ClinicalEvidence

Dysmenorrhoea

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Pallavi M Latthe, Rita Champaneria, and Khalid S Khan

ABSTRACT

INTRODUCTION: Dysmenorrhoea may begin soon after the menarche, after which it often improves with age, or it may originate later in life after the onset of an underlying causative condition. Dysmenorrhoea is common, and in up to 20% of women it may be severe enough to interfere with daily activities. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for primary dysmenorrhoea? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2010 (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 35 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: acupressure, acupuncture, aspirin, behavioural interventions, contraceptives (combined oral), fish oil, herbal remedies, magnets, non-steroidal anti-inflammatory drugs, paracetamol, progestogens (intrauterine), spinal manipulation, surgical interruption of pelvic nerve pathways, thiamine, toki-shakuyaku-san, topical heat, transcutaneous electrical nerve stimulation (TENS), vitamin B12, and vitamin E.

QUESTIONS

INTERVENTIONS

TREATING DYSMENORRHOEA

Covered elsewhere in Clinical Evidence

Endometriosis

Key points

- Dysmenorrhoea may begin soon after the menarche, where it often improves with age, or may originate later in life after the onset of an underlying causative condition.

  Dysmenorrhoea is very common, and in up to 20% of women it may be severe enough to interfere with daily activities.

  Dysmenorrhoea is more likely in women who smoke, and those with an earlier age at menarche or longer duration of menstruation.

- NSAIDs reduce moderate to severe pain in women with primary dysmenorrhoea compared with placebo, but we don't know whether any one NSAID is superior to the others.

  Simple analgesics such as aspirin and paracetamol may reduce pain in the short term, although few studies have been of good quality.

  The herbal remedies toki-shakuyaku-san and Iranian herbal remedy (saffron, celery, and anise) may reduce pain compared with placebo. We don't know whether Chinese herbal remedies are beneficial compared with placebo, but we found limited evidence that they may be effective compared with other treatments for dysmenorrhoea.

  Thiamine and vitamin E may reduce pain compared with placebo in young women with primary dysmenorrhoea.

- Combined oral contraceptives may be more effective at reducing pain in women with primary dysmenorrhoea compared with placebo; however, few trials have been of good quality.

- Topical heat (about 39 °C) may be as effective as ibuprofen and more effective than paracetamol at reducing pain.

  High-frequency transcutaneous electrical nerve stimulation (TENS) may reduce pain compared with sham TENS, but seems to be less effective than ibuprofen.

  Acupressure may be more effective than sham acupressure or no treatment at relieving dysmenorrhoea.

  Spinal manipulation may be no more effective than placebo at reducing pain after 1 month in women with primary dysmenorrhoea.

  Relaxation may be better than no treatment at relieving dysmenorrhoea.

  We don't know whether acupuncture, fish oil, vitamin B_{12} , magnets, or intrauterine progestogens reduce dysmenorrhoea.

  Surgical interruption of pelvic nerve pathways is not beneficial in treating dysmenorrhoea, and may be associated with adverse effects including constipation.

DEFINITION

Dysmenorrhoea is painful menstrual cramps of uterine origin. It is commonly divided into primary dysmenorrhoea (pain without organic pathology) and secondary dysmenorrhoea (pelvic pain associated with an identifiable pathological condition, such as endometriosis [see review on endometriosis] or ovarian cysts). The initial onset of primary dysmenorrhoea is usually shortly after menarche (6–12 months), when ovulatory cycles are established. Pain duration is commonly 8 to 72 hours and is usually associated with the onset of menstrual flow. Secondary dysmenorrhoea can also occur at any time after menarche, but may arise as a new symptom during a woman's fourth and fifth decades, after the onset of an underlying causative condition. [1] In this review we only consider studies in women with primary dysmenorrhoea. However, the results may also be generalisable to women with secondary dysmenorrhoea. Studies in women with endometriosis, adenomyosis, pelvic congestion, and fibroids may also examine dysmenorrhoea/pain as an outcome. For more information on these conditions and studies, see also reviews on endometriosis, menorrhagia, pelvic inflammatory disease, and fibroids.

INCIDENCE/ PREVALENCE

Variations in the definition of dysmenorrhoea make it difficult to determine prevalence precisely. Studies tend to report on prevalence in adolescent girls, and the type of dysmenorrhoea is not always specified. Adolescent girls tend to have a higher prevalence of primary dysmenorrhoea than older women, as primary dysmenorrhoea can improve with age (see Prognosis). Secondary dysmenorrhoea rates may be lower in adolescents, as onset of causative conditions may not yet have occurred. Therefore, the results from prevalence studies of adolescents may not always be extrapolated to older women, or be accurate estimates of the prevalence of secondary dysmenorrhoea. However, various types of studies have found a consistently high prevalence in women of different ages and nationalities. One systematic review (search date 1996) of the prevalence of chronic pelvic pain, summarising both community and hospital surveys from developed countries, estimated prevalence to be 45% to 95%. [2] A second systematic review of studies in developing countries (search date 2002) found that 25% to 50% of adult women and about 75% of adolescents experienced pain with menstruation, with 5% to 20% reporting severe dysmenorrhoea or pain that prevents them from participating in their usual activities. [3] A third systematic review and meta-analysis of prevalence rates among high-quality studies with samples representative of the general worldwide population (search date 2004) found that prevalence of dysmenorrhoea was 59% (95% CI 49% to 71%). Prevalence rates reported in the UK were between 45% and 97% for any dysmenorrhoea in community-based studies and between 41% and 62% in hospital-based studies. [4]

AETIOLOGY/ RISK FACTORS

A systematic review (search date 2004) of cohort and case-control studies concluded that age <30 years, low BMI, smoking, earlier menarche (<12 years), longer cycles, heavy menstrual flow, nulliparity, premenstrual syndrome, sterilisation, clinically suspected pelvic inflammatory disease, sexual abuse, and psychological symptoms were associated with increased risk of dysmenorrhoea. [5]

PROGNOSIS

Primary dysmenorrhoea is a chronic recurring condition that affects most young women. Studies of the natural history of this condition are sparse. One longitudinal study in Scandinavia found that primary dysmenorrhoea often improves in the third decade of a woman's reproductive life, and is also reduced after childbirth. [6] We found no studies that reliably examined the relationship between the prognosis of secondary dysmenorrhoea and the severity of the underlying pathology, such as endometriosis.

AIMS OF INTERVENTION

To relieve pain from dysmenorrhoea, with minimal adverse effects.

OUTCOMES

Pain: pain relief, measured either by a visual analogue scale, other pain scales (such as the TOTPAR [TOPAR] score, TOTPAR-8 [TOPAR-8], or SPID-8), or as a dichotomous outcome (pain

relief achieved yes/no); overall improvement in dysmenorrhoea measured by change in dysmenorrhoeic symptoms either self reported or observed, proportion of women requiring analgesics in addition to their assigned treatment. **Quality of life:** quality of life scales, or other similar measures such as the Menstrual Distress or Menstrual Symptom Questionnaires. **Daily activities and work:** proportion of women reporting activity restriction or absences from work or school and hours or days of absence as a more selective measure. **Adverse effects** of treatment (incidence and type of adverse effects).

METHODS

Clinical Evidence search and appraisal January 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to January 2010, Embase 1980 to January 2010, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We aimed to include studies in women with primary dysmenorrhoea or where a subgroup analysis was carried out in women with primary dysmenorrhoea. However, where studies included a mixture of primary and secondary dysmenorrhoea, we included studies in which at least 66% of women had primary dysmenorrhoea. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use 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 57). 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 primary dysmenorrhoea?

OPTION NSAIDS (OTHER THAN ASPIRIN)

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- NSAIDs reduce moderate to severe pain in women with primary dysmenorrhoea compared with placebo, but we don't know whether any one NSAID is superior to the others.
- It remains unclear from direct comparisons which NSAIDs have better safety. The harms of NSAIDs include gastrointestinal ulceration and haemorrhage for traditional NSAIDs and, for at least some of the COX-2 inhibitors, increased cardiovascular risk.

Benefits and harms

NSAIDs versus placebo:

We found one systematic review (search date 2003, 36 RCTs, see further information on studies) [7] and 5 subsequent RCTs. [8] [9] [10] [11] [12]

Pain

Compared with placebo NSAIDs may be more effective at reducing pain after 8 to 12 hours in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[7] Systematic review	599 women with moderate to severe pain 14 RCTs in this analysis	**Proportion of women with pain relief** 192/288 (67%) with NSAIDs (naproxen [7 RCTs], diclofenac [2 RCTs], indometacin, mefenamic acid, niflumic acid, nimesulide, and piroxicam [1 RCT each]) 61/311 (20%) with placebo	RR 3.43 95% CI 2.70 to 4.35	●●○	NSAIDs
[8] RCT **Crossover design** **5-armed trial**	104 women with primary dysmenorrhoea No washout period between treatments	**Pain outcomes (TOTPAR scores at 8 and 12 hours, time to pain relief, and time to remedication)** with ibuprofen arginate 200 mg with ibuprofen arginate 400 mg with ibuprofen 200 mg with ibuprofen 400 mg with placebo Absolute results not reported Results post-crossover	The RCT reported significantly improved pain outcomes with ibuprofen arginate 200 mg or 400 mg and ibuprofen 400 mg compared with placebo, further details not reported P values not reported	○○○	ibuprofen arginate 200 mg or 400 mg and ibuprofen 400 mg
[9] RCT **Crossover design** **3-armed trial**	73 women with moderate to severe primary dysmenorrhoea The remaining arm evaluated naproxen sodium (550 mg, taken at the onset of painful menses)	**Pain, assessed by TOPAR-8 score , over 8 hours** 20.0 with etoricoxib (120 mg, taken at the onset of painful menses) 12.6 with placebo (taken at the onset of painful menses)	P <0.001	○○○	etoricoxib
[9] RCT **Crossover design** **3-armed trial**	73 women with moderate to severe primary dysmenorrhoea The remaining arm evaluated etoricoxib (120 mg, taken at the onset of painful menses)	**Pain, assessed by TOPAR-8 score , over 8 hours** 21.5 with naproxen sodium (550 mg, taken at the onset of painful menses) 12.6 with placebo (taken at the onset of painful menses)	P <0.001	○○○	naproxen sodium
[10] RCT **Crossover design** **4-armed trial** Multicentre design	144 women with moderate to severe primary dysmenorrhoea The remaining arms evaluated lumiracoxib (2 different dosage regimens), see further information on studies	**Pain intensity, assessed by SPID-8 score , over the first 8 hours** 12.11 with naproxen (500 mg twice daily) 8.22 with placebo	P <0.001	○○○	naproxen
[11] RCT **Crossover design** **3-armed trial**	149 women aged between 18 and 44 years, with primary dysmenorrhoea The remaining arm evaluated naproxen sodium (550 mg twice daily on day 1, then 550 mg twice daily as nec-	**Pain intensity, assessed by mean TOTPAR-8 scores , over the first 8 hours** 18.28 with celecoxib (400 mg, followed by 200 mg on day 1, then 200 mg twice daily as necessary on days 2 and 3) 12.82 with placebo	P <0.001	○○○	celecoxib

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	essary on days 2 and 3)	The RCT used 6-sequence, 3-period, complete-block crossover design over 3 menstrual cycles, and presented results post-crossover only			
[11] RCT **Crossover design** **3-armed trial**	149 women aged between 18 and 44 years, with primary dysmenorrhoea The remaining arm evaluated celecoxib (400 mg, followed by 200 mg on day 1, then 200 mg twice daily as necessary on days 2 and 3)	**Pain intensity, assessed by mean TOTPAR-8 scores , over the first 8 hours** 20.59 with naproxen sodium (550 mg twice daily on day 1, then 550 mg twice daily as necessary on days 2 and 3) 12.82 with placebo The RCT used 6-sequence, 3-period, complete-block crossover design over 3 menstrual cycles, and presented results post-crossover only	P <0.001	○○○	naproxen sodium
[11] RCT **Crossover design** **3-armed trial**	149 women aged between 18 and 44 years, with primary dysmenorrhoea The remaining arm evaluated naproxen sodium (550 mg twice daily on day 1, then 550 mg twice daily as necessary on days 2 and 3)	**Pain intensity, assessed by mean SPID-8 values , over the first 8 hours** 10.06 with celecoxib (400 mg, followed by 200 mg on day 1, then 200 mg twice daily as necessary on days 2 and 3) 5.96 with placebo The RCT used 6-sequence, 3-period, complete-block crossover design over 3 menstrual cycles, and presented results post-crossover only	P <0.001	○○○	celecoxib
[11] RCT **Crossover design** **3-armed trial**	149 women aged between 18 and 44 years, with primary dysmenorrhoea The remaining arm evaluated celecoxib (400 mg, followed by 200 mg on day 1, then 200 mg twice daily as necessary on days 2 and 3)	**Pain intensity, assessed by mean SPID-8 values , over the first 8 hours** 11.48 with naproxen sodium (550 mg twice daily on day 1, then 550 mg twice daily as necessary on days 2 and 3) 5.96 with placebo The RCT used 6-sequence, 3-period, complete-block crossover design over 3 menstrual cycles, and presented results post-crossover only	P <0.001	○○○	naproxen sodium
[12] RCT **3-armed trial**	180 women with primary dysmenorrhoea The remaining arm evaluated Iranian herbal medicine (highly purified saffron, celery seed, and anise)	**Pain scores, assessed by visual analogue scale [scale 0–10, higher scores indicating more severe pain] , 2 months** 3.6 with mefenamic acid 5 with placebo 106 women in this analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding	P <0.01	○○○	mefenamic acid
[12] RCT **3-armed trial**	180 women with primary dysmenorrhoea The remaining arm evaluated Iranian herbal medicine (highly purified saf-	**Pain scores, assessed by visual analogue scale [scale 0–10, higher scores indicating more severe pain] , 3 months** 2.4 with mefenamic acid 6 with placebo	P <0.01	○○○	mefenamic acid

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	fron, celery seed, and anise)	106 women in this analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding			
[12] RCT **3-armed trial**	180 women with primary dysmenor-rhoea The remaining arm evaluated Iranian herbal medicine (highly purified saf-fron, celery seed, and anise)	**Pain duration , 2 months** 3 hours with mefenamic acid 16.2 hours with placebo 106 women in this analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding	P <0.01	○○○	mefenamic acid
[12] RCT **3-armed trial**	180 women with primary dysmenor-rhoea The remaining arm evaluated Iranian herbal medicine (highly purified saf-fron, celery seed, and anise)	**Pain duration , 3 months** 3 hours with mefenamic acid 15.4 hours with placebo 106 women in this analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding	P <0.001	○○○	mefenamic acid
Need for additional medication					
[7] Systematic review	667 women 10 RCTs in this analysis	**Need for additional analgesia** 104/390 (27%) with NSAIDs 150/277 (54%) with placebo	RR 0.57 95% CI 0.47 to 0.69 Analysis included data from 1 arm of an RCT (85 women; 4 treatment arms), which compared aspirin versus placebo	●○○	NSAIDs

Daily activities and work

Compared with placebo NSAIDs may be more effective at reducing restriction of daily activities and increasing the ability to work (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Restriction of daily activities					
[7] Systematic review	216 women 3 RCTs in this analysis	**Restriction of daily activities** 49/125 (39%) with NSAIDs 62/91 (68%) with placebo	RR 0.65 95% CI 0.51 to 0.83 Analysis included data from 1 arm of an RCT (85 women; 4 treatment arms), which compared aspirin *v* placebo	●○○	NSAIDs
Absence from work or school					
[7] Systematic review	229 women 4 RCTs in this analysis	**Absence from work or school** 36/109 (33%) with NSAIDs 86/120 (72%) with placebo	RR 0.46 95% CI 0.34 to 0.61	●●○	NSAIDs

No data from the following reference on this outcome. [8] [9] [10] [11] [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[7] Systematic review	599 women with moderate to severe pain 14 RCTs in this analysis	**Adverse effects** with NSAIDs with placebo Most commonly reported adverse effects were mild neurological and gastrointestinal symptoms	RR (NSAIDs [analysed as a group] *v* placebo) 1.29 95% CI 1.05 to 1.59 However, no significant difference between any 1 NSAID and placebo	●○○	placebo
[8] RCT **Crossover design** **5-armed trial**	104 women with primary dysmenorrhoea No washout period between treatments	**Adverse effects** with ibuprofen arginate 200 mg with ibuprofen arginate 400 mg with ibuprofen 200 mg with ibuprofen 400 mg with placebo Absolute results not reported No participants discontinued treatment because of adverse effects Most common adverse effects were headache, nausea, and dizziness	Reported as no significant difference between active treatments and placebo	⟷	Not significant
[9] RCT **Crossover design** **3-armed trial**	73 women with moderate to severe primary dysmenorrhoea	**Incidence of adverse effects** 12% with etoricoxib 25% with naproxen sodium 15% with placebo Absolute numbers not reported The most common adverse effects were headache and nausea; the RCT reported no "serious" adverse experiences	Significance assessment not performed		
[9] RCT **Crossover design** **3-armed trial**	73 women with moderate to severe primary dysmenorrhoea	**Headache** 1.5% with etoricoxib 7.5% with naproxen sodium 4.5% with placebo Absolute numbers not reported	Significance assessment not performed		
[9] RCT **Crossover design** **3-armed trial**	73 women with moderate to severe primary dysmenorrhoea	**Nausea** 3% with etoricoxib 3% with naproxen sodium 1.5% with placebo Absolute numbers not reported	Significance assessment not performed		
[10] RCT **Crossover design** **4-armed trial** Multicentre design	144 women with moderate to severe primary dysmenorrhoea The remaining arms evaluated lumiracoxib (2 different dosage regimens), see further information on studies	**Proportion of people reporting adverse effects** 23% with naproxen 13% with placebo Absolute numbers not reported The most frequent adverse events in all groups included nausea, headaches, dizziness, and urinary tract infection	Significance assessment not reported		
[11]	149 women aged between 18 and 44	**Adverse effects**			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
RCT **Crossover design** **3-armed trial**	years, with primary dysmenorrhoea	40/129 (31%) with celecoxib 46/126 (37%) with naproxen sodium 38/127 (30%) with placebo The RCT used 6-sequence, 3-period, complete-block crossover design over 3 menstrual cycles, and presented results post-crossover only The majority of adverse effects were related to primary dysmenorrhoea; the most common adverse effects included nausea, headaches, insomnia, dizziness, and constipation			
[12] RCT **3-armed trial**	180 women with primary dysmenorrhoea The remaining arm evaluated Iranian herbal medicine (highly purified saffron, celery seed, and anise)	**Adverse effects** with mefenamic acid with placebo The RCT reported nausea in 1 woman who received mefenamic acid but gave no further information			

Different NSAIDs versus each other:

We found one systematic review (search date 2003) [7] and three subsequent RCTs. [8] [9] [13] The systematic review identified 26 RCTs, which compared different NSAIDs, [7] but the review reported that only three RCTs reported data that were suitable for meta-analysis (see further information on studies).

Pain

Different NSAIDs compared with each other We don't know how effective different NSAIDs are, compared with each other, at reducing pain after 8 to 12 hours in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[7] Systematic review	73 women Data from 1 RCT	**Pain intensity (assessed by visual analogue scale, scale not defined)** 3.17 with mefenamic acid (500 mg three times daily) 2.94 with tolfenamic acid (200 mg three times daily)	WMD +0.23 95% CI –0.64 to +1.10	⟷	Not significant
[7] Systematic review	304 women Data from 1 RCT	**Proportion of women with pain relief** 125/155 (81%) with diclofenac (50 mg up to 3 times daily as required) 128/149 (86%) with nimesulide (100 mg up to 3 times daily as required)	OR 0.69 95% CI 0.38 to 1.25	⟷	Not significant
[7] Systematic review	81 women Data from 1 RCT	**Proportion of women with pain relief** 14/40 (35%) with ibuprofen (up to a maximum daily dose of 1200 mg)	OR 0.57 95% CI 0.23 to 1.38	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		20/41 (49%) with naproxen sodium (up to a maximum daily dose of 660 mg)			
[8] RCT **Crossover design** **5-armed trial**	104 women with primary dysmenorrhoea The remaining arm evaluated placebo, conventional ibuprofen 400 mg, and ibuprofen arginate 200 mg No washout period between treatments	**Time to pain relief** 56 minutes with ibuprofen arginate 400 mg 90 minutes with conventional ibuprofen 200 mg Results post-crossover	P <0.05	○○○	ibuprofen arginate 400 mg
[8] RCT **Crossover design** **5-armed trial**	104 women with primary dysmenorrhoea The remaining arm evaluated placebo, conventional ibuprofen 200 mg, and ibuprofen arginate 200 mg No washout period between treatments	**Time to pain relief** 56 minutes with ibuprofen arginate 400 mg 86 minutes with conventional ibuprofen 400 mg Results post-crossover	P <0.05	○○○	ibuprofen arginate 400 mg
[8] RCT **Crossover design** **5-armed trial**	104 women with primary dysmenorrhoea The remaining arm evaluated placebo No washout period between treatments	**Time to remedication** with ibuprofen arginate 200 mg or 400 mg with conventional ibuprofen 200 mg or 400 mg Absolute results not reported Results post-crossover	Reported no significant difference between all active treatments (P >0.05)	⟷	Not significant
[9] RCT **Crossover design** **3-armed trial**	73 women with moderate to severe primary dysmenorrhoea The remaining arm evaluated placebo	**Pain, assessed by mean TOTPAR-8 score , over 8 hours** 20.0 units with etoricoxib (120 mg, taken at the onset of painful menses) 21.5 units with naproxen sodium (550 mg, taken at the onset of painful menses)	P = 0.33	⟷	Not significant
[13] RCT **3-armed trial**	337 women with primary dysmenorrhoea	**Proportion of women who rated treatment as good , over 3 to 5 days and 3 menstrual cycles** 43/100 (43%) with meloxicam 7.5 mg daily 44/104 (42%) with meloxicam 15 mg daily 37/104 (35%) with mefenamic acid (500 mg three times daily)	P value for all groups *v* each other reported as not significant	⟷	Not significant

Daily activities and work

No data from the following reference on this outcome. [7] [8] [9] [13]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[7] Systematic review	111 women Data from 1 RCT	**Adverse effects** with ibuprofen with fenoprofen Absolute results not reported	OR 1.51 95% CI 0.72 to 3.18	⟷	Not significant
[7] Systematic review	323 women 2 RCTs in this analysis	**Adverse effects** with naproxen with other NSAIDs Absolute results not reported	OR 1.09 95% CI 0.54 to 2.22	⟷	Not significant
[13] RCT **3-armed trial**	337 women with primary dysmenorrhoea	**Adverse effects, primarily gastrointestinal** 11/113 (10%) with meloxicam 7.5 mg daily 13/114 (11%) with meloxicam 15 mg daily 25/110 (23%) with mefenamic acid (500 mg three times daily)	P value reported as significant	○○○	meloxicam
[8] RCT **Crossover design** **5-armed trial**	104 women with primary dysmenorrhoea The remaining arm evaluated placebo No washout period between treatments	**Adverse effects** with ibuprofen arginate 200 mg or 400 mg with conventional ibuprofen 200 mg or 400 mg Absolute results not reported No participants discontinued treatment because of adverse effects Most common adverse effects were headache, nausea, and dizziness (similar incidence with each active treatment)	Between group statistical assessment not reported		
[9] RCT **Crossover design** **3-armed trial**	73 women with moderate to severe primary dysmenorrhoea The remaining arm evaluated placebo	**Clinical adverse effects** 12% with etoricoxib 25% with naproxen sodium Absolute numbers not reported The most common adverse effects were headache and nausea; no serious adverse effects were found	Significance assessment not reported		
[9] RCT **Crossover design** **3-armed trial**	73 women with moderate to severe primary dysmenorrhoea The remaining arm evaluated placebo	**Headache** 1.5% with etoricoxib 7.5% with naproxen sodium Absolute numbers not reported	Significance assessment not reported		
[9] RCT **Crossover design**	73 women with moderate to severe primary dysmenorrhoea	**Nausea** 3% with etoricoxib 3% with naproxen sodium	Significance assessment not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	The remaining arm evaluated placebo	Absolute numbers not reported			

NSAIDs versus aspirin:
See option on simple analgesics, p 15 .

NSAIDs versus paracetamol:
See option on simple analgesics, p 15 .

NSAIDs versus TENS:
See option on TENS, p 26 .

NSAIDs versus acupressure:
See option on acupressure, p 12 .

NSAIDs versus topical heat:
See option on topical heat, p 22 .

NSAIDs versus acupuncture:
See option on acupuncture, p 33 .

NSAIDs versus herbal remedies:
See option on herbal remedies, p 41 .

Further information on studies

[7] The systematic review included only double-blind RCTs with <20% loss to follow-up. Only 5 of the included RCTs clearly described methods of randomisation and allocation concealment. The measurement and reporting of adverse effects by individual RCTs were generally poor, even taking into account the challenge of distinguishing between dysmenorrhoeic symptoms and medication effects. Methods of collecting this information varied: about one third of the RCTs described the use of prospective self-report forms or diaries, but another third assessed adverse effects retrospectively (at follow-up appointments), and the others were not specific about their methods. In some cases, the adverse effects recorded were those deemed by the study investigator to be medication related. Few RCTs provided adverse-effect data suitable for meta-analysis, and many provided no numerical data at all. **NSAIDs versus placebo:** The review found that 14 of 36 included RCTs examining NSAIDs versus placebo reported data suitable for meta-analysis. Of the 24 additional comparisons of 12 different NSAIDs versus placebo that were not suitable for meta-analysis, 19 found that NSAIDs significantly relieved pain (P <0.05), three found no significant difference (aspirin, diclofenac, and ibuprofen), and two did not report sta-

tistical results. **Different NSAIDs versus each other:** Despite the large number of included trials, it was not clear which NSAIDs were most effective for dysmenorrhoea. This was because most of the trials were relatively small, they covered a large number of different comparisons, and few of them provided data suitable for meta-analysis.

[10] We have only reported the data on the comparison of naproxen versus placebo from this 4-armed trial; however, results should be interpreted with caution because the RCT may not have been powered to look at this comparison and results were presented post-crossover.

Comment: The harms of NSAIDs, including the COX-2 inhibitor class, are considered in detail elsewhere in *Clinical Evidence* (see review on NSAIDs), and include gastrointestinal ulceration and haemorrhage for traditional NSAIDs and, for at least some of the COX-2 inhibitors, increased cardiovascular risk.

Clinical guide:
NSAIDs can be given as suppositories, which seem to have a similar effect on overall pain relief but less effect than oral treatment on spasmodic pain. [14]

NSAIDs are an effective treatment for dysmenorrhoea, although women using them need to be aware of the significant risk of adverse effects. There is insufficient evidence to determine which (if any) individual NSAID is the safest and most effective for the treatment of dysmenorrhoea.

OPTION ACUPRESSURE

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- Acupressure may be more effective than sham acupressure or no treatment at relieving dysmenorrhoea.

Benefits and harms

Acupressure versus sham acupressure or no treatment:

We found one systematic review (search date 2008, 2 RCTs) [16] and one additional RCT [17] comparing the use of acupressure with sham acupressure or no treatment for treating primary dysmenorrhoea. The review did not pool the data because of heterogeneity of the RCTs. It did not give information on follow-up or absolute results for the individual RCTs (see further information on studies). [16]

Pain

Compared with no treatment or sham acupressure Acupressure may be more effective than placebo acupressure or waiting list control at reducing pain after 2 to 3 months in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[18] RCT **3-armed trial**	216 adolescent women with primary dysmenorrhoea; aged 14 to 18 years; not previously sexually active In review [16] The remaining arm evaluated ibuprofen for 3 menstrual cycles	**Proportion of women reporting no pain , after 3 months** 36/72 (50%) with self-administered acupressure for 3 menstrual cycles 13/72 (18%) with placebo acupressure (using incorrect pressure points) for 3 menstrual cycles	Reported as significant P value not reported		
[17] RCT	61 women with primary dysmenorrhoea, aged 20 to 40 years	**Mean pain score for "worst" menstrual pain, assessed by Descriptive Numeric Rating Scale of Pain Intensity and Distress Inventory , after 2 menstrual cycles** 3.9 with specially designed cotton acupressure brief containing 10 latex foam pads fixed over lower	P <0.001	○○○	acupressure brief

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		abdominal and lower back acupressure points 7.3 with waiting list control, who received usual care The acupressure brief was worn on the first 3 days of menses, for 2 menstrual cycles, for as long as possible without discomfort Pain measured on 11-point scale, where 0 = no pain and 10 = worst pain imaginable			
[17] RCT	61 women with primary dysmenorrhoea, aged 20 to 40 years	**Mean pain score for "worst" menstrual pain, assessed by Menstrual Pain Symptom Intensity Scale , after 2 menstrual cycles** 2.9 with specially designed cotton acupressure brief containing 10 latex foam pads fixed over lower abdominal and lower back acupressure points 7.1 with waiting list control, who received usual care The acupressure brief was worn on the first 3 days of menses, for 2 menstrual cycles, for as long as possible without discomfort Pain measured on scale where 0 = no pain and 12 = most severe pain	P <0.05	○○○	acupressure brief
[17] RCT	61 women with primary dysmenorrhoea, aged 20 to 40 years	**Proportion of women experiencing a clinically significant drop in pain scores** 25/28 (89%) with specially designed cotton acupressure brief containing 10 latex foam pads fixed over lower abdominal and lower back acupressure points 2/26 (8%) with waiting list control, who received usual care The acupressure brief was worn on the first 3 days of menses, for 2 menstrual cycles, for as long as possible without discomfort Clinically significant drop defined as at least a 25% reduction in pain score	P <0.05	○○○	acupressure brief

Daily activities and work

No data from the following reference on this outcome. [17] [18]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] RCT	61 women with primary dysmenorrhoea, aged 20 to 40 years	**Adverse effects** with specially designed cotton acupressure brief containing 10 latex foam pads fixed over lower abdominal and lower back acupressure points with waiting list control, who received usual care 4 women (14%) found the discomfort from wearing the acupressure briefs so great that they did not use them in the second menstrual cycle			

No data from the following reference on this outcome. [16] [18]

Acupressure versus NSAIDs:

We found one systematic review (search date 2008, 4 RCTs) comparing the use of acupressure with NSAIDs. [16] The review did not pool the data because of heterogeneity of the RCTs. It did not give information on follow-up or absolute results for the individual RCTs. Three of the included RCTs were written in Chinese (see further information on studies).

Pain

Compared with NSAIDs We don't know how effective acupressure and ibuprofen are, compared with each other, at reducing pain in women with dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[18] RCT **3-armed trial**	216 adolescent women with primary dysmenorrhoea; aged 14 to 18 years; not previously sexually active In review [16] The remaining arm evaluated placebo acupressure (using incorrect pressure points) for 3 menstrual cycles	**Proportion of women reporting no pain , 3 months** 36/72 (50%) with acupressure 26/72 (36%) with ibuprofen	Difference between acupressure and ibuprofen reported as not significant P value not reported	⟷	Not significant

Daily activities and work

No data from the following reference on this outcome. [16] [18]

Adverse effects

No data from the following reference on this outcome. [16] [18]

Acupressure versus herbal remedies:

We found one systematic review (search date 2008, 1 RCT, 160 women) comparing acupressure with Chinese herbal medicine. [16] The RCT was written in Chinese, see further information on studies.

Further information on studies

[16] A meta-analysis could not be carried out because of heterogeneity of the included RCTs in types (acupuncture, acupressure, acupoint injections, and moxibustion) and duration of treatments. None of the 32 included RCTs in the review were considered by the review as high quality, 6 were of average quality, and 26 were of low quality. Only three RCTs reported a sample size calculation, one was double-blind, three RCTs reported intention-to-treat analyses, and the follow-up was >1 year in only 4 of 32 RCTs. The systematic review concluded that because of the small sample sizes of included trials and the poor methodological quality, there is no convincing evidence for acupuncture-related treatments being an effective treatment for primary dysmenorrhoea. **Acupressure versus sham acupressure or no treatment:** One of the RCTs identified did not fulfil *Clinical Evidence* inclusion criteria because the follow-up was too low (<80%). **Acupressure versus NSAIDs:** Three RCTs comparing acupressure with indometacin or ibuprofen were written in Chinese. One of these RCTs did not fulfil *Clinical Evidence* inclusion criteria because the adequacy of randomisation was unclear (although the trial stated that women were "randomly divided", the methods section described allocation by clinical number suggesting pseudo-randomisation). [19] We are awaiting full-text translation of the other two RCTs, and will assess these for inclusion at the next update. **Acupressure versus herbal remedies:** The review found no significant differences between groups in pain relief, but gave no further information. We are awaiting the full-text translation of the RCT, and will assess this for inclusion at the next update.

Comment: None.

OPTION ASPIRIN, PARACETAMOL, AND COMPOUND ANALGESICS

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- Simple analgesics such as aspirin and paracetamol may reduce pain in the short term, although few studies have been of good quality.
- **Note:**
  A drug safety alert has been issued by the Food Drug Administration (FDA) on the risk of rare but serious skin reactions with paracetamol (acetaminophen).

Benefits and harms

Aspirin versus placebo:

We found two systematic reviews (search date 1997, 8 RCTs, 486 women with primary dysmenorrhoea; [20] and search date 2003, 2 RCTs, 143 women; [7] see further information on studies).

Pain

Aspirin compared with placebo Aspirin may be more effective at reducing pain in women with dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[20] Systematic review	486 women with primary dysmenorrhoea 8 RCTs in this analysis	**Proportion of women with at least moderate pain relief** with aspirin (650 mg four times daily) with placebo	RR 1.60 95% CI 1.12 to 2.29 NNT 10 95% CI 5 to 50	●○○	aspirin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
Need for additional medication					
[20] Systematic review	205 women with primary dysmenorrhoea 3 RCTs in this analysis	**Need for additional medication** with aspirin (650 mg four times daily) with placebo Absolute results not reported	RR 0.79 95% CI 0.58 to 1.08	⟷	Not significant
[7] Systematic review	36 women Data from 1 RCT	**Need for additional medication** 12/24 (50%) with aspirin (650 mg/day during menses) 7/12 (58%) with placebo	RR 0.86 95% CI 0.46 to 1.60	⟷	Not significant

Daily activities and work

Aspirin compared with placebo We don't know whether aspirin is more effective at reducing restriction of daily activity and absence from work in women with dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Daily activities					
[20] Systematic review	203 women with primary dysmenorrhoea 3 RCTs in this analysis	**Restriction of daily activity** with aspirin (650 mg four times daily) with placebo Absolute results not reported	RR 0.82 95% CI 0.64 to 1.04	⟷	Not significant
Absence from work					
[20] Systematic review	37 women with primary dysmenorrhoea Data from 1 RCT	**Absence from work** with aspirin (650 mg four times daily) with placebo Absolute results not reported	RR 1.28 95% CI 0.24 to 6.76	⟷	Not significant

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					
[20] Systematic review	Women with primary dysmenorrhoea	**Adverse effects** with aspirin (650 mg four times daily) with placebo Absolute results not reported	RR 1.3 95% CI 0.79 to 2.17	⟷	Not significant
[20] Systematic review	Women with primary dysmenorrhoea	**Nausea** with aspirin (650 mg four times daily) with placebo	RR 1.66 95% CI 0.59 to 4.67	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[20] Systematic review	Women with primary dysmenorrhoea	**Dizziness** with aspirin (650 mg four times daily) with placebo Absolute results not reported	RR 1.29 95% CI 0.28 to 5.89	⟷	Not significant
[20] Systematic review	Women with primary dysmenorrhoea	**Headache** with aspirin (650 mg four times daily) with placebo Absolute results not reported	RR 0.60 95% CI 0.18 to 2.04	⟷	Not significant
[7] Systematic review	36 women with dysmenorrhoea Data from 1 RCT	**Adverse effects** 12/24 (50%) with aspirin 4/12 (33%) with placebo	OR 1.93 95% CI 0.49 to 7.62	⟷	Not significant
[7] Systematic review	36 women with dysmenorrhoea Data from 1 RCT	**Gastrointestinal adverse effects** 7/24 (29%) with aspirin 2/12 (17%) with placebo	OR 1.91 95% CI 0.39 to 9.26	⟷	Not significant
[7] Systematic review	36 women with dysmenorrhoea Data from 1 RCT	**Nervous system adverse effects** 8/24 (33%) with aspirin 1/12 (8%) with placebo	OR 3.66 95% 0.75 to 17.71	⟷	Not significant

Paracetamol versus placebo:

We found one systematic review (search date 1997, 1 RCT). [20]

Pain

Paracetamol compared with placebo Paracetamol may be no more effective at reducing pain in women with dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[20] Systematic review	35 women randomised, 30 women in analysis Data from 1 RCT RCT had crossover design, 3-armed trial The remaining arm evaluated aspirin	**Median pain relief** 1.6 with paracetamol (500 mg four times daily) 0.9 with placebo Results after crossover	Reported as no significant difference	⟷	Not significant

Daily activities and work

No data from the following reference on this outcome. [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] Systematic review	35 women randomised, 30 women in analysis Data from 1 RCT RCT had crossover design, 3-armed trial The remaining arm evaluated aspirin	**Frequency of any adverse effect** with paracetamol (500 mg four times daily) with placebo Absolute results not reported	RR 1.00 95% CI 0.36 to 2.75	⟷	Not significant

Paracetamol versus aspirin:

We found one systematic review (search date 1997, 1 RCT). [20]

Pain

Aspirin compared with paracetamol We don't know how effective aspirin and paracetamol are, compared with each other, at reducing pain in women with dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[20] Systematic review	35 women randomised, 30 women in analysis Data from 1 RCT RCT had crossover design, 3-armed trial The remaining arm evaluated placebo	**Median pain relief** 1.2 with aspirin (500 mg four times daily) 1.6 with paracetamol (500 mg four times daily) Post-crossover results	Reported no significant difference	⟷	Not significant

Daily activities and work

No data from the following reference on this outcome. [20]

Adverse effects

No data from the following reference on this outcome. [20]

Aspirin versus NSAIDs:

We found two systematic reviews (search dates 1997 [20] and 2003 [7]). The first review identified two RCTs, which compared aspirin versus NSAIDs (ibuprofen or naproxen). [20] However, one RCT did not meet *Clinical Evidence*

inclusion criteria because of a high loss to follow-up. The second review identified no RCTs comparing NSAIDs versus aspirin that were suitable for meta-analysis. [7]

Pain

Aspirin compared with NSAIDs Aspirin may be less effective than naproxen at reducing pain in women with dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[20] Systematic review	34 women randomised, 32 women in analysis Data from 1 RCT RCT had crossover design	**Pain relief** with aspirin (650 mg four times daily) with naproxen (500 mg loading dose followed by 275 mg four times daily) Absolute results not reported Post-crossover results	RR 2.29 95% CI 1.09 to 4.79	●●○	naproxen

Daily activities and work

No data from the following reference on this outcome. [20]

Adverse effects

No data from the following reference on this outcome. [20]

Paracetamol versus NSAIDs:

We found two systematic reviews (search dates 1997 [20] and 2003 [7]).

Pain

Paracetamol compared with NSAIDs We don't know how effective paracetamol and NSAIDs are, compared with each other, at reducing pain in women with dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[7] Systematic review	68 women in analysis for this comparison Data from 1 RCT RCT had crossover design	**Proportion of women with pain relief** 9/33 (27%) with paracetamol (1000 mg up to 3 times daily) 16/35 (46%) with naproxen (220 mg up to 3 times daily) Pre-crossover results	OR 2.25 95% CI 0.81 to 6.19	⟷	Not significant
[20] Systematic review	67 women randomised, 60 women in analysis Data from 1 RCT	**Pain relief** with paracetamol (1000 mg three times daily) with ibuprofen (400 mg three times daily)	RR 0.86 95% CI 0.68 to 1.10	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	RCT had crossover design	Absolute results not reported Post-crossover results			

Daily activities and work

No data from the following reference on this outcome. [7] [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[7] Systematic review	78 women in analysis for this comparison Data from 1 RCT RCT had crossover design	**Gastrointestinal adverse effects** 1/39 (3%) with paracetamol (1000 mg up to 3 times daily) 1/39 (3%) with naproxen (220 mg up to 3 times daily) Pre-crossover results	OR 1.00 95% CI 0.06 to 16.58	⟷	Not significant
[7] Systematic review	78 women in analysis for this comparison Data from 1 RCT RCT had crossover design	**Gastrointestinal adverse effects** 2/39 (5%) with paracetamol (1000 mg up to 3 times daily) 3/39 (8%) with naproxen (220 mg up to 3 times daily) Pre-crossover results	OR 1.54 95% CI 0.24 to 9.78	⟷	Not significant

No data from the following reference on this outcome. [20]

Paracetamol versus topical heat:

See option on topical heat, p 22 .

Further information on studies

[20] Most RCTs included in the systematic review were short (usually only 1 menstrual cycle on each treatment), small, and used a crossover design without a washout period. All the RCTs used double-blinding. All the RCTs used oral administration of treatment in the form of tablets or capsules. Negative RCTs may have been too small to detect clinically important differences between aspirin, paracetamol, or compound analgesics and placebo.

[7] The systematic review included only double-blind RCTs with <20% loss to follow-up. It found no RCTs for which the results were suitable for quantitative analysis of effects on pain relief.

Comment: None.

OPTION THIAMINE

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- Thiamine may reduce pain compared with placebo in young women with primary dysmenorrhoea.

Benefits and harms

Thiamine versus placebo:

We found one systematic review (search date 2000, 1 RCT). [21]

Pain

Compared with placebo Thiamine seems more effective at reducing pain after 60 days in Indian adolescent women with moderate to very severe primary dysmenorrhoea (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[21] Systematic review	556 Indian adolescents attending school with moderate to very severe primary dysmenorrhoea Data from 1 RCT RCT had a crossover design	**Proportion of women with no pain , after 60 days and before crossover** 142/277 (51%) with thiamine 100 mg daily for 90 days 0/279 (0%) with placebo for 60 days	NNT 2 95% CI 2 to 3	○○○	thiamine

Daily activities and work

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

Adverse effects

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

Further information on studies

[21] After completion of the RCT, 87% of all women experienced no pain.

Comment: None.

OPTION TOKI-SHAKUYAKU-SAN (HERBAL REMEDY)

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- The herbal remedy toki-shakuyaku-san may reduce pain compared with placebo.

Benefits and harms

Toki-shakuyaku-san versus placebo:

We found one systematic review (search date 2000, 1 RCT). [21]

Pain

Compared with placebo Toki-shakuyaku-san may be more effective at reducing pain after 6 months in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[21] Systematic review	50 women Data from 1 RCT	**Pain, as measured by a visual analogue scale , after 6 months** with toki-shakuyaku-san (2.5 g three times daily) with placebo Absolute results reported graphically	P <0.005	○○○	toki-shakuyaku-san
Need for additional medication					
[21] Systematic review	50 women Data from 1 RCT	**Need for additional medication (diclofenac sodium) , after 6 months** with toki-shakuyaku-san (2.5 g three times daily) with placebo Absolute results reported graphically	P <0.01	○○○	toki-shakuyaku-san

Daily activities and work

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

Adverse effects

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

Further information on studies

[21] The allocation method was not clearly described in the RCT.

Comment: Toki-shakuyaku-san is a mixture of 6 herbs, including angelica and peony root.

OPTION TOPICAL HEAT (ABOUT 39 °C)

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .

- Topical heat (about 39 °C) may be as effective as ibuprofen and more effective than paracetamol at reducing pain.

Benefits and harms

Topical heat versus placebo:

We found one RCT. [22]

Pain

Compared with placebo Topical heat plus placebo tablets may be more effective than an unheated patch plus placebo at reducing pain in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[22] RCT **4-armed trial** Efficacy RCT; double-dummy design	84 women with moderate or greater pain in at least 4 of their last 6 cycles who experienced pain relief with non-prescription analgesics and had a history consistent with a diagnosis of primary dysmenorrhoea The remaining arms evaluated heated patch plus ibuprofen, and unheated patch plus ibuprofen	**Mean pain relief score , after 2 days of treatment from the start of menses** 3.27 with abdominal heated (to 38.9 °C) patch for about 12 hours daily plus placebo 1.95 with unheated patch plus placebo Pain relief was measured on a scale from 0 (no relief) to 5 (complete relief) 40 women in this analysis	P <0.001	○○○	heated patch plus placebo
[22] RCT **4-armed trial** Efficacy RCT; double-dummy design	84 women with moderate or greater pain in at least 4 of their last 6 cycles who experienced pain relief with non-prescription analgesics and had a history consistent with a diagnosis of primary dysmenorrhoea The remaining arms evaluated heated patch plus ibuprofen, and unheated patch plus ibuprofen	**Mean pain intensity reduction , after 2 days of treatment from the start of menses** 40.4 with abdominal heated (to 38.9 °C) patch for about 12 hours daily plus placebo 21.9 with unheated patch plus placebo Pain intensity measured on a 100-point numerical scale ranging from 0 (no pain) to 100 (worst possible pain) 40 women in this analysis	P <0.003	○○○	heated patch plus placebo

Daily activities and work

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] RCT **4-armed trial** Efficacy RCT; double-dummy design	84 women with moderate or greater pain in at least 4 of their last 6 cycles who experienced pain relief with non-prescription analgesics and had a history consistent with a diagnosis of primary dysmenorrhoea The remaining arms evaluated heated patch plus ibuprofen, and unheated patch plus ibuprofen	**Proportion of women reporting pinkness or redness of the skin , end of day 2 (after 12 continuous hours of use)** 23/40 (58%) with heated patch plus placebo or ibuprofen 5/41 (12%) with unheated patch plus placebo or ibuprofen All women reported normal skin 3 to 7 days after starting treatment	OR 9.74 95% CI 3.16 to 30.04	●●●	unheated patch

Topical heat versus NSAIDs:

We found one RCT. [22]

Pain

Compared with NSAIDs We don't know how effective topical heat treatment plus placebo and an unheated topical patch plus ibuprofen are, compared with each other, at reducing pain in women with dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[22] RCT **4-armed trial** Efficacy RCT; double-dummy design	84 women with moderate or greater pain in at least 4 of their last 6 cycles who experienced pain relief with non-prescription analgesics and had a history consistent with a diagnosis of primary dysmenorrhoea The remaining arms evaluated heated patch plus placebo, and unheated patch plus placebo	**Mean pain relief score , after 2 days of treatment from the start of menses** 3.27 with abdominal heated (to 38.9 °C) patch for about 12 hours daily plus placebo 3.07 with unheated patch plus ibuprofen Pain relief was measured on a scale from 0 (no relief) to 5 (complete relief) 41 women in this analysis	Significance not assessed		
[22] RCT **4-armed trial** Efficacy RCT; double-dummy design	84 women with moderate or greater pain in at least 4 of their last 6 cycles who experienced pain relief with non-prescription analgesics and had a history consistent with a diagnosis of primary dysmenorrhoea	**Mean pain intensity reduction , after 2 days of treatment from the start of menses** 40.4 with abdominal heated (to 38.9 °C) patch for about 12 hours daily plus placebo 39.0 with unheated patch plus ibuprofen Pain intensity measured on a 100-point numerical scale ranging from 0 (no pain) to 100 (worst possible pain)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arms evaluated heated patch plus placebo, and un-heated patch plus placebo	40 women in this analysis			

Daily activities and work

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

Adverse effects

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

Topical heat versus paracetamol:
We found one RCT. [23]

Pain

Compared with paracetamol Topical heat treatment may be more effective at reducing pain in women with primary dysmenorrhoea after 8 hours (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[23] RCT **4-armed trial**	362 women with primary dysmenor-rhoea The remaining arms evaluated unheated abdomi-nal wrap (for same time period as for heated wrap), and placebo	**Mean pain score , after 8 hours of treatment** 2.48 with abdominal heat wrap (heated to 40 °C for 8 hours from the first morning after the start of menses) 2.17 with high-dose paracetamol (1000 mg four times daily) Pain relief was measured on a scale from 1 to 6, which was converted to a TOTPAR score 301 women in this analysis	P = 0.015	◌◌◌	heated wrap

Daily activities and work

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

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] RCT **4-armed trial**	362 women with primary dysmenorrhoea The remaining arms evaluated unheated abdominal wrap (for same time period as for heated wrap), and placebo	**Number of women reporting adverse effects** 2 with abdominal heat wrap (heated to 40 °C for 8 hours from the first morning after the start of menses) 4 with high-dose paracetamol (1000 mg four times daily) Adverse effects included conjunctivitis and pink skin with abdominal heat wrap and headache, rhinitis, upper respiratory infection, and anxiety with paracetamol The RCT reported that all adverse effects other than pink skin were most likely unrelated to the study interventions; pink skin resolved within 1 hour of removing the heated wrap			

Topical heat versus Chinese herbal remedies:
See option on herbal remedies, p 41 .

Further information on studies

[22] Participants in the RCT included volunteer women. Dysmenorrhoea in these women may have a different pattern and response to treatment from dysmenorrhoea in women seeking health care.

[23] No data were reported for the placebo groups.

Comment: None.

OPTION TENS

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- High-frequency transcutaneous electrical nerve stimulation (TENS) may reduce pain compared with sham TENS, but seems to be less effective than ibuprofen.

Benefits and harms

High-frequency TENS versus placebo TENS:
We found one systematic review (search date 2009, 4 RCTs) [24] and one subsequent RCT [25] in women with primary dysmenorrhoea.

Pain

High-frequency TENS compared with placebo High-frequency TENS may be more effective than placebo TENS at reducing pain in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[24] Systematic review	53 women with primary dysmenorrhoea 2 RCTs in this analysis Both RCTs had crossover design	**Pain relief, as measured by subjective assessment** 30/53 (57%) with high-frequency TENS 8/53 (15%) with placebo TENS Results post-crossover	OR 7.2 95% CI 3.1 to 16.5	●●●	high-frequency TENS
[25] RCT **Crossover design**	26 women with primary dysmenorrhoea	**Change in visual analogue scale pain score , after treatment** From 4.81 to 2.18 with TENS for 1 cycle From 4.44 to 3.07 with sham TENS for 1 cycle Results post-crossover 22 women in this analysis Pain score on a scale from 0 to 10, where 0 = no pain, 10 = severe pain	P = 0.018	○○○	TENS
Need for additional medication					
[24] Systematic review	32 women with primary dysmenorrhoea Data from 1 RCT RCT had crossover design	**Proportion of women needing additional analgesics** 22/32 (69%) with high-frequency TENS 28/32 (88%) with placebo TENS Results post-crossover	OR 0.3 95% CI 0.1 to 1.1	⟷	Not significant
[24] Systematic review	24 women with primary dysmenorrhoea Data from 1 RCT RCT had multi-arm crossover design	**Mean number of analgesic tablets taken each day** 6.92 with high-frequency TENS 6.78 with placebo TENS	WMD +0.1 tablets 95% CI –2.1 tablets to +2.4 tablets Randomisation and blinding unclear	⟷	Not significant

Daily activities and work

High-frequency TENS compared with placebo We don't know whether high-frequency TENS is more effective than placebo TENS at reducing absence from work or school in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Absence from work or school					
[24] Systematic review	24 women with primary dysmenorrhoea Data from 1 RCT RCT had multi-arm crossover design	**Mean number of lost hours each menstrual cycle** 1.46 hours with high-frequency TENS 1.42 hours with placebo TENS	WMD +0.04 hours 95% CI –0.4 hours to +0.5 hours Randomisation and blinding unclear	⟷	Not significant

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

Quality of life

High-frequency TENS compared with placebo We don't know whether high-frequency TENS is more effective than placebo at improving quality of life, assessed by the Menstrual Distress Questionnaire or the Short-Form (SF)-36 Health Survey in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[25] RCT **Crossover design**	26 women with primary dysmenorrhoea	**Menstrual Distress Questionnaire total score** 25.4 with TENS for 1 cycle 27.4 with sham TENS for 1 cycle Results post-crossover	P = 0.079	⟷	Not significant
[25] RCT **Crossover design**	26 women with primary dysmenorrhoea	**Short-Form (SF)-36 questionnaire** with TENS for 1 cycle with sham TENS for 1 cycle Results post-crossover Total scores not presented	No significant difference in any subcategory score P = 0.173 to 0.992	⟷	Not significant

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

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] Systematic review	32 women with primary dysmenorrhoea Data from 1 RCT RCT had crossover design	**Adverse effects** 4/32 (13%) with high-frequency TENS 0/32 (0%) with placebo TENS Post-crossover results Adverse effects with high-frequency TENS included muscle vibrations, tightness, headaches, and slight burning or redness after use	RR 9.0 95% CI 0.50 to 160.59	⟷	Not significant

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

Low-frequency TENS versus placebo TENS or placebo tablet:

We found one systematic review (search date 2009, 5 RCTs) [24] in women with primary dysmenorrhoea.

Pain

Low-frequency TENS compared with placebo We don't know whether low-frequency TENS is more effective than placebo TENS at reducing pain in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[24] Systematic review	42 women with primary dysmenorrhoea 2 RCTs in this analysis 1 RCT had crossover design	**Pain relief by subjective assessment** 18/31 (58%) with low-frequency TENS 15/32 (47%) with placebo TENS or tablet	OR 1.8 95% CI 0.6 to 5.1	⟷	Not significant
[24] Systematic review	20 women with primary dysmenorrhoea Data from 1 RCT	**Pain relief** with low-frequency TENS with placebo TENS or tablet Absolute results not reported	P <0.05	○○○	low-frequency TENS
Need for additional medication					
[24] Systematic review	24 women with primary dysmenorrhoea Data from 1 RCT RCT had crossover multi-arm design	**Mean number of additional tablets of analgesic used** 3.7 with low-frequency TENS 6.8 with placebo TENS or tablet	WMD –3.1 tablets 95% CI –5.5 tablets to –0.7 tablets Randomisation and blinding unclear	○○○	low-frequency TENS

Daily activities and work

Low-frequency TENS compared with placebo We don't know whether low-frequency TENS is more effective than placebo TENS at reducing absence from work or school in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Absence from work/school					
[24] Systematic review	24 women with primary dysmenorrhoea Data from 1 RCT RCT had crossover multi-arm design	**Mean hours of absence from work or school** 1.23 hours with low-frequency TENS 1.42 hours with placebo TENS or tablet	WMD –0.2 hours 95% CI –0.6 hours to +0.2 hours Randomisation and blinding unclear	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] Systematic review	21 women with primary dysmenorrhoea Data from 1 RCT	**Adverse effects** 0/10 (0%) with low-frequency TENS 0/11 (0%) with placebo TENS or tablet There were no reported adverse effects from low-frequency TENS or placebo TENS			

High-frequency TENS versus low-frequency TENS:

We found one systematic review (search date 2009, 3 RCTs) in women with primary dysmenorrhoea. [24]

Pain

High-frequency TENS compared with low-frequency TENS We don't know whether high-frequency TENS is more effective than low-frequency TENS at reducing pain in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[24] Systematic review	21 women with primary dysmenorrhoea Data from 1 RCT RCT had crossover design	**Proportion of women with pain relief measured by subjective assessment** 16/21 (76%) with high-frequency TENS 9/21 (43%) with low-frequency TENS Post-crossover results	OR 3.9 95% CI 1.1 to 13.0	●●○	high-frequency TENS
Need for additional medication					
[24] Systematic review	24 women with primary dysmenorrhoea Data from 1 RCT RCT had crossover multi-arm design	**Mean number of additional analgesic tablets taken** 6.9 with high-frequency TENS 3.7 with low-frequency TENS	WMD 3.2 tablets 95% CI 0.5 tablets to 5.9 tablets Randomisation and blinding unclear	○○○	low-frequency TENS

Daily activities and work

High-frequency TENS compared with low-frequency TENS We don't know whether high-frequency TENS is more effective than low-frequency TENS at reducing absence from work or school in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Absence from work or school					
[24] Systematic review	24 women with primary dysmenorrhoea Data from 1 RCT RCT had crossover multi-arm design	**Mean hours of absence from work or school** 1.46 hours with high-frequency TENS 1.23 hours with low-frequency TENS	WMD +0.2 hours 95% CI –0.2 hours to +0.6 hours Randomisation and blinding unclear	⟷	Not significant

Adverse effects

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

High-frequency TENS versus NSAIDs:

We found one systematic review (search date 2009, 2 RCTs) [24] in women with primary dysmenorrhoea. One of the included RCTs did not meet *Clinical Evidence* inclusion criteria (see comment). [26]

Pain

High-frequency TENS compared with NSAIDs High-frequency TENS may be less effective than ibuprofen NSAIDs at reducing pain in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[27] RCT **Crossover design** **3-armed trial**	32 women In review [24] The remaining arm evaluated placebo	**Proportion of women experiencing pain relief** 14/32 (44%) with high-frequency TENS 24/32 (75%) with ibuprofen	OR 0.26 95% CI 0.09 to 0.75	●●○	ibuprofen

Daily activities and work

No data from the following reference on this outcome. [27]

Adverse effects

No data from the following reference on this outcome. [27]

Further information on studies

[24] **High-frequency TENS versus low-frequency TENS:** One additional RCT, which could not be included in the meta-analysis, found that low-frequency TENS significantly reduced pain compared with high-frequency TENS (P <0.05).

Comment:

High-frequency TENS versus NSAIDs:
One RCT (open label, crossover design, 12 women), which did not meet *Clinical Evidence* inclusion criteria, compared high-frequency TENS versus naproxen and found no significant difference in pain relief between groups. [26] It reported an increase in the number of adverse effects experienced by women with high-frequency TENS compared with naproxen, particularly pain from TENS treatment. The women who reported pain from TENS stated that they were prepared to accept the short-term pain from the treatment in return for relief of dysmenorrhoea. [24]

OPTION VITAMIN E

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- Vitamin E may reduce pain compared with placebo in young women with primary dysmenorrhoea.

Benefits and harms

Vitamin E versus placebo:

We found one systematic review (search date 2002, 2 RCTs) [28] and one subsequent RCT. [29]

Pain

Compared with placebo Vitamin E tablets may be more effective at reducing pain at 2 to 4 months in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[30] RCT	100 adolescent women with primary dysmenorrhoea, aged 16 to 18 years In review [28]	**Pain assessed by median 10 cm visual analogue scale pain scores , 2 months** 3.5 cm with vitamin E (500 units/day [about 333 mg], from 2 days before expected menses until the third day of menses) 4.3 cm with placebo	P = 0.02	○○○	vitamin E
[28] Systematic review	100 women aged 18 to 21 years Data from 1 RCT	**Proportion with improvement in pain , 3 months** 34/50 (68%) with vitamin E (50 mg three times daily from 10 days before expected menses until the fourth day of menses) 9/50 (18%) with placebo	Significance assessment not performed This RCT may not have been truly randomised (alternate allocation)		
[29] RCT	278 adolescent women with primary dysmenorrhoea aged 15 to 17 years	**Median visual analogue scale score , at 4 months** 0.5 with vitamin E (200 units/day, from 2 days before expected menses until the third day of menses) 6.0 with placebo Pain severity on a score from 0 to 10, where 0–3.0 = mild, 3.1–6.0 = moderate, and 6.1–10.0 = severe	P <0.001	○○○	vitamin E
[29] RCT	278 adolescent women with primary dysmenorrhoea aged 15 to 17 years	**Mean pain duration , at 4 months** 1.6 hours with vitamin E (200 units/day, from 2 days before expected menses until the third day of menses) 17.0 hours with placebo	P <0.0001	○○○	vitamin E

Daily activities and work

No data from the following reference on this outcome. [28] [29]

Adverse effects

No data from the following reference on this outcome. [28] [29]

Further information on studies

Comment: We found one systematic review (search date 2000), which identified one RCT (crossover design, 50 women) comparing vitamin E plus ibuprofen versus ibuprofen alone. However, the RCT was open label and so does not fulfil *Clinical Evidence* inclusion criteria. It found no significant difference between vitamin E plus ibuprofen and ibuprofen alone in pain relief. [21]

OPTION ACUPUNCTURE

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- We don't know whether acupuncture reduces dysmenorrhoea.

Benefits and harms

Acupuncture versus placebo acupuncture or no treatment:

We found one systematic review (search date 2008, 2 RCTs) comparing acupuncture versus placebo acupuncture or no treatment for primary dysmenorrhoea. [16] The review did not pool the data because of heterogeneity of the RCTs. [16] It did not give information on follow-up or absolute results for the individual RCTs (see further information on studies). We found two subsequent RCTs. [31] [32]

Pain

Compared with placebo acupuncture or no treatment Acupuncture may be more effective than placebo acupuncture or no treatment at reducing pain in women with dysmenorrhoea, but we don't know whether laser acupuncture is more effective than placebo laser acupuncture (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[33] RCT **4-armed trial**	43 women In review [16]	**Proportion of women with reduction in pain of more than half the admission score , after 3 months** 10/11 (91%) with weekly acupuncture (30–40 minutes) for 3 weeks of each menstrual cycle 4/11 (36%) with placebo acupuncture 1/10 (10%) with monthly medical visits 2/11 (18%) with no medical treatment Pain was assessed using non-validated pain scales and symptom questionnaires	P <0.05 for acupuncture *v* all other treatments	○○○	acupuncture
[31] RCT **Crossover design**	201 women with primary or secondary dysmenorrhoea aged 18 years or older, number of women with primary dysmenorrhoea not reported	**Average pain intensity , after 3 months** 3.1 with acupuncture 5.4 with waiting list control The acupuncture group received 15 sessions of treatment over 3 months Pre-crossover results Pain score on numeric rating scale (scale 0 = no pain to 10 = maximal pain)	Difference –2.3 P <0.001	○○○	acupuncture
[32] RCT	48 women with primary dysmenorrhoea, aged 18 to 50 years	**Proportion of women with successful pain reduction** 3/18 (17%) with laser acupuncture for 3 menstrual cycles (total 8 sessions of 20 minutes each)	OR 1.25 95% CI 0.22 to 8.85	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		6/30 (20%) with placebo laser acupuncture for 3 menstrual cycles (total 8 sessions of 20 minutes each) Acupuncture was applied to 8 acupuncture points Successful pain reduction defined as a 50% reduction in mean menstrual pain, assessed by visual analogue scale, from baseline			

Daily activities and work

No data from the following reference on this outcome. [33] [31] [32]

Quality of life

Compared with placebo acupuncture or no treatment Acupuncture may be more effective than waiting list control at improving some measures of quality of life (assessed by the Short-Form [SF]-36 questionnaire) in women with dysmenorrhoea; however, we don't know about all measures because of baseline differences between groups (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[31] RCT **Crossover design**	201 women with primary or secondary dysmenorrhoea aged 18 years or older, number of women with primary dysmenorrhoea not reported	**Quality of life scores (assessed by SF-36) , after 3 months** with acupuncture with waiting list control The acupuncture group received 15 sessions of treatment over 3 months; pre-crossover results Total SF-36 quality-of-life score not reported	Acupuncture significantly improved scores on all SF-36 subscales, except general health perception, compared with no treatment: all subscales except for general health perception P <0.001 to P = 0.021 Result should be interpreted with caution because of baseline differences between groups in quality-of-life measures (see further information on studies)		

No data from the following reference on this outcome. [33] [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[31] RCT **Crossover design**	Women with primary or secondary dysmenorrhoea aged 18 years or older, number of women with primary dysmenorrhoea not reported	**Adverse effects** with acupuncture with waiting list control Reported adverse effects in 59 (12%) women who received acupuncture. Adverse effects with acupuncture included minor local bleeding or haematoma, and needling pain. No life-threatening adverse effects were reported	Analysis included women who were randomised to receive acupuncture as part of the RCT, and women who were not randomised as part of the study but who also received acupuncture		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[32] RCT	48 women with primary dysmenorrhoea, aged 18 to 50 years	**Adverse effects** with laser acupuncture with placebo laser acupuncture The RCT found that no adverse effects were reported			

No data from the following reference on this outcome. [33]

Acupuncture versus NSAIDs:

We found one systematic review (search date 2008), which found two RCTs comparing acupuncture versus indometacin and one three-armed RCT comparing acupuncture versus placebo or versus ibuprofen (see further information on studies). [16]

Pain

Compared with NSAIDs Acupuncture may be more effective than indometacin at improving pain scores in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[34] RCT	120 women with primary dysmenorrhoea In review [16]	**Change in pain score from baseline (composite pain score, range not defined) , after 3 menstrual periods** From 11.26 to 1.94 with acupuncture (superficial needling at Sanyinjiao SP-6) for 2 days each menstrual period From 11.02 to 4.49 with indometacin (oral) for 2 days each menstrual period	P <0.001 (between groups after treatment)	○○○	acupuncture

Daily activities and work

No data from the following reference on this outcome. [16] [34]

Adverse effects

No data from the following reference on this outcome. [16] [34]

Acupuncture versus Chinese herbal medicine:

See option on herbal remedies, p 41 .

Further information on studies

[16] A meta-analysis could not be carried out because of heterogeneity of the included RCTs in types (acupuncture, acupressure, acupoint injections, and moxibustion) and duration of treatments. None of the 32 included RCTs were considered by the review as high quality, 6 were of average quality, and 26 were of low quality. Only three RCTs reported a sample size calculation, one was double-blind, three RCTs reported intention-to-treat analyses, and the follow-up was >1 year in only 4 of 32 RCTs. The systematic review concluded that because of the small sample sizes of included trials and the poor methodological quality, there is no convincing evidence for acupuncture-related treatments being an effective treatment for primary dysmenorrhoea. **Acupuncture versus placebo acupuncture or no treatment:** The review reported that one RCT (122 women) compared acupuncture versus placebo or versus ibuprofen. It reported that acupuncture significantly improved pain relief compared with placebo. However, this RCT was written in Chinese and we are awaiting full-text translation of this trial and will assess it for inclusion at the next update. **Acupuncture versus NSAIDs:** The review reported that one RCT (58 women) found no significant difference between auricular acupuncture and indometacin in pain relief. However, it was unclear from the review whether this RCT in fact examined acupuncture or acupressure, and we were unable to access the full text of this RCT. The review reported that another RCT (122 women) found that acupuncture significantly improved pain relief compared with ibuprofen. However, this study was written in Chinese and we are awaiting full-text translation of this study and will assess it for inclusion at the next update.

[31] The waiting list control group subsequently crossed over to receive acupuncture from 3 to 6 months. However, we have reported the pre-crossover results here. The RCT reported that there were no significant baseline differences between groups except for significantly lower scores on the physical component scale, and subscales of physical functioning and bodily pain of the Short-Form (SF)-36 questionnaire with waiting list control compared with acupuncture.

Comment: None.

OPTION BEHAVIOURAL INTERVENTIONS

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- Relaxation may be better than no treatment at relieving dysmenorrhoea.

Benefits and harms

Relaxation treatment versus no treatment/waiting list control:

We found two systematic reviews (search date 2002, 4 RCTs; [28] and search date 2005, 5 RCTs [35]) assessing behavioural interventions in women with dysmenorrhoea. The systematic reviews did not carry out meta-analyses, and so we have reported the one RCT that met *Clinical Evidence* inclusion criteria (see comment for information on other studies).

Pain

Relaxation treatment compared with waiting list control Relaxation treatment may be more effective at reducing symptoms of dysmenorrhoea in women with spasmodic or congestive dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[36] RCT **3-armed trial**	69 women with congestive or spasmodic dysmenorrhoea In review [35] The remaining arm evaluated self-directed group discussion about menstruation Groups were divided into women with congestive or spasmodic dysmenorrhoea using the	**Dysmenorrhoeic symptoms** with relaxation treatment plus positive imagery regarding menstruation with waiting list control Absolute results not reported Reported significantly improved with relaxation treatment compared with waiting list control in women with spasmodic or congestive dysmenorrhoea	P <0.01	○○○	relaxation treatment plus positive imagery regarding menstruation

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Menstrual Symptom Questionnaire				
[36] RCT **3-armed trial**	69 women with congestive or spasmodic dysmenorrhoea In review [35] Groups were divided into women with congestive or spasmodic dysmenorrhoea using the Menstrual Symptom Questionnaire	**Pain** with relaxation treatment plus positive imagery regarding menstruation with self-directed group discussion about menstruation with waiting list control Absolute results not reported Reported that only the women with spasmodic dysmenorrhoea experienced significantly less pain with relaxation compared with either group discussion or waiting list control	P <0.001 in women with spasmodic dysmenorrhoea	○○○	relaxation treatment plus positive imagery regarding menstruation in women with spasmodic dysmenorrhoea

Daily activities and work

No data from the following reference on this outcome. [36]

Adverse effects

No data from the following reference on this outcome. [36]

Further information on studies

[36] In the RCT on relaxation, spasmodic dysmenorrhoea was defined as spasms of pain mainly in the abdomen, and congestive dysmenorrhoea was defined as a dull aching pain in the lower abdomen and other areas of the body. However, the classification of dysmenorrhoea into spasmodic and congestive categories is no longer commonly used and has little meaning.

Comment: The first systematic review [28] identified one RCT comparing a training group that participated in 30 minutes of aerobic exercise 3 days a week for 3 months versus a sedentary control group. [37] The RCT analysed results for the 26/36 (72%) women who completed the trial and so did not meet *Clinical Evidence* inclusion criteria. It found that aerobic exercise significantly lowered Menstrual Distress Questionnaire scores. The systematic review included three additional studies comparing different types of exercise that it described as RCTs; however, there was no mention of randomisation in the original publications. [28] Therefore, we have not included these studies.

The second review [35] identified one RCT, which examined the effectiveness of relaxation or relaxation plus imagery versus waiting list control in women with premenstrual or menstrual discomfort for at least 2 years. [38] However, the review was unable to extract data suitable for analysis, and the original publication of the RCT [38] did not give sufficient information to appraise this study for inclusion in this *Clinical Evidence* review. The RCT was an incomplete factorial design study. It analysed women with spasmodic symptoms (33 women) and congestive symptoms (29 women) separately. In the case of women with spasmodic symptoms, it compared three treatment arms: relaxation treatment, relaxation plus imagery, and waiting list control. In the case of women with congestive symptoms, it compared two treatment arms: relaxation treatment and waiting list control.

It reported that 88 women were interviewed, but did not report how many women were randomised, or the method of randomisation, and so we could not determine the follow-up from this study. The review reported that the RCT did not present data suitable for meta-analysis. However, it commented that relaxation with imagery or relaxation alone were effective treatments for reducing symptom scores compared with control in women with spasmodic symptoms, but found no difference in women with congestive symptoms (no clear data other than MANOVA F scores presented in the RCT).

Although there is some evidence from RCTs that behavioural interventions may be effective for dysmenorrhoea, these results should be viewed with caution as they varied greatly between trials because of inconsistency in the reporting of data, small trial size, poor methodological quality, and age of the trials.

OPTION CONTRACEPTIVES (COMBINED ORAL)

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- Combined oral contraceptives may be more effective at reducing pain in women with primary dysmenorrhoea compared with placebo; however, few trials have been of good quality.

Benefits and harms

Combined oral contraceptives versus placebo/no treatment:

We found one systematic review (search date 2008, 6 RCTs) comparing combined oral contraceptives versus placebo/no treatment for primary dysmenorrhoea. [39] Two RCTs examined low-dose oestrogen plus progestogen and 4 RCTs examined medium-dose oestrogen plus progestogen. [39]

Pain

Compared with placebo Combined oral contraceptives may be more effective at reducing pain in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[39] Systematic review	497 women with primary dysmenorrhoea 6 RCTs in this analysis	**Proportion of women with pain improvement , after 2 to 6 cycles** 142/307 (46%) with combined oral contraceptives (OCP) 51/190 (27%) with placebo or no treatment	OR 2.01 95% CI 1.32 to 3.08 Significant statistical heterogeneity in this analysis, see further information on studies	●●○	OCP

Daily activities and work

No data from the following reference on this outcome. [39]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[39] Systematic review	165 women with primary dysmenorrhoea 2 RCTs in this analysis	**Proportion of people who experienced any adverse effect** 44/87 (51%) with combined oral contraceptives (OCP) 36/78 (46%) with placebo or no treatment	OR 1.45 95% 0.71 to 2.94	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Adverse effects included nausea, headaches, and weight gain			

Further information on studies

[39] Most of the RCTs identified by the systematic review had weak methodology, including inadequate blinding. RCTs included women with a range of severities of dysmenorrhoea and used different ways of assessing pain or pain relief. Follow-up length and the timing of outcome assessment also differed between RCTs. There was significant statistical heterogeneity in the analysis of proportion of women with pain improvement (I^2 = 64%, P = 0.02). A sensitivity analysis, removing RCTs with inadequate allocation concealment, found that heterogeneity was no longer significant but did not affect the significance of the result.

Comment: None.

OPTION FISH OIL

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- We don't know whether fish oil reduces dysmenorrhoea.

Benefits and harms

Fish oil versus placebo:

We found one systematic review (search date 2000, 1 RCT) [21] and one additional RCT, [40] which compared fish oil versus placebo.

Pain

Compared with placebo We don't know whether fish oil is more effective than placebo at reducing pain in women with dysmenorrhoea at 3 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[21] Systematic review	42 women Data from 1 RCT RCT had crossover design	**Menstrual symptom scores** with fish oil capsules (twice daily for 1 month) with placebo (twice daily for 1 month) Absolute results not reported Reported lower with fish oil Results post-crossover	P = 0.04	○○○	fish oil
[40] RCT **4-armed trial**	78 women with primary dysmenorrhoea The remaining arms evaluated fish oil plus vitamin B_{12}, and seal oil (higher in saturated fat than fish oil)	**Mean reduction in pain scores (measured on a 10 cm visual analogue scale)** 0.15 cm with fish oil (0.5–1.0 g five times daily) for a minimum of 3 months 0.19 cm with placebo for a minimum of 3 months	P = 0.62	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional pain medication					
[21] Systematic review	42 women Data from 1 RCT RCT had crossover design	**Mean number of tablets of ibuprofen (200 mg) taken** 4.7 tablets with fish oil capsules (twice daily for 1 month) 10.1 tablets with placebo (twice daily for 1 month) Results post-crossover	P = 0.015	○○○	fish oil

Daily activities and work

No data from the following reference on this outcome. [21] [40]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] Systematic review	42 women Data from 1 RCT RCT had crossover design	**Number of women reporting adverse effects** 3 with fish oil capsules (twice daily for 1 month) 0 with placebo (twice daily for 1 month) 2 women taking fish oils reported nausea and 1 woman reported acne			
[40] RCT **4-armed trial**	78 women with primary dysmenorrhoea The remaining arms evaluated fish oil plus vitamin B_{12}, and seal oil (higher in saturated fat than fish oil)	**Adverse effects** with fish oil (0.5–1.0 g five times daily) for a minimum of 3 months with placebo for a minimum of 3 months Absolute results not reported Adverse effects reported in 8 women in the study included stomach upset, slight nausea, and bad taste			

Further information on studies

[21] [40] Both RCTs included women with dysmenorrhoea and no additional health problems. This could include women with either primary or secondary dysmenorrhoea.

[21] The results from the RCT identified by the review refer to the average of the two groups after the allocated treatments were crossed over, and should be interpreted with caution, as treatment effects may persist after crossover.

Comment: None.

OPTION HERBAL REMEDIES OTHER THAN TOKI-SHAKUYAKU-SAN

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- Iranian herbal remedy (saffron, celery, and anise) may reduce pain compared with placebo. We don't know whether Chinese herbal remedies are beneficial compared with placebo, but we found limited evidence that they may be effective compared with other treatments for dysmenorrhoea.

Benefits and harms

Chinese herbal medicine versus placebo/no treatment:

We found one systematic review (search date 2007, 4 RCTs, see further information on studies) [15] and one subsequent RCT. [41]

Pain

Chinese herbal medicine compared placebo/no treatment We don't know whether Chinese herbal remedies are more effective at reducing pain in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[15] Systematic review	90 women with primary dysmenorrhoea Data from 1 RCT	**Proportion of women with pain relief , at 3 months** 5/60 (8%) with Chinese herbal medicine (data from 2 different regimens combined) 0/30 (0%) with placebo	RR 5.59 95% CI 0.32 to 97.87	⟷	Not significant
[15] Systematic review	36 women with primary dysmenorrhoea Data from 1 RCT	**Maximum pain intensity score** 61 with Chinese herbal medicine 60 with placebo Pain assessed by visual analogue scale (VAS; scale not defined)	Mean difference +1.00 95% CI –17.95 to +19.95	⟷	Not significant
[41] RCT	78 women with primary dysmenorrhoea	**Mean overall pain intensity , over first 5 days of cycle 1** 3.54 with Chinese herbal medicine (Four Agents Decoction [Si Wu Tang]) for 5 days starting from the onset of bleeding or pain 3.77 with placebo for 5 days starting from the onset of bleeding or pain Pain intensity assessed by VAS; scale from 0 cm (no pain) to 10 cm (severe pain)	Reported as not significant P value not reported	⟷	Not significant
[41] RCT	78 women with primary dysmenorrhoea	**Mean overall pain intensity , over first 5 days of cycle 2** 3.91 with Chinese herbal medicine (Four Agents Decoction [Si Wu Tang]) for 5 days starting from the onset of bleeding or pain 3.25 with placebo for 5 days starting from the onset of bleeding or pain Pain intensity assessed by VAS; scale from 0 cm (no pain) to 10 cm (severe pain)	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[41] RCT	78 women with primary dysmenorrhoea	**Mean overall pain intensity , over first 5 days of cycle 3** 3.75 with Chinese herbal medicine (Four Agents Decoction [Si Wu Tang]) for 5 days starting from the onset of bleeding or pain 3.50 with placebo for 5 days starting from the onset of bleeding or pain Pain intensity assessed by VAS; scale from 0 cm (no pain) to 10 cm (severe pain)	Reported as not significant P value not reported	⟷	Not significant
[41] RCT	78 women with primary dysmenorrhoea	**Peak pain (maximal single-day pain intensity) , over first 5 days of cycle 1** 4.49 with Chinese herbal medicine (Four Agents Decoction [Si Wu Tang]) for 5 days starting from the onset of bleeding or pain 4.56 with placebo for 5 days starting from the onset of bleeding or pain Pain intensity assessed by VAS; scale from 0 cm (no pain) to 10 cm (severe pain)	Reported as not significant P value not reported	⟷	Not significant
[41] RCT	78 women with primary dysmenorrhoea	**Peak pain (maximal single-day pain intensity) , over first 5 days of cycle 2** 4.94 with Chinese herbal medicine (Four Agents Decoction [Si Wu Tang]) for 5 days starting from the onset of bleeding or pain 3.94 with placebo for 5 days starting from the onset of bleeding or pain Pain intensity assessed by VAS; scale from 0 cm (no pain) to 10 cm (severe pain)	Reported as not significant P value not reported	⟷	Not significant
[41] RCT	78 women with primary dysmenorrhoea	**Peak pain (maximal single-day pain intensity) , over first 5 days of cycle 3** 3.75 with Chinese herbal medicine (Four Agents Decoction [Si Wu Tang]) for 5 days starting from the onset of bleeding or pain, 3.50 with placebo for 5 days starting from the onset of bleeding or pain Pain intensity assessed by VAS; scale from 0 cm (no pain) to 10 cm (severe pain)	Reported as not significant P value not reported	⟷	Not significant

Daily activities and work

No data from the following reference on this outcome. [15] [41]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] Systematic review	166 women with primary dysmenorrhoea 3 RCTs in this analysis	**Adverse effects** 13/97 (13%) with Chinese herbal medicine 18/69 (26%) with placebo The review reported no serious adverse effects in any of the 3 RCTs	RR 0.81 95% CI 0.61 to 1.07	⟷	Not significant
[41] RCT	78 women with primary dysmenorrhoea	**Adverse effects (described as inner heat reaction, abnormal menses, PMS-like symptoms, respiratory disorder, and gastrointestinal disorder)** with Chinese herbal medicine (Four Agents Decoction [Si Wu Tang]) for 5 days starting from the onset of bleeding or pain, for 4 cycles with placebo for 5 days starting from the onset of bleeding or pain, for 4 cycles Absolute results not reported Reported similar rates with both groups	Statistical analysis not reported		

Chinese herbal medicine versus NSAIDs:

We found one systematic review (search date 2007, 14 RCTs) comparing Chinese herbal medicine versus conventional treatment (predominantly NSAIDs, see further information on studies). [15]

Pain

Chinese herbal medicine compared with NSAIDs Chinese herbal medicine may be more effective than conventional treatments (predominantly NSAIDs) at improving pain relief and overall symptoms in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[15] Systematic review	1441 women with primary dysmenorrhoea 14 RCTs in this analysis	**Proportion of women with pain relief** 538/768 (70%) with Chinese herbal medicine 244/673 (36%) with conventional treatment (predominantly NSAIDs, see further information on studies)	RR 1.99 95% CI 1.52 to 2.60 The review found significant statistical heterogeneity in this analysis (I^2 = 82%, P <0.00001), which was not explained by the herbal formula, RCT quality, or follow-up time	●○○	Chinese herbal medicine
[15] Systematic review	482 women with primary dysmenorrhoea 6 RCTs in this analysis	**Proportion of women with improvement in overall symptoms** 150/253 (59%) with Chinese herbal medicine 63/229 (28%) with conventional treatment (predominantly	RR 2.17 95% CI 1.73 to 2.73	●●○	Chinese herbal medicine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		NSAIDs, see further information on studies)			

Daily activities and work

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

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] Systematic review	Women with primary dysmenorrhoea	**Adverse effects** with Chinese herbal medicine with conventional treatment (predominantly NSAIDs, see further information on studies) The review gave no information on adverse effects, other than it reported that 2 RCTs (418 people) found no adverse effects with either Chinese herbal medicine or conventional treatment			

Chinese herbal medicine versus acupuncture:

We found one systematic review (search date 2007, 2 RCTs) comparing Chinese herbal medicine with acupuncture. [15]

Pain

Chinese herbal medicine compared with acupuncture Chinese herbal medicine may be more effective at improving pain relief in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[15] Systematic review	156 women 2 RCTs in this analysis	**Pain relief** 40/88 (45%) with Chinese herbal medicine 18/68 (26%) with acupuncture	RR 1.75 95% CI 1.09 to 2.82 The review reported that the RCTs did not state the method of randomisation, blinding, or follow-up	●○○	Chinese herbal medicine

Daily activities and work

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

Adverse effects

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

Chinese herbal medicine versus topical heat:

We found one systematic review (search date 2007, 1 RCT) comparing Chinese herbal medicine with heat compression (using a hot-water bottle). [15]

Pain

Chinese herbal medicine compared with topical heat Chinese herbal medicine may be more effective than heat compression (using a hot-water bottle) at improving pain relief in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[15] Systematic review	55 women Data from 1 RCT	**Proportion of women with cure (defined as disappearance of abdominal pain symptoms and no relapse during 3 cycles of follow-up)** 27/35 (77%) with Chinese herbal medicine 0/20 (0%) with heat compression (using a hot-water bottle)	RR 32.08 95% CI 2.06 to 499.18 The review reported that the RCT did not state the method of randomisation or follow-up	●●●	Chinese herbal medicine

Daily activities and work

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

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] Systematic review	55 women Data from 1 RCT	**Adverse effects** with Chinese herbal medicine with heat compression (using a hot-water bottle) The review reported that there were no adverse effects with either Chinese herbal medicine or heat compression			

Chinese herbal medicine versus acupressure:

See option on acupressure, p 12 .

Iranian herbal medicine versus placebo/no treatment:

We found one RCT comparing Iranian herbal medicine (highly purified saffron, celery seed, and anise) and mefenamic acid versus placebo. [12]

Pain

Iranian herbal medicine compared with placebo Iranian herbal medicine seems more effective at reducing pain scores and duration of pain after 2 or 3 months in women with dysmenorrhoea (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[12] RCT **3-armed trial**	180 women, aged 18 to 30 years, with primary dysmenorrhoea The remaining arm evaluated mefenamic acid	**Pain scores, assessed by visual analogue scale (VAS; scale 0–10, higher scores indicating more severe pain) , 2 months** 3 with Iranian herbal medicine (highly purified saffron, celery seed, and anise) 5 with placebo 108 women in analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding	P <0.001	○○○	Iranian herbal medicine
[12] RCT **3-armed trial**	180 women, aged 18 to 30 years, with primary dysmenorrhoea The remaining arm evaluated mefenamic acid	**Pain scores, assessed by VAS (scale 0–10, higher scores indicating more severe pain) , 3 months** 0.5 with Iranian herbal medicine (highly purified saffron, celery seed, and anise) 6 with placebo 108 women in analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding	P <0.001	○○○	Iranian herbal medicine
[12] RCT **3-armed trial**	180 women, aged 18 to 30 years, with primary dysmenorrhoea The remaining arm evaluated mefenamic acid	**Pain duration , 2 months** 2.3 with Iranian herbal medicine (highly purified saffron, celery seed, and anise) 16.2 with placebo 108 women in analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding	P <0.001	○○○	Iranian herbal medicine
[12] RCT **3-armed trial**	180 women, aged 18 to 30 years, with primary dysmenorrhoea The remaining arm evaluated mefenamic acid	**Pain duration , 3 months** 2.4 hours with Iranian herbal medicine (highly purified saffron, celery seed, and anise) 15.4 hours with placebo 108 women in analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding	P <0.001	○○○	Iranian herbal medicine

Daily activities and work

No data from the following reference on this outcome. [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] RCT **3-armed trial**	180 women, aged 18 to 30 years, with primary dysmenorrhoea The remaining arm evaluated mefenamic acid	**Adverse effects** with Iranian herbal medicine (highly purified saffron, celery seed, and anise) with placebo The RCT reported no adverse effects with Iranian herbal medicine			

Iranian herbal medicine versus mefenamic acid:

We found one RCT comparing Iranian herbal medicine (highly purified saffron, celery seed, and anise) and mefenamic acid versus placebo (see above). The RCT did not present a direct comparison between herbal medicine and mefenamic acid for the outcome of pain. [12]

Pain

Iranian herbal medicine compared with NSAIDs We don't know how effective Iranian herbal medicine and mefenamic acid are, compared with each other, at improving pain relief and duration of pain in women with dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[12] RCT **3-armed trial**	180 women, aged 18 to 30 years, with primary dysmenorrhoea The remaining arm evaluated placebo	**Pain scores, assessed by visual analogue scale (VAS; scale 0–10, higher scores indicating more severe pain) , 2 months** 3 with Iranian herbal medicine (highly purified saffron, celery seed, and anise) 3.6 with mefenamic acid 106 women in analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding	Significance not reported		
[12] RCT **3-armed trial**	180 women, aged 18 to 30 years, with primary dysmenorrhoea The remaining arm evaluated placebo	**Pain scores, assessed by VAS (scale 0–10, higher scores indicating more severe pain) , 3 months** 0.5 with Iranian herbal medicine (highly purified saffron, celery seed, and anise) 2.4 with mefenamic acid 106 women in analysis	Significance not reported		
[12] RCT	180 women, aged 18 to 30 years,	**Pain duration , 2 months**	Significance not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	with primary dysmenorrhoea The remaining arm evaluated placebo	2.3 hours with Iranian herbal medicine (highly purified saffron, celery seed, and anise) 3 hours with mefenamic acid 106 women in analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding			
[12] RCT **3-armed trial**	180 women, aged 18 to 30 years, with primary dysmenorrhoea The remaining arm evaluated placebo	**Pain duration , 3 months** 2.4 hours with Iranian herbal medicine (highly purified saffron, celery seed, and anise) 3 hours with mefenamic acid 106 women in analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding	Significance not reported		

Daily activities and work

No data from the following reference on this outcome. [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] RCT **3-armed trial**	180 women, aged 18 to 30 years, with primary dysmenorrhoea The remaining arm evaluated placebo	**Adverse effects** with Iranian herbal medicine (highly purified saffron, celery seed, and anise) with mefenamic acid The RCT reported nausea in 1 woman who received mefenamic acid			

Further information on studies

[15] **Chinese herbal medicine versus placebo/no treatment:** The review did not pool the data for pain relief from three RCTs comparing Chinese herbal medicine versus placebo. However, it reported details of study design and absolute numbers from the included RCTs. It reported that one RCT did not provide data suitable for meta-analysis. [15] The fourth RCT [42] identified by the review compared Chinese herbal medicine (rose tea) versus no treatment. However, this RCT was open label, and so does not fulfil *Clinical Evidence* inclusion criteria and we have not reported it further. **Chinese herbal medicine versus NSAIDs:** Conventional treatments included indometacin alone (8 RCTs), indometacin plus vitamin B6 with or without heat (2 RCTs), indometacin plus atropome (1 RCT), ibuprofen (2 RCTs), piroxicam (1 RCT).

Comment: **Ginger versus NSAIDs:** We found one blinded comparative trial (150 women with primary dysmenorrhoea, aged >18 years) comparing ginger rhizome powder (250 mg), mefenamic acid (250 mg), and ibuprofen (400 mg), each taken 4 times a day for 3 days at onset of menstrual periods. [43] Women were alternately allocated into each of the three groups. There were no significant differences between groups in baseline characteristics (P >0.05). A verbal multidimensional scoring system was used to assess the severity of primary dysmenorrhoea after one menstruation. At the end of treatment, severity of dysmenorrhoea decreased in all groups with no differences between the groups in severity of dysmenorrhoea, pain relief, or satisfaction with the treatment (P >0.05). No severe adverse effects were reported. [43]

OPTION MAGNETS

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- We don't know whether magnets reduce dysmenorrhoea.

Benefits and harms

Magnets:

We found no systematic review. We found one RCT (written in Korean); however, we were unable to access the full text of this RCT (see comment).

Further information on studies

Comment: The RCT (English abstract only; 23 women with primary dysmenorrhoea) compared an applied magnet (800–1299 gauss for 3 hours on the first day of pain) versus a control group that applied a non-magnet to the suprapubic area, lumbar area, and inner ankles. [44] The RCT found that magnet treatment significantly improved pain and symptom scores compared with control immediately after treatment. Magnet treatment also improved pain and symptom scores compared with control 3 hours after treatment. The English language abstract of the RCT did not present any information on adverse effects. [44]

OPTION SURGICAL INTERRUPTION OF PELVIC NERVE PATHWAYS

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- Surgical interruption of pelvic nerve pathways is not beneficial in treating dysmenorrhoea, and may be associated with adverse effects including constipation.
- Laparoscopic presacral neurectomy has been associated with constipation and advanced laparoscopic skills are needed to perform the procedure.

Benefits and harms

Laparoscopic uterine nerve ablation versus diagnostic laparoscopy:

We found one systematic review (search date 2004) reported in two publications, [45] [46] which examined surgical pelvic nerve interruption for primary and secondary dysmenorrhoea. Two RCTs identified by the review compared laparoscopic uterine nerve ablation (LUNA) versus diagnostic laparoscopy for women with primary dysmenorrhoea.

Pain

Laparoscopic uterine nerve ablation compared with diagnostic laparoscopy We don't know how laparoscopic uterine nerve ablation and diagnostic laparoscopy (control) compare for at reducing pain at 6 months but laparoscopic presacral neurectomy may be more effective at reducing pain at 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[45] Systematic review	68 women with primary dysmenorrhoea 2 RCTs in this analysis	**Pain relief , 6 months' follow-up postoperatively** 12/30 (40%) with laparoscopic uterine nerve ablation (LUNA) 11/38 (29%) with diagnostic laparoscopy	OR 1.43 95% CI 0.56 to 3.69	⟷	Not significant
[45] Systematic review	68 women with primary dysmenorrhoea 2 RCTs in this analysis	**Pain relief , 12 months** 13/30 (43%) with LUNA 4/38 (11%) with diagnostic laparoscopy	OR 6.12 95% CI 1.78 to 21.03	●●●	LUNA

Daily activities and work

No data from the following reference on this outcome. [45]

Adverse effects

No data from the following reference on this outcome. [45]

Laparoscopic uterine nerve ablation versus laparoscopic presacral neurectomy:

We found one systematic review (search date 2004) reported in two publications, [45] [46] which examined surgical pelvic nerve interruption for primary and secondary dysmenorrhoea. One RCT identified by the review compared laparoscopic uterine nerve ablation (LUNA) with laparoscopic presacral neurectomy (LPSN). [45]

Pain

Laparoscopic uterine nerve ablation compared with presacral neurectomy We don't know how effective laparoscopic uterine nerve ablation and presacral neurectomy are, compared with each other, at reducing pain at up to 6 months. However, laparoscopic presacral neurectomy may be more effective at reducing pain at 12 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[45] Systematic review	68 women with primary dysmenorrhoea Data from 1 RCT	**Pain relief , up to 6 months' follow-up** 29/35 (83%) with laparoscopic uterine nerve ablation (LUNA) 29/33 (88%) with laparoscopic presacral neurectomy (LPSN)	OR 0.67 95% CI 0.17 to 2.61	⟷	Not significant
[45] Systematic review	68 women with primary dysmenorrhoea Data from 1 RCT	**Pain relief , at 12 months' follow-up** 11/35 (31%) with LUNA 27/33 (82%) with LPSN	OR 0.10 95% CI 0.03 to 0.32	●●●	LPSN

Daily activities and work

No data from the following reference on this outcome. [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] Systematic review	68 women with primary dysmenorrhoea Data from 1 RCT	**Constipation** 0/35 (0%) with LUNA 31/33 (94%) with LPSN	OR 0.02 95% CI 0.01 to 0.06	●●●	LUNA

Further information on studies

[45] The review identified 6 additional RCTs that included women with dysmenorrhoea associated with endometriosis or uterine myomas, which is not the focus of this review. **Laparoscopic uterine nerve ablation versus diagnostic laparoscopy:** The review found no significant difference between groups in satisfaction rates at 12 months (1 RCT; 15/18 [83%] with LUNA *v* 22/32 [69%] with control; P >0.05).

Comment:

We found one subsequent RCT, which did not fulfil *Clinical Evidence* inclusion criteria because of low follow-up (<80%). [47] However, we have included a brief comment on this study because of the paucity of data on surgical treatments. The RCT (487 women with chronic pelvic pain [dysmenorrhoea, non-cyclical pain, dyspareunia, or multiple types of pain]) compared LUNA versus diagnostic laparoscopy alone. The RCT did not present a subgroup analysis in women with primary dysmenorrhoea; however, it reported on dysmenorrhoea pain as an outcome. It found no significant difference between LUNA and diagnostic laparoscopy in dysmenorrhoea pain at 12 months.

Clinical guide:
The current NICE guidance has stated that evidence on LUNA for chronic pelvic pain suggests that it is not efficacious and therefore should not be used. [48]

OPTION VITAMIN B12

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- We don't know whether vitamin B_{12} reduces dysmenorrhoea.

Benefits and harms

Vitamin B_{12} versus placebo:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION SPINAL MANIPULATION

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- Spinal manipulation may be no more effective than placebo at reducing pain after 1 month in women with primary dysmenorrhoea.

Benefits and harms

Spinal manipulation versus sham manipulation or no treatment:

We found one systematic review (search date 2006, 3 RCTs meeting *Clinical Evidence* inclusion criteria), which compared spinal manipulation versus placebo or no treatment. [49] The review did not perform a meta-analysis because of heterogeneity among the trials in methods of spinal manipulation used, parts of the spine manipulated, and duration of treatment.

Pain

High-velocity low-amplitude spinal manipulation compared with placebo manipulation We don't know whether high-velocity low-amplitude spinal manipulation is more effective at reducing pain in women with primary dysmenorrhoea at 1 month (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[49] Systematic review	137 women Data from 1 RCT	**Pain (as measured by mean change in 100 mm visual analogue scale [VAS] pain score) , after 1 menstrual cycle** 10.09 with high-velocity, low-amplitude (HVLA) manipulation 8.01 with placebo manipulation	WMD +2.08 95% CI –3.20 to +7.36	⟷	Not significant
[49] Systematic review	44 women Data from 1 RCT	**Pain intensity, as measured by a 10 cm VAS pain score , after 1 treatment and 1 menstrual cycle** 3.78 with HVLA manipulation 5.19 with placebo manipulation	WMD –1.41 95% CI –2.55 to –0.27	○○○	HVLA manipulation
[49] Systematic review	26 women Data from 1 RCT	**Pain intensity, assessed on a 10 cm VAS scale , at 3 months** 5.6 with Toftness manipulation for 3 months 3.4 with placebo manipulation for 3 months	WMD 2.20 95% CI 1.38 to 3.02	○○○	placebo manipulation
[49] Systematic review	26 women Data from 1 RCT	**Pain intensity, assessed on a 10 cm VAS scale , at 6 months** 1.7 with Toftness manipulation for 3 months 3.1 with placebo manipulation for 3 months	WMD –1.40 95% CI –2.21 to –0.59	○○○	Toftness manipulation

Daily activities and work

No data from the following reference on this outcome. [49]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[49] Systematic review	138 women Data from 1 RCT	**Proportion of women experiencing soreness in the lower back region , within 48 hours of the intervention** 3/69 (4%) with HVLA manipulation 2/69 (3%) with placebo manipulation Soreness resolved within 24 hours No other adverse effects were reported	RR 1.50 95% CI 0.26 to 8.70	⟷	Not significant

Further information on studies

[49] Two of the three RCTs included in the review had small sample sizes and methodological weaknesses, such as inadequate allocation concealment and lack of blinding of outcome assessors. The study receiving the highest methodological score was also the largest study, and was therefore considered to be the most reliable.

Comment: None.

OPTION **PROGESTOGENS (INTRAUTERINE)** New

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 57 .
- We don't know whether intrauterine progestogens reduce dysmenorrhoea.

Benefits and harms

Intrauterine progestogens:

We found one systematic review (search date 2005), which found no RCTs examining the effectiveness of intrauterine progestogens in women with primary dysmenorrhoea (see comment). [50]

Further information on studies

Comment: A 3-year observational study examined the acceptability of a long-term contraceptive levonorgestrel-releasing intrauterine system. This study did not fulfil *Clinical Evidence* inclusion criteria as it was not an RCT, and included women who required long-term contraception, rather than women with dysmenorrhoea. However, we have included a brief comment on it because it reported on the outcome of menstrual pain. It found that the proportion of women reporting menstrual pain was significantly reduced at 3 years compared with baseline (165 women in analysis: proportion of women with menstrual pain reduced from 60% at baseline to 29% at 3 years, P = 0.025). [51]

Levonorgestrel-releasing intrauterine system was originally developed as a method of contraception but is now licensed for use in menorrhagia. There are no RCTs looking at dysmenorrhoea as a primary outcome.

GLOSSARY

Behavioural interventions Treatments attempting modification of thought and beliefs (cognition) about symptoms and pain, or treatments that attempt modification of behavioural or physiological responses to symptoms, pain, or both; for example, relaxation and exercise.

Congestive dysmenorrhoea A dull aching pain in the lower abdomen as well as other areas of the body that may begin several days before menstruation and can include other premenstrual symptoms such as irritability. [52]

Double dummy Design pertaining to an RCT in which multiple treatments are compared (usually against a placebo) and the treatments have dissimilar presentations. Each participant will receive either active treatment or placebo for each treatment. Because multiple treatments are being compared (at least 2), it allows identification of treatment effects against placebo, as well as the additive effects of treatments.

Laparoscopic presacral neurectomy (LPSN) Involves the total removal of the presacral nerves lying within the boundaries of the interiliac triangle. This procedure interrupts most of the cervical sensory nerve fibres and is used to diminish uterine pain.

Laparoscopic uterine nerve ablation (LUNA) Involves laparoscopic surgery to transect (usually involves cutting and then electrocauterisation) the uterosacral ligaments at their insertion into the cervix. This procedure interrupts most of the cervical sensory nerve fibres and is used to diminish uterine pain.

Placebo acupuncture Also known as sham acupuncture, this is a commonly used control intervention involving the use of acupuncture needles to stimulate non-acupuncture points in areas outside of Chinese meridians. These points can be identified by a point detector as areas of the skin that do not have skin electrical activity similar to acupuncture points. There is some disagreement over correct needle placement, as placement of a needle in any position may elicit some biological response that can complicate the interpretation of results.

Placebo manipulation Also known as sham manipulation, this is a control intervention. The main principle is to use a non-therapeutic level of torque. There are two common techniques for placebo manipulation. In one, thrust is given but the posture of the participant is such that the mechanical torque of the manipulation is substantially reduced. In the other, an activator adjusting tool is used; this can make spinal adjustments using spring recoil, whereby the spring is set so that no force is exerted on the spine.

SPID-8 An outcome measure commonly used in pharmaceutical trials of treatments for pain. The difference in pain intensity from baseline up to 8 hours after dosing is measured. The SPID-8 is the sum of the pain intensity differences of all participants up to 8 hours after dosing. Pain intensity can be measured on any categorical scale, but typically a low score will mean less pain and a high score more pain.

Spasmodic dysmenorrhoea Spasms of acute pain that typically begin on the first day of menstruation. [26]

TOTPAR (TOPAR) score An outcome measure commonly used in pharmaceutical trials of treatment for pain. The pain relief scores for all participants at various time points after dosing are totalled and a mean calculated. Pain relief can be measured on any categorical scale, but typically a low score will mean less pain relief and a high score more pain relief.

TOTPAR-8 (TOPAR-8) score The same as TOTPAR (see above), but measured up to 8 hours after dosing.

Efficacy RCT A trial designed to study if an intervention works in ideal conditions (e.g., when people receive treatments exactly as prescribed). By contrast, effectiveness trials evaluate the effects of treatments in “real life” conditions. Analysis in efficacy trials usually involves only the participants who were fully compliant with the therapeutic regimen. The applicability of the results from efficacy trials may be limited because conditions are artificial and hence response may be different in real life situations.

High-velocity, low-amplitude (HVLA) manipulation A technique of spinal manipulation that uses high-velocity, low-amplitude thrusts to manipulate vertebral joints. The technique is designed to restore motion to a restricted joint and improve function. The physician positions the person at the barrier of restricted motion and then gives a rapid, accurate thrust in the direction of the restricted barrier to resolve the restriction and improve motion.

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.

Toftness manipulation A low-force technique of chiropractic adjustment that uses a sensometer to detect sites of abnormal electromagnetic radiation, and to determine which sites to adjust. Adjustment is then delivered using a metered, hand held-pressure applicator.

Transcutaneous electrical nerve stimulation (TENS) Electrodes are placed on the skin and different electrical pulse rates and intensities are used to stimulate the area. Low-frequency TENS (also referred to as acupuncture-

like TENS) usually consists of pulses delivered at 1 to 4 Hz at high intensity, so they evoke visible muscle fibre contractions. High-frequency TENS (conventional TENS) usually consists of pulses delivered at 50 to 120 Hz at a low intensity, so there are no muscle contractions.

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

Visual analogue scale A commonly used scale in pain assessment. It is a 10-cm horizontal or vertical line with word anchors at each end, such as "no pain" and "pain as bad as it could be". The person is asked to make a mark on the line to represent pain intensity. This mark is converted to distance in either centimetres or millimetres from the "no pain" anchor to give a pain score that can range from 0 to 10 cm or 0 to 100 mm.

SUBSTANTIVE CHANGES

Progestogens (intrauterine) New option added. [50] Categorised as Unknown effectiveness as we found no RCTs to assess its effects in women with primary dysmenorrhoea.

Acupressure New evidence added. [16] Categorisation unchanged (Likely to be beneficial).

Acupuncture New evidence added. [15] [16] [31] [32] [34] Categorisation unchanged (Unknown effectiveness). Because of the small sample sizes of included trials and their poor methodological quality, there remains no convincing evidence to assess whether acupuncture-related treatments are an effective treatment for primary dysmenorrhoea.

NSAIDs New evidence added. [10] [11] [12] [15] Categorisation unchanged (Beneficial).

Surgical interruption of pelvic nerve pathways Evidence reassessed. Categorisation changed (from Unknown effectiveness to Likely to be ineffective or harmful).

TENS New evidence added. [24] [25] Categorisation unchanged (Likely to be beneficial).

Topical heat New evidence added. [15] Categorisation unchanged (Likely to be beneficial).

Behavioural interventions New evidence added. [35] Categorisation changed (from Unknown effectiveness to Likely to be beneficial).

Contraception (combined oral) New evidence added. [39] Categorisation changed (from Unknown effectiveness to Likely to be beneficial).

Herbal remedies other than toki-shakuyaku-san New evidence added. [12] [15] [16] [41] Categorisation changed (from Unknown effectiveness to Likely to be beneficial).

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Pallavi Manish Latthe
Consultant Obstetrician and Gynaecologist
Birmingham Women's NHS Foundation Trust
Birmingham
UK

Rita Champaneria
Systematic reviewer
University of Birmingham
Birmingham
UK

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Disclaimer

GRADE **Evaluation of interventions for Dysmenorrhoea.**

Important outcomes			Daily activities and work, Pain, Quality of life						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments for primary dysmenorrhoea?									
19 (1175) [7] [8] [9] [10] [11] [12]	Pain	NSAIDs versus placebo	4	–2	0	0	0	Low	Quality points deducted for unclear randomisation methodology and reporting of results post-crossover
at least 4 (at least 229) [7]	Daily activities and work	NSAIDs versus placebo	4	–1	0	–1	0	Low	Quality point deducted for unclear randomisation methodology. Directness point deducted for inclusion of data on aspirin *v* placebo
6 (972) [7] [8] [9] [13]	Pain	Different NSAIDs versus each other	4	–2	0	–1	0	Very low	Quality points deducted for unclear randomisation methodology and reporting of results post-crossover. Directness point deducted for large number of comparators
2 (205) [18] [17]	Pain	Acupressure versus sham acupressure or no treatment	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for narrow inclusion criteria
1 (144) [18]	Pain	Acupressure versus NSAIDs	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for narrow inclusion criteria
9 (522) [20] [7]	Pain	Aspirin versus placebo	4	–2	–1	0	0	Very low	Quality points deducted for short follow-up and reporting of results post-crossover. Consistency point deducted for different results for different outcomes
at least 3 (at least 203) [20]	Daily activities and work	Aspirin versus placebo	4	–2	0	0	0	Low	Quality points deducted for short follow-up and reporting of results post-crossover
1 (30) [20]	Pain	Paracetamol versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting, and reporting of results post-crossover
1 (30) [20]	Pain	Paracetamol versus aspirin	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting, and reporting of results post-crossover
1 (32) [20]	Pain	Aspirin versus NSAIDs	4	–3	0	0	0	Very low	Quality point deducted for sparse data, incomplete reporting, and methodological weaknesses including short follow-up, and reporting of results post-crossover
2 (128) [7] [20]	**Pain**	Paracetamol versus NSAIDs	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting, and methodological weaknesses including short follow-up, and reporting of results post-crossover
1 (556) [21]	Pain	Thiamine versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for restricted population (Indian adolescent women)
1 (50) [21]	Pain	Toki-shakuyaku-san versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, unclear allocation methodology, and incomplete reporting of results
1 (40) [22]	Pain	Topical heat versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of volunteer women as well as those presenting for medical care

Important outcomes			Daily activities and work, Pain, Quality of life						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (41) [22]	Pain	Topical heat versus NSAIDs	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of volunteer women as well as those presenting for medical care
1 (301) [23]	Pain	Topical heat versus paracetamol	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and short follow-up
at least 3 (at least 75) [24] [25]	Pain	High-frequency TENS versus placebo TENS	4	–3	0	0	0	Very low	Quality points deducted for sparse data, reporting of results post-crossover, and uncertainty about randomisation and blinding
1 (24) [24]	Daily activities and work	High-frequency TENS versus placebo TENS	4	–3	0	0	0	Very low	Quality points deducted for sparse data and uncertainty about randomisation and blinding
1 (26) [25]	Quality of life	High-frequency TENS versus placebo TENS	4	–2	0	0	0	Low	Quality points deducted for sparse data and reporting of results post-crossover
4 (86) [24]	Pain	Low-frequency TENS versus placebo TENS or placebo tablet	4	–3	–1	0	0	Very low	Quality points deducted for sparse data, reporting of results post-crossover, and uncertainty about randomisation and blinding. Consistency point deducted for different results for different outcomes
1 (24) [24]	Daily activities and work	Low-frequency TENS versus placebo TENS or placebo tablet	4	–3	0	0	0	Very low	Quality points deducted for sparse data and uncertainty about randomisation and blinding
3 (at least 39) [24]	Pain	High-frequency TENS versus low-frequency TENS	4	–3	0	0	0	Very low	Quality points deducted for sparse data, reporting of results post-crossover, and uncertainty about randomisation and blinding
1 (24) [24]	Daily activities and work	High-frequency TENS versus low-frequency TENS	4	–3	0	0	0	Very low	Quality points deducted for sparse data and uncertainty about randomisation and blinding
1 (32) [27]	Pain	High-frequency TENS versus NSAIDs	4	–2	0	0	0	Low	Quality points deducted for sparse data and reporting of results after crossover
3 (478) [28] [30] [29]	Pain	Vitamin E versus placebo	4	–2	0	0	0	Low	Quality points deducted for uncertainty about method of randomisation and no significance assessment performed in 1 RCT
3 (292) [33] [31] [32]	Pain	Acupuncture versus placebo acupuncture or no treatment	4	0	0	–2	0	Low	Directness points deducted for uncertainty about method for assessing outcomes (use of non-validated pain scales in 1 RCT), inclusion of women with secondary dysmenorrhoea in 1 RCT, and large number of comparators
1 (201) [31]	Quality of life	Acupuncture versus placebo acupuncture or no treatment	4	–1	0	–1	0	Low	Quality point deducted for significant baseline differences. Directness point deducted for inclusion of women with secondary dysmenorrhoea
1 (120) [34]	Pain	Acupuncture versus NSAIDs	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (69) [36]	**Pain**	Relaxation treatment versus no treatment/waiting list control	4	–1	–1	–1	0	Very low	Quality point deducted for sparse data. Consistency point deducted for different results for subgroups. Directness point deducted for older classification of disease no longer used

Important outcomes			Daily activities and work, Pain, Quality of life						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
6 (497) [39]	Pain	Combined oral contraceptives versus placebo/no treatment	4	–1	–1	0	0	Low	Quality point deducted for methodological flaws in included RCTs. Consistency point deducted for statistical heterogeneity
2 (<120) [21] [40]	Pain	Fish oil versus placebo	4	–2	–1	–1	0	Very low	Quality points deducted for sparse data and reporting of results post-crossover. Consistency point deducted for conflicting results. Directness point deducted for uncertainty about diagnosis
3 (204) [15] [41]	Pain	Chinese herbal medicine versus placebo/no treatment	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of different regimens
14 (1441) [15]	Pain	Chinese herbal medicine versus NSAIDs	4	0	–1	–2	0	Very low	Consistency point deducted for statistical heterogeneity. Directness points deducted for large number of comparators and inclusion of additional treatments
2 (156) [15]	Pain	Chinese herbal medicine versus acupuncture	4	–3	0	0	0	Very low	Quality points deducted for sparse data and methodological weakness in RCTs (uncertainty about follow-up, randomisation method, and blinding)
1 (55) [15]	Pain	Chinese herbal medicine versus topical heat	4	–3	0	–1	+2	Low	Quality points deducted for sparse data and methodological weaknesses (uncertainty about follow-up and randomisation method). Directness point deducted for uncertainty about method of assessment of outcome. Effect-size points added for large effect size
1 (108) [12]	Pain	Iranian herbal medicine versus placebo/no treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (106) [12]	Pain	Iranian herbal medicine versus mefenamic acid	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for no direct statistical comparison between groups
2 (68) [45]	Pain	Laparoscopic uterine nerve ablation versus diagnostic laparoscopy	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for different results at different time points
1 (68) [45]	Pain	Laparoscopic uterine nerve ablation versus laparoscopic presacral neurectomy	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for different results at different time points
3 (207) [49]	Pain	Spinal manipulation versus sham manipulation or no treatment	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and methodological weaknesses (poor allocation concealment and poor blinding). Consistency point deducted for different results at different time points and between studies

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.