancy, renal dialysis, or venous insufficiency. This review does not currently cover leg cramps associated with renal dialysis or venous insufficiency.

INCIDENCE/ PREVALENCE

Leg cramps are common and their incidence increases with age. About half of people attending a general medicine clinic have had leg cramps within 1 month of their visit, and more than two-thirds of people aged over 50 years have experienced leg cramps. [1]

AETIOLOGY/ RISK FACTORS

Little is known about the causes of leg cramps. Risk factors include pregnancy, exercise, electrolyte imbalances, salt depletion, renal dialysis, peripheral vascular disease (both venous and arterial), peripheral nerve injury, polyneuropathies, motor neurone disease, and certain drugs (including beta agonists and potassium-sparing diuretics). Other causes of acute calf pain include trauma, DVT (see review on Thromboembolism), and ruptured Baker's cyst.

PROGNOSIS

Leg cramps may cause severe pain and sleep disturbance.

AIMS OF INTERVENTION

To reduce the frequency and severity of attacks of leg cramp, with minimal adverse effects of treatment.

OUTCOMES

Leg cramp symptoms (e.g., frequency, duration, severity of attacks, and number of disturbed nights), **adverse effects**.

METHODS

BMJ Clinical Evidence search and appraisal January 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to January 2014, Embase 1980 to January 2014, and The Cochrane Database of Systematic Reviews 2014, issue 1 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts were identified in an initial search, run by an information specialist, which an evidence scanner then assessed against predefined criteria. An evidence analyst then assessed full texts for potentially relevant studies against predefined criteria. An expert contributor was consulted on studies selected for inclusion. An evidence analyst then extracted all data relevant to the review. Study design criteria for inclusion in this review were published RCTs or systematic reviews of RCTs in the English language. RCTs could be open or blinded, and there was no minimum length of follow-up required to include studies. There was no minimum number of individuals to include studies, but at least 80% of individuals had to be followed up. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, all serious adverse effects, or those adverse effects that were reported as statistically significant, were data extracted for inclusion in the review. Prespecified adverse effects identified as being clinically important were reported, even if the results were not significant. In addition, we used a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 20). 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 treatments for idiopathic leg cramps?

OPTION ANALGESICS FOR IDIOPATHIC LEG CRAMPS

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We found no clinically important results from RCTs about the effects of analgesics on idiopathic leg cramps.

Benefits and harms

Analgesics versus placebo:

We found one systematic review (search date 2008), which identified no RCTs of sufficient quality. [2] We found no subsequent RCTs.

Comment: None.

OPTION ANTI-EPILEPTIC DRUGS FOR IDIOPATHIC LEG CRAMPS

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We found no clinically important results from RCTs about the effects of anti-epileptic drugs on idiopathic leg cramps.

Benefits and harms

Anti-epileptic drugs versus placebo:

We found one systematic review (search date 2008), which identified no RCTs of sufficient quality. [2] We found no subsequent RCTs.

Comment: Harms associated with the use of anti-epileptic drugs are well described (see review on Epilepsy).

OPTION DILTIAZEM FOR IDIOPATHIC LEG CRAMPS New

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We found insufficient evidence on the effects of diltiazem on idiopathic leg cramps.

Benefits and harms

Diltiazem versus placebo:

We found one systematic review (search date 2008), [2] which found one small, weak crossover RCT comparing diltiazem with placebo. [3] The results of this study should be interpreted with caution (see Comment, p 3).

Leg cramp symptoms

Diltiazem compared with placebo We don't know whether diltiazem is more effective than placebo at reducing idiopathic leg cramps (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Leg cramp symptoms					
[2] Systematic review	13 people experiencing 2 or more leg cramps per week 1 crossover RCT in this analysis	**Number of cramps , 2-week treatment phase** with diltiazem hydrochloride with placebo Absolute results not reported 12 people in analysis	P = 0.04 Caution should be taken in interpreting this result (see Comment, p 3)	◌◌◌	diltiazem

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[2] Systematic review	13 people experiencing 2 or more leg cramps per week 1 crossover RCT in this analysis	**Intensity of leg cramps (1–3 point scale, measure of intensity not further defined)** with diltiazem hydrochloride with placebo Absolute results not reported 12 people in analysis	P = 0.347 Caution should be taken in interpreting this result (see Comment, p 3)	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[2] Systematic review	13 people experiencing 2 or more cramps per week 1 crossover RCT in this analysis	**Adverse effects** with diltiazem hydrochloride with placebo The RCT reported that no one reported adverse effects			

Comment: The review included one small crossover RCT [3] (13 people). [2] The RCT had been reported as a letter to the editor, and the review did not report further details on methods. The RCT reported results for 12/13 (92%) of included participants, and one person who started on medication for high blood pressure was excluded from the analysis. Baseline characteristics were not reported, people were given allocated treatments for a 2-week period with a 2-week washout period, and results were not reported beyond 2 weeks. It was unclear how people in the trial had been recruited. [3] As detailed methods were not presented, results from this trial should be interpreted with great caution.

OPTION MAGNESIUM SALTS FOR IDIOPATHIC LEG CRAMPS

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We don't know whether magnesium citrate is more effective than placebo at reducing idiopathic leg cramps at 4 weeks.

Benefits and harms

Magnesium salts versus placebo:

We found one systematic review (search date 2011), [4] which included four RCTs. Only one RCT specified leg cramps (45 people) while the other three RCTs specified that the included population were 'rest cramp sufferers' (46 people, 73 people, 40 people). The review reported that the RCTs involved the treatment of idiopathic cramps in older adults "most of whom are presumed to have been suffering from nocturnal leg cramps". One RCT was unpublished, and further unpublished data were made available to the review on two other RCTs. Two RCTs were crossover in design. In one RCT (73 people), only data from the first period of the study were used because of a large difference in treatment effect resulting from sequence allocation (see Further information on studies). Three RCTs gave magnesium orally, while one RCT (46 people) gave magnesium via intravenous infusion.

Leg cramp symptoms

Magnesium citrate compared with placebo Magnesium citrate may be no more effective than placebo at reducing idiopathic leg cramps at 4 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Leg cramp symptoms					
[4] Systematic review	People with cramps 2 RCTs in this analysis	**Percentage change in cramp frequency , from baseline to 4 weeks** with magnesium with placebo 83 people in this analysis	Mean difference –3.93 95% CI –21.12 to +13.26 P = 0.65	⟷	Not significant
[4] Systematic review	People with cramps 2 RCTs in this analysis	**Proportion of people with at least 25% reduction in cramp frequency , 4 weeks** 24/42 (57%) with magnesium 27/41 (66%) with placebo	Risk difference –0.08 95% CI –0.28 to +0.12 P = 0.44	⟷	Not significant
[4] Systematic review	People with cramps 4 RCTs in this analysis	**Number of cramps per week , 4 weeks** with magnesium with placebo 213 people in this analysis	Mean difference +0.01 95% CI –0.52 to +0.55 P = 0.96	⟷	Not significant
[4] Systematic review	People with cramps 3 RCTs in this analysis	**Cramp intensity (pain) on a 3-point scale (1 = mild; 2 = moderate; 3 = severe) , 4 weeks** with magnesium with placebo 175 people in this analysis	Mean difference –0.04 95% CI –0.18 to +0.11 P = 0.62	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[5] RCT **Crossover design**	45 people with at least 6 cramps during the previous month In review [4]	**Diarrhoea, nausea, and vomiting** 11% with magnesium 10% with placebo Absolute numbers not reported 4-week washout period	Significance not assessed		
[6] RCT **Crossover design**	68 people with at least 2 leg cramps per week for 3 months In review [4]	**Diarrhoea** 30% with magnesium 17% with placebo Absolute numbers not reported 47 people completed the study 2-week washout period	P = 0.1	⟷	Not significant
[4] Systematic review	People with cramps In 1 RCT (46 people) in this analysis, magnesium was given via IV route	**Adverse effects** with magnesium with placebo The review reported that adverse effects included asymptomatic hypotension (3/24 [13%] with magnesium *v* 0/22 [0%] with placebo); facial flushing (9/24	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		[38%] *v* 7/22 [32%]); and burning at the IV administration site (12/24 [50%] *v* 0/22 [0%]) P values not reported			

Further information on studies

[4] The risk of selection bias (randomisation or allocation) was unclear in three of the four RCTs. In the fourth RCT, randomisation blocks were either unbalanced initially or became so because of non-completers, and data from only the first period of this crossover trial was used. Blinding was unclear in two RCTs, one RCT had a dropout rate of 37%, and one unpublished study was at high risk of bias for selective reporting because only a subset of outcomes were available.

Comment: The systematic review we found concluded that it was unlikely that magnesium supplementation provides clinically meaningful cramp prophylaxis to older adults experiencing skeletal muscle cramps. [4]

OPTION QUININE FOR IDIOPATHIC LEG CRAMPS

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- Quinine may reduce the frequency of idiopathic leg cramps at night compared with placebo.
- **CAUTION**
  Quinine may be associated with severe (including fatal) adverse effects, including cardiac arrhythmias, thrombocytopenia, and severe hypersensitivity reactions. It is a known teratogen and the risks are not outweighed by any potential benefits of its use in pregnancy.

Benefits and harms

Quinine versus placebo:

We found two systematic reviews, both of which included unpublished data. [7] [8] The first review (search date 1997) [7] only included RCTs on nocturnal leg cramps and pooled data. The second and later review (search date 2010) [8] included muscle cramps generally, including cramps in any body part and from any cause. It also pooled data and reported slightly different outcomes. We have, therefore, reported both reviews. The second review reported that 20 RCTs investigating idiopathic leg cramps were "most often in elderly participants suffering from nocturnal leg cramps". [8] However, we have reported where the included population in the RCTs was reported as 'muscle cramps' in the trial description (see Further information on studies).

Leg cramp symptoms

Quinine compared with placebo Quinine may be more effective than placebo at reducing idiopathic leg cramps at 2 to 4 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Leg cramp symptoms					
[7] Systematic review	People with nocturnal leg cramps 7 RCTs in this analysis	**Reduction in frequency of nocturnal leg cramps , 4 weeks** with quinine with placebo Absolute results reported graphically 409 people in this analysis	ARR for quinine *v* placebo 3.60 cramps/month 95% CI 2.15 to 5.05 cramps/month RR 0.21 95% CI 0.12 to 0.30	●●○	quinine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[8] Systematic review	People with cramps 14 RCTs in this analysis	**Difference in number of cramps (occurring day or night) , 2-week treatment period** with quinine with placebo 982 people in this analysis This analysis included 6 of the 7 RCTs included in the earlier meta-analysis; of the 14 RCTs in this analysis, 4 RCTs (271 people) were in people with muscle cramps (leg cramps not further specified) and 1 RCT (31 people) was in people with liver failure	Mean difference in the number of cramps –1.81 95% CI –1.42 to –2.20 P <0.00001 Significant heterogeneity in analysis (I^2 = 89%; P value for heterogeneity <0.0001) See Further information on studies	○○○	quinine
[8] Systematic review	People with cramps 7 RCTs in this analysis	**Difference in cramp intensity (measured on a 3-point scale where 1 = mild pain; 2 = moderate pain; 3 = severe pain)** with quinine with placebo 666 people in this analysis Of the 7 RCTs in analysis, 1 RCT (9 people) included muscle cramps (leg cramps not further specified)	Cramp intensity –0.12 95% CI –0.20 to –0.05 P = 0.0011	○○○	quinine
[8] Systematic review	People with leg cramps 2 RCTs in this analysis	**Change in cramp duration (minutes)** with quinine with placebo 28 people in this analysis	Change in duration –1.35 minutes 95% CI –4.00 to +1.30 minutes P = 0.32 The review reported that of 6 further RCTs that did not present data in a form that allowed them to be added to the meta-analysis, 5 found no significant difference with regard to cramp duration	⟷	Not significant
[8] Systematic review	People with cramps 7 RCTs in this analysis	**Difference in number of cramp days , 2 weeks** with quinine with placebo 842 people in this analysis Of the 7 RCTs in this analysis, 2 RCTs (200 people) included muscle cramps (leg cramps not further specified)	Cramp days –1.15 95% CI –1.93 to –0.38 P = 0.0036 Significant heterogeneity in analysis (I^2 = 86%; P <0.00001); this was following the exclusion of 1 RCT which was causing heterogeneity; further sensitivity analysis not reported	○○○	quinine

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[7] Systematic review	People with nocturnal leg cramps 8 RCTs in this analysis	**Tinnitus** 20/659 (3%) with quinine 7/659 (1%) with placebo Other adverse effects of quinine include headache, digestive dis-	RR 2.86 95% CI 1.22 to 6.71 NNH 50 95% CI 27 to 230	●●○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	7 of the 8 RCTs used crossover design	orders, fever, blurred vision, dizziness, and pruritus			
[8] Systematic review	People with cramps 16 RCTs in this analysis	**Minor adverse events** 93/725 (13%) with quinine 68/722 (9%) with placebo	Risk difference 0.03% 95% CI 0.00% to 0.06% P = 0.026	○○○	placebo
[8] Systematic review	People with cramps 18 RCTs in this analysis	**Major adverse events** 12/806 (1%) with quinine 11/807 (1%) with placebo	Risk difference 0.00% 95% CI –0.01% to +0.02% P = 0.86	⟷	Not significant
[8] Systematic review	People with cramps 18 RCTs in this analysis	**Gastrointestinal adverse effects** 39/790 (5%) with quinine 16/791 (2%) with placebo	Risk difference 0.03% 95% CI 0.01% to 0.05% P = 0.003	○○○	placebo
[8] Systematic review	People with cramps 18 RCTs in this analysis	**Tinnitus** 10/790 (1%) with quinine 1/791 (0%) with placebo	Risk difference 0.01% 95% CI 0.00% to 0.02% P = 0.083	⟷	Not significant

Quinine versus vitamin E:

See option on Vitamin E, p 11 .

Further information on studies

[7] Of the eight included RCTs, seven were crossover. The review noted in a sub-group analysis that the point estimate of benefit for quinine was larger when the analysis was confined to published trials than seen when the analysis was confined to unpublished trials. It noted that the treatment periods of all the unpublished studies was 1 to 2 weeks, and that this may have not been long enough to show any full benefit.

[8] *General* Of the 23 included studies, 13 RCTs were crossover, nine were parallel in design, and one was an 'N-of-1' trial. Five RCTs were unpublished (acquired via the FDA), including the two largest RCTs (556 people; 205 people) which contributed 58% of all the participants in the meta-analysis. The review reported that, in total, 20 RCTs investigated idiopathic muscle cramps, most often older participants with nocturnal leg cramps (absolute numbers in this group not reported). *Methods* The review reported that quality varied considerably, with only 8/23 (33%) studies describing the method of randomisation, and 8/23 (33%) describing how allocation was concealed. It reported that almost all of the included trials had methodological limitations, including inadequate washout periods, small number of participants, inadequate explanation of methods, and poor statistical presentation. *Heterogeneity* For cramp number, a sensitivity analysis excluding one RCT (30 people) that used a higher dose of quinine and only included men did not resolve the heterogeneity (cramp number –2.45, 95% CI –1.36 to –3.54; I^2 = 71%; P value for heterogeneity = 0.00003). Further sensitivity analysis excluding trials with high/unclear risk of bias for allocation sequence generation, allocation concealment, and blinding resulted in changes to the overall heterogeneity (I^2 = 50%, 67%, and 91%, respectively). In general, the review reported that significant unexplained heterogeneity was notable in many of the meta-analyses. *Adverse effects* The review noted that quinine had been implicated in accidental and intentional poisoning, and that many of the included trials failed to elaborate on adverse events, which lies at the heart of the debate on quinine's risk-benefit ratio.

Comment: The review commented on the difference between the US and Europe in the use of quinine for muscle cramps. [8] It reported that it could only be used off-label in the US, while in the UK quinine was used (although with strict advice), and in Germany it could be bought over the counter. The

BNF states that, because of potential toxicity, quinine is not recommended for routine treatment. [9] One review [2] concluded that quinine "should only be considered when cramps are very disabling, no other agents relieve symptoms, and there is careful monitoring of side effects".

Dose and length of treatment

We found one open-label RCT (191 people aged at least 60 years who had received quinine for leg cramps in the previous 3 months), which did not directly assess the duration of treatment, but assessed stretching exercises, also compared advice to stop taking quinine for 6 weeks versus no advice. [10] All participants who were advised to stop quinine were told that, at 6 weeks, they could decide whether to resume medication. The RCT found that, at 12 weeks, significantly more people who had been advised to stop quinine had stopped medication compared with people not receiving advice (OR 3.32, 95% CI 1.37 to 8.06; absolute numbers not reported).

Drug safety alert

An FDA alert in 2012 highlighted the serious risks associated with using quinine to prevent or treat nocturnal leg cramps (www.fda.gov). [11] It highlighted that it is not considered safe and effective for the treatment or prevention of leg cramps and is an 'off-label' (non-FDA approved) use. It reported that quinine is associated with thrombocytopenia, hypersensitivity reactions, and QT prolongation. In addition, the thrombocytopenia includes immune thrombocytopenia, haemolytic uraemic syndrome, and thrombotic thrombocytic purpura with associated renal insufficiency. There have also been reports of fatalities and renal insufficiency requiring haemodialysis. Quinine is highly toxic in overdose.

Clinical guide

The results of the RCT assessing advice to stop taking quinine [10] suggest that it is possible to advise people who have been taking quinine long term that they may be able to stop medication without any increase in cramps. Quinine is a known teratogen in high doses and, for treatment of cramp, the risk outweighs any possible benefit in pregnancy. Elevated quinine levels may cause cinchonism, a syndrome caused by derivatives of cinchona bark. This usually presents with nausea, vomiting, headache, tinnitus, deafness, vertigo, and visual disturbance. [12]

OPTION STRETCHING EXERCISES FOR IDIOPATHIC LEG CRAMPS

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We don't know whether stretching exercises are effective at reducing idiopathic leg cramps.

Benefits and harms

Stretching exercises versus passive non-stretching exercises:

We found one systematic review (search date 2011), [13] which included one RCT (191 people). [10] The RCT included people who had, and had not, been advised to discontinue quinine (which had been taken for the 3 months prior to trial commencement). There was no washout period for those discontinuing quinine. In order to avoid confounding, the review only included the 97 participants advised to continue taking quinine in its analysis, and also obtained further unpublished data from the original trial authors. [13]

Leg cramp symptoms

Stretching exercises compared with passive non-stretching exercises We don't know whether stretching 'standing' exercises are more effective than passive non-stretching 'lying' exercises (placebo stretching exercise) at reducing idiopathic leg cramps (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Leg cramp symptoms					
[13] Systematic review	People with leg cramps Data from 1 RCT	**Mean number of cramps , last 4 weeks of 12-week follow-up** 10.02 with calf muscle stretching 'standing' 8.83 with passive non-stretching 'lying' exercise (placebo stretching) 94 people in this analysis (everyone in the analysis was taking quinine)	Mean difference +1.19 95% CI –5.86 to +8.25 See Further information on studies	⟷	Not significant

Adverse effects

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

Further information on studies

[13] The review noted that, after 6 weeks, participants in both the stretching exercise and passive 'lying' exercise (placebo stretching) groups were allowed to swap or discontinue stretching treatments and to decide whether or not to continue taking quinine. The review excluded the other participants who had been advised to discontinue quinine at the start of the trial in order to avoid the confounding effects of changing interventions. It reported that the RCT was at high risk of reporting bias and, as participants were allowed to discontinue or swap treatments at 6 weeks, the results at 12 weeks might not reflect the effects of the intervention at baseline. It also reported that the study design did not reflect clinical practice and interpretations of results are limited as it was impossible to isolate the effects of the intervention assigned at baseline.

Comment: **Clinical guide**
It has been widely assumed that stretching exercises would reduce the number and severity (or both) of cramps, possibly because of the common experience that stretching a muscle aborts an actual attack. Although the evidence we found seemed to show no benefit, it is possible that the passive 'lying' exercises were effective, and the researchers had inadvertently found an active sham treatment.

OPTION VERAPAMIL FOR IDIOPATHIC LEG CRAMPS New

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We found no clinically important results from RCTs about the effects of verapamil on idiopathic leg cramps.

Benefits and harms

Verapamil versus placebo:
We found one systematic review (search date 2008), [2] which identified no RCTs. We found no subsequent RCTs.

Comment: None.

OPTION VITAMIN B6 (PYRIDOXINE) FOR IDIOPATHIC LEG CRAMPS New

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We found no clinically important results from RCTs about the effects of vitamin B6 (pyridoxine) on idiopathic leg cramps.

Benefits and harms

Vitamin B6 (pyridoxine) versus placebo:
We found one systematic review (search date 2008), [2] which identified no RCTs of sufficient quality. We found no subsequent RCTs.

Comment: None.

OPTION VITAMIN E FOR IDIOPATHIC LEG CRAMPS

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We don't know whether vitamin E reduces idiopathic leg cramps.

Benefits and harms

Vitamin E versus placebo:

We found one systematic review (search date 2008), [2] which included one crossover RCT. [14] We have reported directly from the RCT. [14]

Leg cramp symptoms

Vitamin E compared with placebo We don't know whether vitamin E is more effective than placebo at reducing idiopathic leg cramps in men (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Leg cramp symptoms					
[14] RCT **Crossover design** **3-armed trial**	27 men In review [2]	**Median number of nights with leg cramps** 14 nights with vitamin E 15 nights with placebo The third intervention assessed was quinine 4-week washout period	P >0.05	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] RCT **Crossover design** **3-armed trial**	27 men In review [2]	**Adverse effects** with vitamin E with placebo The third intervention assessed was quinine 4-week washout period Adverse effects were reported as similar in the vitamin E and placebo groups, but no details were reported			

Vitamin E versus quinine:

We found one systematic review (search date 2010), [8] which included four RCTs, and included both published and unpublished data (see option on Quinine for idiopathic leg cramps), p 6 .

Leg cramp symptoms

Vitamin E compared with quinine We don't know whether vitamin E and quinine differ in effectiveness at reducing idiopathic leg cramps (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Leg cramp symptoms					
[8] Systematic review	People with leg cramps 3 RCTs in this analysis	**Difference in number of cramps , 2 weeks** with quinine with vitamin E Absolute results not reported	Number of cramps –0.24 95% CI –1.29 to +0.81 P = 0.66 This analysis excluded 1 RCT that used a higher dose of quinine and included only men, and which increased heterogeneity (I^2 of 94% reduced to 29% on exclusion)	⟷	Not significant
[8] Systematic review	People with leg cramps 3 RCTs in this analysis	**Difference in cramp intensity** with quinine with vitamin E 513 people in this analysis	Cramp intensity –0.06 95% CI –0.17 to +0.04 P = 0.24 This analysis excluded 1 RCT that used a higher dose of quinine and included only men	⟷	Not significant
[8] Systematic review	People with leg cramps 2 RCTs in this analysis	**Difference in number of cramp days , 2 weeks** with quinine with vitamin E 483 people in this analysis	Cramp days –0.28 95% CI –0.98 to +0.43 P = 0.44 This analysis excluded 1 RCT that used a higher dose of quinine and included only men, and which increased heterogeneity (I^2 of 98% reduced to 48% on exclusion)	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[8] Systematic review	People with leg cramps 2 RCTs in this analysis	**Minor adverse events** 69/346 (20%) with quinine 57/342 (17%) with vitamin E	Risk difference +0.02% 95% CI –0.04% to +0.09% P = 0.51	⟷	Not significant
[8] Systematic review	People with leg cramps 3 RCTs in this analysis	**Major adverse events** 4/376 (1%) with quinine 1/372 (0%) with vitamin E	Risk difference +0.01% 95% CI –0.01% to +0.02% P = 0.56	⟷	Not significant

Further information on studies

[8] Of the four included RCTs, all had unclear sequence allocation, and three had unclear allocation concealment. One crossover RCT had a short washout period, and another RCT had a high dropout rate (27%). Two of the four RCTs were previously unpublished.

Comment: None.

QUESTION What are the effects of treatments for leg cramps in pregnancy?

OPTION CALCIUM SALTS FOR LEG CRAMPS IN PREGNANCY

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We don't know whether calcium salts reduce leg cramps in pregnant women.

Benefits and harms

Calcium salts versus no treatment or vitamin C placebo:

We found one systematic review (search date 2011), [15] which included two RCTs. [16] [17] We have reported directly from the RCTs. [16] [17]

Leg cramp symptoms

Calcium salts compared with no treatment or vitamin C placebo We don't know how calcium salts compare with no treatment or with vitamin C 'placebo' in treating leg cramps in pregnant women (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Leg cramp symptoms					
[16] RCT	42 pregnant women In review [15]	**Women with persisting leg cramps** 2/21 (10%) with calcium 18/21 (86%) with no treatment	OR 0.05 95% CI 0.02 to 0.17 See Comment, p 13 for details of methodological limitations	●●●	calcium
[17] RCT	60 pregnant women In review [15]	**Women with persisting leg cramps** 11/30 (37%) with calcium 8/30 (27%) with vitamin C placebo	OR 1.58 95% CI 0.54 to 4.63 See Comment, p 13 for details of methodological limitations	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [15] [16] [17]

Further information on studies

[15] The systematic review was updated from a previous search date of 2001 to 2011, but it did not include any new data further to the two RCTs identified previously. [16] [17] It identified one further study (a report at an annual congress in 1998) that was awaiting further assessment. The review noted that the first RCT [16] did not state the method of allocation and was at high risk for allocation concealment, as was the second RCT. [17] Neither RCT reported on adverse effects.

Comment: The lack of a placebo group in the first RCT makes the results difficult to interpret, as the benefits seen with calcium salts might have been due in part to a placebo effect. [16] In the second RCT, vitamin C was used as a placebo, as it was not known to have an effect on leg cramps. [17] However, there was a marked difference in the response of the control group in the two included RCTs. In the first RCT, 18/21 (86%) women with no treatment had no improvement in cramps. [16] In the

second RCT, 8/30 (27%) women with vitamin C had no improvement. [17] It is unclear whether this difference was due to a beneficial effect of vitamin C on leg cramps, differences between the population in the RCTs, or another cause.

OPTION MAGNESIUM SALTS FOR LEG CRAMPS IN PREGNANCY

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We don't know whether magnesium is more effective than placebo or no treatment at reducing leg cramps in pregnant women, as the evidence is weak and contradictory.

Benefits and harms

Magnesium salts versus placebo or no treatment:

We found one systematic review (search date 2011), [4] which included three RCTs that "involved treatment of pregnancy associated leg cramps". The review could not pool data because of the different outcome measures used in the trials. We have, therefore, reported the results of RCTs individually.

Leg cramp symptoms

Magnesium salts compared with placebo or no treatment We don't know whether magnesium is more effective than placebo or no treatment at reducing leg cramps in pregnant women as we found inconsistent evidence (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Leg cramp symptoms					
[4] Systematic review	73 pregnant women Data from 1 RCT	**Frequency of symptoms, from initial average of every other day to:** "1 to 2 times a week" with magnesium "every 3 days" with placebo Absolute results not reported	P <0.05 The review noted that this outcome measure did not correlate with the 5-point ordinal scale used to measure this outcome	○○○	magnesium
[4] Systematic review	73 pregnant women Data from 1 RCT	**Participant evaluation of treatment, women self-rating they had "improved considerably" or "become asymptomatic"** 27/34 (79%) with magnesium 14/35 (40%) with placebo	P = 0.0002	○○○	magnesium
[4] Systematic review	45 pregnant women with rest cramps Data from 1 RCT	**Mean number of days and nights with leg cramps present , 2 weeks** 9.5 days with magnesium 7.7 days with placebo Absolute results not reported	P = 0.27	⟷	Not significant
[4] Systematic review	84 pregnant women Data from 1 RCT 4-armed trial	**Change in muscle spasms, 'absolute improvement' (complete resolution of cramping) , 4 weeks** with magnesium with no treatment Absolute results not reported Further numerical details not reported The other arms evaluated calcium carbonate tablets, and combined vitamin B1 and B6 supplement	Reported as no significant difference P value not reported The review reported there was no significant difference in 'relative improvement' (partial improvement) between groups (further details not reported)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[4] Systematic review	73 pregnant women Data from 1 RCT	**Cramp intensity (0–100 mm VAS score) , from baseline to end of treatment** 70.4 mm to 30.3 mm with magnesium 68.2 mm to 47.8 mm with placebo Absolute results not reported	P <0.05	○○○	magnesium
[4] Systematic review	45 pregnant women with rest cramps Data from 1 RCT	**Mean cramp intensity score (scale where 0 = no pain to 4 = severe pain) , 2 weeks** 13.2 with magnesium 11.4 with placebo Absolute results not reported	P = 0.46	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[4] Systematic review	45 pregnant women with rest cramps Data from 1 RCT	**Minor adverse effects, gastrointestinal** 6/23 (26%) with magnesium 6/22 (27%) with placebo Adverse effects grouped as 'gastrointestinal in nature' and included nausea, flatulence, diarrhoea, intestinal air	Significance not assessed		

Further information on studies

[4] The first RCT (73 women) had unclear randomisation and allocation concealment, and it was unclear how well the outcomes were predefined; the second RCT (45 women) had unclear allocation concealment; the third RCT (84 women) had unclear randomisation and allocation concealment, and had an unusual design where each treatment was given over 2 weeks but efficacy was assessed at 4 weeks. It was published as a 'brief communication' letter only. Only the second RCT used a cramp diary, the other two RCTs recalling cramp frequency at the time of the exit interview.

Comment: The review reported that it was unclear whether magnesium supplementation provided an advantage over placebo as the two relevant studies were discordant and did not report results in such a way as to allow the pooling of data. [4] The two placebo-comparison studies were double-blind RCTs in Scandinavian maternity clinics and used the same intervention (a chewable tablet taken once each morning). The RCT (84 women) which compared magnesium with no treatment found no significant benefit. The review noted that for women suffering pregnancy associated muscle cramps the literature was conflicting and unclear, and further trials were needed.

OPTION MULTIVITAMINS AND MINERAL SUPPLEMENTS FOR LEG CRAMPS IN PREGNANCY

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .

- We don't know how multivitamin and mineral supplements compare with placebo at reducing leg cramps in pregnant women.

Benefits and harms

Multivitamin and mineral supplements versus placebo:

We found one systematic review (search date 2011), [15] which identified one RCT. [18] We have reported directly from the RCT. [18]

Leg cramp symptoms

Multivitamin and mineral supplements compared with placebo We don't know how multivitamin and mineral supplements compare with placebo at reducing leg cramps in pregnant women (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Leg cramp symptoms					
[18] RCT	62 pregnant women In review [15]	**Proportion of women reporting persistent leg cramps , ninth month of pregnancy** 2/11 (18%) with multivitamin plus mineral tablet (containing 12 different ingredients) 10/18 (56%) with placebo Supplements and placebo were given from 3 months' gestation	OR 0.23 95% CI 0.05 to 1.01 The RCT had a high dropout rate, and may be underpowered; see Further information on studies for full details	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT	62 pregnant women In review [15]	**Adverse effects** with multivitamin plus mineral tablet (containing 12 different ingredients) with placebo The RCT found that 4% of women had adverse effects (nausea, vomiting, and diarrhoea), but did not make clear how many of these women were taking an active treatment.			

Further information on studies

[18] The RCT was primarily undertaken to examine the effects of a multivitamin plus mineral supplement on zinc and copper levels in maternal plasma during pregnancy. The supplement contained zinc gluconate, copper gluconate, iron gluconate, magnesium lactate, chromium chloride, ascorbic acid, thiamine nitrate, riboflavin (riboflavine), pyridoxal chlorhydrate, folic acid, cyanocobalamin, and alpha tocopherol acetate. *Methodological limitations* The RCT may have lacked power to detect a clinically important difference between treatment groups given that the confidence interval lies close to significance. In total, 29/62 (48%) women were assessed for cramp at 9 months' gestation. The high withdrawal rate was not explained.

Comment: It is not possible to draw robust conclusions from this RCT given its methodological limitations.

OPTION SODIUM CHLORIDE FOR LEG CRAMPS IN PREGNANCY

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We found no clinically important information from RCTs about sodium chloride in the treatment of leg cramps in pregnant women.

Benefits and harms

Sodium chloride versus placebo:

We found one systematic review (search date 2011), [15] which identified no RCTs (see Comment, p 17).

Comment: The systematic review [15] identified one controlled clinical trial, [19] which was of poor quality. Initially, sodium chloride and calcium lactate were given to alternate participants. [19] It was then decided, based on the difference between the results of the two treatments, to use two additional control groups (saccharin and no treatment). [19] The dose of sodium chloride changed during the course of the study. [15]

OPTION VITAMIN B6 (PYRIDOXINE) FOR LEG CRAMPS IN PREGNANCY New

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We found no clinically important information from RCTs about vitamin B6 (pyridoxine) in the treatment of leg cramps in pregnant women.

Benefits and harms

Vitamin B6 (pyridoxine) versus placebo:

We found one systematic review (search date 2011), [15] which identified no RCTs. We found no subsequent RCTs.

Comment: None.

OPTION VITAMIN E FOR LEG CRAMPS IN PREGNANCY

- For GRADE evaluation of interventions for Leg cramps, see table, p 20 .
- We found no clinically important information from RCTs about vitamin E in the treatment of leg cramps in pregnant women.

Benefits and harms

Vitamin E versus placebo:

We found one systematic review (search date 2011), [15] which identified no RCTs of vitamin E in pregnant women with leg cramps. We found no subsequent RCTs that met *BMJ Clinical Evidence* inclusion criteria.

Comment: We found one non-systematic review, [20] which identified one trial, [21] which we were unable to obtain through any of the sources available to us. Therefore, we were unable to assess it for possible inclusion in the review.

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.

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

SUBSTANTIVE CHANGES

Diltiazem for idiopathic leg cramps New option. One systematic review [2] and one small crossover RCT added. [3] Categorised as 'unknown effectiveness'.

Verapamil for idiopathic leg cramps New option. One systematic review added. [2] Categorised as 'unknown effectiveness'.

Vitamin B6 (pyridoxine) for idiopathic leg cramps New option. One systematic review added. [2] Categorised as 'unknown effectiveness'.

Vitamin B6 (pyridoxine) for leg cramps in pregnancy New option. One systematic review added. [15] Categorised as 'unknown effectiveness'.

Analgesics for idiopathic leg cramps One systematic review added. [2] Categorisation unchanged (unknown effectiveness).

Anti-epileptic drugs for idiopathic leg cramps One systematic review added. [2] Categorisation unchanged (unknown effectiveness).

Calcium salts for leg cramps in pregnancy One systematic review updated. [15] Categorisation unchanged (unknown effectiveness).

Magnesium salts for idiopathic leg cramps One systematic review added. [4] Categorisation unchanged (unknown effectiveness).

Multivitamins and mineral supplements for leg cramps in pregnancy One systematic review updated. [15] Categorisation unchanged (unknown effectiveness).

Quinine for idiopathic leg cramps One systematic review added. [8] Categorisation unchanged (trade-off between benefits and harms).

Sodium chloride for leg cramps in pregnancy One systematic review updated. [15] Categorisation unchanged (unknown effectiveness).

Stretching exercises for idiopathic leg cramps One systematic review added. [13] Categorisation unchanged (unknown effectiveness).

Vitamin E for idiopathic leg cramps Two systematic reviews added. [8] [2] Categorisation unchanged (unknown effectiveness).

Vitamin E for leg cramps in pregnancy One systematic review updated. [15] Categorisation unchanged (unknown effectiveness).

Magnesium salts for leg cramps in pregnancy One systematic review added. [4] Categorisation changed from 'likely to be beneficial' to 'unknown effectiveness'.

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Competing interests: GY is the author of a reference cited in this review.

Disclaimer

GRADE **Evaluation of interventions for Leg cramps.**

Important outcomes			Leg cramp symptoms						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments for idiopathic leg cramps?									
1 (12) [2]	Leg cramp symptoms	Diltiazem versus placebo	4	–3	0	0	0	Very low	Quality points deducted for weak methods, sparse data, and incomplete reporting.
4 (213) [4]	Leg cramp symptoms	Magnesium salts versus placebo	4	–1	0	–1	0	Low	Quality point deducted for weak methods; directness point deducted for uncertainty about included population (skeletal cramps)
14 (at least 982) [7] [8]	Leg cramp symptoms	Quinine versus placebo	4	–1	–1	0	0	Low	Quality point deducted for weak methods; consistency point deducted for statistical heterogeneity
1 (94) [13]	Leg cramp symptoms	Stretching exercises versus passive non-stretching exercises	4	–2	0	–2	0	Very low	Quality points deducted for weak methods and sparse data; directness points deducted for choice given to participants of treatment at 6 weeks, and use of co-intervention (quinine)
1 (27) [14]	Leg cramp symptoms	Vitamin E versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for restricted population (inclusion only of men)
4 (at least 513) [8]	Leg cramp symptoms	Vitamin E versus quinine	4	–1	–1	–1	0	Very low	Quality point deducted for weak methods; consistency point deducted for statistical heterogeneity; directness point deducted for uncertainty about included population (skeletal cramps)
What are the effects of treatments for leg cramps in pregnancy?									
2 (102) [15] [16] [17]	Leg cramp symptoms	Calcium salts versus no treatment or vitamin C placebo	4	–2	–1	–1	0	Very low	Quality points deducted for sparse data and weak methods; consistency point deducted for conflicting results; directness point deducted for uncertain benefits from control treatment
3 (202) [4]	Leg cramp symptoms	Magnesium salts versus placebo or no treatment	4	–2	0	–1	0	Very low	Quality points deducted for weak methods and incomplete reporting of results; directness point deducted for unclear outcomes in one RCT
1 (62) [18]	Leg cramp symptoms	Multivitamin and mineral supplements versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and poor follow-up; directness point deducted as study not designed to assess treatment for cramps

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.