Dysmenorrhoea

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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 pharmacological treatments for primary dysmenorrhoea? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2013 (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 eight 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: contraceptives (combined oral), non-steroidal anti-inflammatory drugs (NSAIDs), progestogens (intrauterine), and simple analgesics (aspirin, paracetamol) .

QUESTIONS

INTERVENTIONS

Key points

- Dysmenorrhoea may begin soon after the menarche, where it often improves with age; or it 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.
- This review has searched for evidence on pharmacological interventions for primary dysmenorrhoea.
- Non-steroidal anti-inflammatory drugs (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.
- For simple analgesics, aspirin may reduce pain in women with primary dysmenorrhoea in the short term compared with placebo, although few studies have been of good quality.

  We don't know whether paracetamol is more effective than placebo at reducing pain in women with primary dysmenorrhoea as we found insufficient evidence.
- 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.
- We found insufficient evidence on whether intrauterine progestogens reduce dysmenorrhoea.

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]). 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 in a woman's 40s or 50s, after the onset of an underlying causative condition. [1] In this review we only consider trials 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 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 (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] A further review of longitudinal, case-control, or cross-sectional studies with large community-based samples included 15 primary studies, published between 2002 and 2011. It found the prevalence of dysmenorrhoea to vary between 16% and 91% in women of reproductive age, with severe pain in 2% to 29% of women studied. [5]

AETIOLOGY/ RISK FACTORS

A systematic review (search date 2004) of cohort and case-control studies concluded that age under 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. [6] Presence of an intrauterine contraceptive device may also be associated with dysmenorrhoea. A further review reported that age, parity, and use of oral contraceptives were inversely associated with dysmenorrhoea, and high stress increased the risk of dysmenorrhoea. [5] The effect sizes were generally modest to moderate, with odds ratios varying between 1 and 4. There was inconclusive evidence for modifiable factors such as cigarette smoking, diet, obesity, depression, and abuse. Family history of dysmenorrhoea strongly increased its risk, with odds ratios between 3.8 and 20.7. [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. [7] 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:** incidence and type of adverse effects.

METHODS

Clinical Evidence search and appraisal December 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to December 2013, Embase 1980 to December 2013, and The Cochrane Database of Systematic Reviews 2013, issue 11 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, at least single-blinded, and containing 20 or more individuals (10 in each arm) of whom more than 80%

were followed up. There was no minimum length of follow-up. 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 RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, 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 23). 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 pharmacological treatments for primary dysmenorrhoea?

OPTION NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), OTHER THAN ASPIRIN

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 23 .
- Non-steroidal anti-inflammatory drugs (NSAIDs) may be more effective at reducing 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.
- Women who take NSAIDs for primary dysmenorrhoea may have reduced interference with daily activities and reduced absence from work or school compared with women taking placebo.
- It is important that women taking NSAIDs for primary dysmenorrhoea are aware of possible adverse effects. Note: measurement and reporting of adverse effects by individual RCTs were generally poor.
- It remains unclear, from direct comparisons of NSAIDS used for treating primary dysmenorrhoea, which NSAIDs have better safety profiles. The harms of NSAIDs include gastrointestinal ulceration and haemorrhage for non-selective 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 2009, 41 RCTs; see Further information on studies [8]) and two subsequent RCTs. [9] [10] The review included double-blind RCTs in women of reproductive age with primary dysmenorrhoea. Pain was reported using a Visual Analogue Scale (VAS) or dichotomous data (at least moderate pain relief/no pain relief). If other scales or labels were used, these were (if possible) collapsed into dichotomous data, so that women experiencing 'at least moderate' pain relief were reported as having pain relief, whereas women with only mild pain relief were reported as having no pain relief (see Further information about studies).

Pain

NSAIDs compared with placebo NSAIDs may be more effective at reducing pain and decreasing the need for additional analgesia compared with placebo in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[8] Systematic review	Women with primary dysmenorrhoea 32 RCTs in this analysis	**Moderate or excellent pain relief (duration of treatment in the included studies varied from 1 cycle per treatment to 5 cycles per treatment)** with NSAIDs with placebo Absolute results not reported	OR 4.50 95% CI 3.85 to 5.27 P <0.00001 Significant heterogeneity: I^2 = 53%, P = 0.00011 Analysis of individual NSAIDs versus placebo also significant	●●○	NSAIDs

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
			See Further information about studies		
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Pain relief continuous data: percentage improvement in Visual Analogue Scale (VAS) pain score (scale 1–100)** with NSAIDs (diclofenac) with placebo Absolute results not reported	Mean difference 65.96 95% CI 55.70 to 76.22 P <0.0001	○○○	NSAIDs
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Pain relief continuous data: final pain relief score difference (time-weighted TOTPAR-8 scale)** with NSAIDs with placebo Absolute results not reported	Mean difference 7.21 95% CI 4.65 to 9.76 P <0.00001	○○○	NSAIDs
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Pain relief continuous data: final pain relief score difference (repeated 0–3 scale)** with NSAIDs with placebo Absolute results not reported	Mean difference 4.83 95% CI 3.61 to 6.06 P <0.00001	○○○	NSAIDs
[9] RCT **Crossover design** **3-armed trial**	149 women, aged 18–44 years, with primary dysmenorrhoea	**Pain intensity, assessed by mean TOTPAR-8 scores , over the first 8 hours** 18.28 with celecoxib 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 The remaining arm evaluated naproxen sodium	P <0.001	○○○	celecoxib
[9] RCT **Crossover design** **3-armed trial**	149 women, aged 18–44 years, with primary dysmenorrhoea	**Pain intensity, assessed by mean TOTPAR-8 scores , over the first 8 hours** 20.59 with naproxen sodium 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 The remaining arm evaluated celecoxib	P <0.001	○○○	naproxen sodium
[9] RCT **Crossover design** **3-armed trial**	149 women, aged 18–44 years, with primary dysmenorrhoea	**Pain intensity, assessed by mean SPID-8 values , over the first 8 hours** 10.06 with celecoxib 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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The remaining arm evaluated naproxen sodium			
[9] RCT **Crossover design** **3-armed trial**	149 women, aged 18–44 years, with primary dysmenorrhoea	**Pain intensity, assessed by mean SPID-8 values , over the first 8 hours** 11.48 with naproxen sodium 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 The remaining arm evaluated celecoxib	P <0.001	○○○	naproxen sodium
[10] RCT **3-armed trial**	180 women with primary dysmenorrhoea	**Pain scores, assessed by VAS (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 The remaining arm evaluated Iranian herbal medicine (highly purified saffron, celery seed, and anise)	P <0.01	○○○	mefenamic acid
[10] RCT **3-armed trial**	180 women with primary dysmenorrhoea	**Pain scores, assessed by VAS (scale 0–10, higher scores indicating more severe pain) , 3 months** 2.4 with mefenamic acid 6 with placebo 106 women in this analysis Participants were followed from the beginning of menstruation through the 3 days of bleeding The remaining arm evaluated Iranian herbal medicine (highly purified saffron, celery seed, and anise)	P <0.01	○○○	mefenamic acid
[10] RCT **3-armed trial**	180 women with primary dysmenorrhoea	**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 The remaining arm evaluated Iranian herbal medicine (highly purified saffron, celery seed, and anise)	P <0.01	○○○	mefenamic acid
[10] RCT **3-armed trial**	180 women with primary dysmenorrhoea	**Pain duration , 3 months** 3 hours with mefenamic acid 15.4 hours with placebo 106 women in this analysis	P <0.001	○○○	mefenamic acid

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Participants were followed from the beginning of menstruation through the 3 days of bleeding The remaining arm evaluated Iranian herbal medicine (highly purified saffron, celery seed, and anise)			
Need for additional medication					
[8] Systematic review	990 women 13 RCTs in this analysis	**Additional analgesics required** with NSAIDs with placebo Absolute results not reported	OR 0.33 95% CI 0.26 to 0.42 P <0.00001 Significant heterogeneity: I^2 = 51%, P = 0.01 (see Further information about studies)	●●○	NSAIDs

Daily activities and work

NSAIDs compared with placebo NSAIDs may be more effective at reducing interference with daily activities and reducing absence from work or school compared with placebo in women with primary dysmenorrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Restriction of daily activities					
[8] Systematic review	306 women 5 RCTs in this analysis	**Interference with daily activities** with NSAIDs with placebo Absolute results not reported	OR 0.32 95% CI 0.21 to 0.50 P <0.0001 Data also included 1 RCT of aspirin	●●○	NSAIDs
Absence from work or school					
[8] Systematic review	235 women 4 RCTs in this analysis	**Absence from work or school** with NSAIDs with placebo Absolute results not reported	OR 0.18 95% CI 0.10 to 0.32 P <0.00001	●●●	NSAIDs

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[8] Systematic review	1814 women 23 RCTs in this analysis	**All adverse effects** with NSAIDs with placebo Absolute results not reported	OR 1.37 95% CI 1.12 to 1.66 P = 0.0018 The review reported that the most commonly reported adverse effects were mild neurological and gastrointestinal symptoms	●○○	placebo
[8] Systematic review	702 women 13 RCTs in this analysis	**Gastrointestinal adverse effects** with NSAIDs with placebo	OR 1.47 95% CI 0.99 to 2.18 P = 0.059	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported	Analysis included 2 RCTs of aspirin		
[8] Systematic review	498 women 7 RCTs in this analysis	**Neurological adverse effects** with NSAIDs with placebo Absolute results not reported	OR 2.74 95% CI 1.66 to 4.53 P = 0.00008 Included events such as headache, drowsiness, dizziness, and dryness of mouth Analysis included 1 RCT of aspirin	●●○	placebo
[9] RCT **Crossover design** **3-armed trial**	149 women, aged 18–44 years, with primary dysmenorrhoea	**Adverse effects** 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		
[10] RCT **3-armed trial**	180 women with primary dysmenorrhoea	**Adverse effects** with mefenamic acid with placebo The remaining arm evaluated Iranian herbal medicine (highly purified saffron, celery seed, and anise)	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 2009). [8] The review compared individual named NSAIDs versus other remaining NSAIDs as a group and pooled data (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 or the need for additional analgesics in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Pain relief binary data (numbers reporting relief of pain; further individual definition not supplied)** with diclofenac with other NSAIDs (1 RCT ibuprofen, 1 RCT nimesulide) Absolute results not reported	OR 0.88 95% CI 0.57 to 1.36 P = 0.56	⟷	Not significant
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Pain relief binary data (numbers reporting relief of pain; further individual definition not supplied)** with ibuprofen	OR 0.94 95% CI 0.55 to 1.61 P = 0.82	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with other NSAIDs (1 RCT piroxicam, 1 RCT lysine clonixinate) Absolute results not reported			
[8] Systematic review	337 women Data from 1 RCT	**Pain relief binary data (numbers reporting relief of pain; further individual definition not supplied)** with mefenamic acid with meloxicam Absolute results not reported	OR 0.68 95% CI 0.32 to 1.44 P = 0.31	⟷	Not significant
[8] Systematic review	80 women Data from 1 RCT	**Pain relief (VAS)** with mefenamic acid with tolfenamic acid Absolute results not reported	Mean difference +0.23 95% CI –0.69 to +1.15 P = 0.62	⟷	Not significant
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Pain relief binary data (numbers reporting relief of pain; further individual definition not supplied)** with naproxen with other NSAIDS (1 RCT ketoprofen, 1 RCT piroxicam Absolute results not reported	OR 0.65 95% CI 0.36 to 1.17 P = 0.15	⟷	Not significant
[8] Systematic review	60 women Data from 1 RCT	**Pain intensity (not further defined)** with naproxen with flurbiprofen Absolute results not reported	OR 1.06 95% CI 0.75 to 1.50 P = 0.73	⟷	Not significant
[8] Systematic review	Women with primary dysmenorrhoea 3 RCTs in this analysis	**Pain relief: continuous data, mean difference final scores (scale not reported)** with naproxen with other NSAIDS (1 RCT etoricoxib, 1 RCT ibuprofen, 1 RCT diclofenac) Absolute results not reported	Mean difference –0.16 95% CI –0.38 to +0.07 P = 0.16	⟷	Not significant
[8] Systematic review	42 women Data from 1 RCT	**Pain relief: continuous data, mean difference change scores (VAS)** with naproxen with ketoprofen Absolute results not reported	OR 3.00 95% CI 1.75 to 5.16 P = 0.000067	●●○	naproxen
Need for additional medication					
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Additional analgesics required** with ibuprofen with other NSAIDs (1 RCT fenoprofen, 1 RCT piroxicam) Absolute results not reported	OR 0.83 95% CI 0.32 to 2.18 P = 0.71	⟷	Not significant
[8] Systematic review	60 women Data from 1 RCT	**Additional analgesics required** with naproxen with flurbiprofen	OR 0.59 95% CI 0.18 to 1.93 P = 0.38	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			

Daily activities and work

Different NSAIDs compared with each other We don't know whether NSAIDs differ in effectiveness at improving interference with daily activities or 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
Restriction of daily activities					
[8] Systematic review	80 women Data from 1 RCT	**Interference with daily activities** with mefenamic acid with tolfenamic acid Absolute results not reported	Mean difference +0.54 95% CI –0.34 to +1.42 P = 0.23	⟷	Not significant
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Interference with daily activities** with naproxen with other NSAIDS (1 RCT flurbiprofen, 1 RCT ibuprofen) Absolute results not reported	OR 0.63 95% CI 0.33 to 1.22 P = 0.17	⟷	Not significant
Absence from work or school					
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Absence from work/school** with naproxen with other NSAIDS (1 RCT flurbiprofen, 1 RCT ibuprofen) Absolute results not reported	OR 0.50 95% CI 0.19 to 1.36 P = 0.18	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[8] Systematic review	60 women Data from 1 RCT	**All adverse effects** with diclofenac with ibuprofen Absolute results not reported	OR 3.83 95% CI 0.76 to 19.28 P = 0.1	⟷	Not significant
[8] Systematic review	308 women Data from 1 RCT	**Gastrointestinal adverse effects** with diclofenac with nimesulide Absolute results not reported	OR 2.34 95% CI 0.93 to 5.87 P = 0.07	⟷	Not significant
[8] Systematic review	308 women Data from 1 RCT	**Neurological adverse effects** with diclofenac with nimesulide Absolute results not reported	OR 0.24 95% CI 0.03 to 2.02 P = 0.19	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[8] Systematic review	31 women Data from 1 RCT	**All adverse effects** with etodolac with piroxicam Absolute results not reported	OR 1.00 95% CI 0.06 to 16.70 P = 1.0	⟷	Not significant
[8] Systematic review	166 women Data from 1 RCT	**All adverse effects** with ibuprofen with fenoprofen Absolute results not reported	OR 1.51 95% CI 0.72 to 3.17 P = 0.28	⟷	Not significant
[8] Systematic review	80 women Data from 1 RCT	**All adverse effects** with mefenamic acid with tolfenamic acid Absolute results not reported	Mean difference +0.23 95% CI –0.62 to +1.08 P = 0.6	⟷	Not significant
[8] Systematic review	Women with primary dysmenorrhoea 7 RCTs in this analysis	**All adverse effects** with naproxen with other NSAIDS (1 RCT each of aceclofenac, diclofenac, etoricoxib, meclofenamate, piroxicam, 2 RCTs ketoprofen) Absolute results not reported	OR 1.15 95% CI 0.81 to 1.63 P = 0.44	⟷	Not significant
[8] Systematic review	Women with primary dysmenorrhoea 5 RCTs in this analysis	**Gastrointestinal adverse effects** with naproxen with other NSAIDS (1 RCT each of ibuprofen, ketoprofen, meclofenamate, 2 RCTs piroxicam) Absolute results not reported	OR 1.19 95% CI 0.53 to 2.69 P = 0.68	⟷	Not significant
[8] Systematic review	Women with primary dysmenorrhoea 3 RCTs in this analysis	**Neurological adverse effects** with naproxen with other NSAIDS (1 RCT each of ketoprofen, meclofenamate, piroxicam) Absolute results not reported	OR 0.80 95% CI 0.24 to 2.74 P = 0.73	⟷	Not significant

NSAIDs versus aspirin:

See option on Simple analgesics, p 11 .

NSAIDs versus paracetamol:

See option on Simple analgesics, p 11 .

Further information on studies

[8] Adverse effects: the review noted that 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: the review noted that less than one third of the RCTs described the use of prospective self-report forms or diaries, while the rest assessed adverse effects retrospectively, or were vague about methods, or failed to systematically report adverse effects. NSAIDs versus placebo: overall, the review found that NSAIDs were more effective than placebo at producing moderate or excellent pain relief (32 RCTs, OR 4.50, 95% CI 3.85 to 5.27). There was significant heterogeneity in the overall pooled analysis. The exclusion of two RCTs that reported no or negligible placebo effect resulted in a decrease in heterogeneity and a lower effect size (30 RCTs, OR 4.14, 95% CI 3.52 to 4.86, I^2 = 42%, P value for heterogeneity not reported). Subgroup analysis by individual NSAID was also reported. Diclofenac, ibuprofen, etodolac, ketoprofen, naproxen, indomethacin, piroxicam, mefanamic acid, niflumic acid, nimuselide, and lysine clonixinate were all individually significantly more effective than placebo at improving pain relief. There was also heterogeneity in the analysis of some individual agents versus placebo (piroxicam, ibuprofen, and naproxen). Different NSAIDs versus each other: most of the RCTs in the review found no significant difference in outcomes between different individual NSAIDs in direct one-to-one comparison. Study quality: the review reported, with regard to all RCTs included in the review overall (73 RCTs), that under 20% (14/73) described the randomisation process in detail, fewer than 10% (7/73) described an adequate allocation process, and over 40% (30/73) failed to give details of who was blinded or explicitly state that the placebo was identical to the active treatment. The review reported that at about half of the RCTs (35/73; 48%) were co-authored or financially supported by pharmaceutical companies, and it was unclear how most of the others were funded.

Comment: The review concluded that there was consistent evidence of the effectiveness of NSAIDs compared with placebo in providing pain relief, with no statistical difference in outcomes between different NSAIDs. [8] However, the review also highlighted the need to be aware of the risk of adverse effects.

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. [11]

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. The harms of NSAIDs include gastrointestinal ulcer and haemorrhage for non-selective NSAIDs and, for at least some of the COX-2 inhibitors, increased cardiovascular risk.

OPTION SIMPLE ANALGESICS (ASPIRIN, PARACETAMOL)

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 23 .
- Aspirin may reduce pain in the short term compared with placebo, although few studies have been of good quality.
- There is insufficient evidence as to whether paracetamol is more effective than placebo at reducing pain in women with primary dysmenorrhoea.

Benefits and harms

Aspirin versus placebo:

We found two systematic reviews (search date 1997 [12] and search date 2009; [8] see Further information on studies). The first review included RCTs in primary dysmenorrhoea. [12] It included eight double-blind RCTs comparing aspirin versus placebo. The second review [8] had stricter inclusion criteria than the first review. [12] It only included double-blind trials, and excluded those that had analysed less than 80% of women randomised for at least one primary outcome. Of the eight RCTs included in the first review, it excluded seven RCTs because of varying issues such as insufficient follow-up (< 80%), lack of clarity about randomisation, and some participants also having an IUCD. It included one further RCT not included in the first review.

Pain

Aspirin compared with placebo Aspirin may be more effective than placebo at increasing the proportion of women who report at least moderate pain relief. We don't know whether aspirin is more effective than placebo at reducing the need for additional medication (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[12] Systematic review	Women with primary dysmenorrhoea 5 RCTs in this analysis	**Proportion of women with at least moderate pain relief** with aspirin with placebo Absolute results reported graphically	RR 1.60 95% CI 1.12 to 2.29 NNT 10 95% CI 5 to 50 The figure reported in the text (RR 1.60, 95% CI 1.12 to 2.29) differed slightly from the figure reported in the graph (RR 1.60, 95% CI 1.12 to 3.63)	●○○	aspirin
[8] Systematic review	96 women Data from 1 RCT 4-armed trial, other arms contained different doses of fenoprofen	**Pain intensity, continuous data: mean difference final scores (4–5 point scales)** with aspirin with placebo Absolute results not reported	Mean difference 0.0 95% CI –0.72 to +0.72 P = 1.0	⟷	Not significant
[8] Systematic review	47 women Data from 1 RCT Crossover trial with 3 arms; the other arm was indomethacin	**Number of cycles where treatment gave moderate/good pain relief** 13/89 (15%) with aspirin 9/90 (10%) with placebo	Reported as not significant P value not reported These data are per cycle rather than by participant	⟷	Not significant
Need for additional medication					
[12] Systematic review	205 women with primary dysmenorrhoea 3 RCTs in this analysis	**Need for additional medication** with aspirin with placebo Absolute results not reported	RR 0.79 95% CI 0.58 to 1.08	⟷	Not significant
[8] Systematic review	96 women Data from 1 RCT 4-armed trial; other arms contained different doses fenoprofen	**Additional analgesics required** with aspirin with placebo Absolute results not reported	OR 0.72 95% CI 0.18 to 2.86 P = 0.64	⟷	Not significant

Daily activities and work

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Daily activities					
[12] Systematic review	203 women with primary dysmenorrhoea 3 RCTs in this analysis	**Restriction of daily activity** with aspirin with placebo Absolute results not reported	RR 0.82 95% CI 0.64 to 1.04	⟷	Not significant
[8] Systematic review	96 women Data from 1 RCT 4-armed trial; other arms contained different doses of fenoprofen	**Interference with daily activities** with aspirin with placebo Absolute results not reported	OR 0.44 95% CI 0.11 to 1.75 P = 0.24	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Absence from work					
[12] Systematic review	37 women with primary dysmenorrhoea Data from 1 RCT	**Absence from work** with aspirin with placebo Absolute results not reported	RR 1.28 95% CI 0.24 to 6.76	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review	Women with primary dysmenorrhoea	**Adverse effects** with aspirin with placebo Absolute results not reported	RR 1.3 95% CI 0.79 to 2.17	⟷	Not significant
[12] Systematic review	Women with primary dysmenorrhoea	**Nausea** with aspirin with placebo Absolute results not reported	RR 1.66 95% CI 0.59 to 4.67	⟷	Not significant
[12] Systematic review	Women with primary dysmenorrhoea	**Dizziness** with aspirin with placebo Absolute results not reported	RR 1.29 95% CI 0.28 to 5.89	⟷	Not significant
[12] Systematic review	Women with primary dysmenorrhoea	**Headache** with aspirin with placebo Absolute results not reported	RR 0.60 95% CI 0.18 to 2.04	⟷	Not significant
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Gastrointestinal adverse effects** with aspirin with placebo Absolute results not reported	OR 1.41 95% CI 0.55 to 3.60 P = 0.48	⟷	Not significant
[8] Systematic review	96 women Data from 1 RCT 4-armed trial; other arms evaluated different doses of fenoprofen	**Neurological adverse effects** with aspirin with placebo Absolute results not reported	OR 3.66 95% CI 0.75 to 17.78 P = 0.11	⟷	Not significant

Paracetamol versus placebo:

We found one systematic review (search date 1997, 1 RCT). [12]

Pain

Paracetamol compared with placebo We found insufficient evidence on whether paracetamol is more effective than placebo 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					
[12] Systematic review	35 women randomised, 30 women in analysis Data from 1 RCT 3-armed trial with crossover design; the remaining arm evaluated aspirin	**Median pain relief** 1.6 with paracetamol 0.9 with placebo Results were presented after crossover	Reported as no significant difference Of the 30 women analysed, 9 women had an IUCD	⟷	Not significant

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] Systematic review	35 women randomised, 30 women in analysis Data from 1 RCT 3-armed trial with crossover design; the remaining arm evaluated aspirin	**Frequency of any adverse effect** with paracetamol 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), which included one RCT. [12] We found one further systematic review (search date 2009). [8] This excluded the RCT included in the first review, as some of the participants had an IUCD fitted and there was no separate analysis. It did not find any other RCTs.

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					
[12] Systematic review	35 women randomised, 30 women in analysis Data from 1 RCT 3-armed trial with crossover design;	**Median pain relief** 1.2 with aspirin 1.6 with paracetamol Results were presented post-crossover	No significant difference reported Of the 30 women analysed, 9 women had an IUCD	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	the remaining arm evaluated placebo				

Daily activities and work

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

Adverse effects

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

Aspirin versus NSAIDs:

We found two systematic reviews (search dates 1997 [12] and 2009 [8]). The first review identified two RCTs, which compared aspirin versus NSAIDs (ibuprofen or naproxen). [12] However, one RCT did not meet *Clinical Evidence* inclusion criteria because of a high loss to follow-up. We have, therefore, reported the remaining RCT, which compared aspirin versus naproxen. The second review excluded the RCT included in the first review because of lack of clarity around randomisation. It included two further RCTs, which compared aspirin versus indomethacin and aspirin versus fenoprofen. [8]

Pain

Aspirin compared with NSAIDs Aspirin may be less effective than naproxen, fenoprofen, and indomethacin at reducing pain in women with primary dysmenorrhoea. However, evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[12] Systematic review	34 women randomised, 32 women in analysis Data from 1 RCT RCT used a crossover design	**Pain relief** with aspirin with naproxen Absolute results not reported Results presented post-crossover	RR 2.29 95% CI 1.09 to 4.79	●●○	naproxen
[8] Systematic review	96 women 1 RCT included in this analysis 4-armed trial, other arms evaluated higher-dose fenoprofen and placebo (these results reported on lower-dose fenoprofen)	**Pain intensity continuous data (not further defined)** with aspirin with fenoprofen Absolute results not reported	Mean difference 0.65 95% CI 0.10 to 1.20 P = 0.021	○○○	fenoprofen
[8] Systematic review	47 women Data from 1 RCT 3-armed trial of crossover design; other arm evaluated placebo	**Number of cycles where treatment gave moderate/good pain relief** 13/89 (15%) with aspirin 42/90 (47%) with indomethacin	P <0.001 These data are per cycle rather than by participant	○○○	indomethacin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for additional medication					
[8] Systematic review	96 women Data from 1 RCT 4-armed trial; other arms evaluated higher-dose fenoprofen and placebo (these results report on lower-dose fenoprofen)	**Additional analgesics required** with aspirin with fenoprofen Absolute results not reported	OR 2.06 95% CI 0.73 to 5.83 P = 0.17	⟷	Not significant

Daily activities and work

Aspirin compared with NSAIDs We don't know whether aspirin and fenoprofen differ in effectiveness at preventing interference with daily activities in women with primary dysmenorrhoea (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Daily activities					
[8] Systematic review	96 women Data from 1 RCT 4-armed trial; other arms evaluated higher-dose fenoprofen and placebo (these results report on lower-dose fenoprofen)	**Interference with daily activities** with aspirin with fenoprofen Absolute results not reported	OR 2.57 95% CI 0.81 to 8.17 P = 0.11	⟷	Not significant

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					
[8] Systematic review	96 women Data from 1 RCT 4-armed trial; there were two arms with fenoprofen (lower- and higher-dose) For adverse effects the review pooled data for both arms; the remaining arm evaluated placebo	**All adverse effects** with aspirin with fenoprofen Absolute results not reported	OR 1.46 95% CI 0.52 to 4.08 P = 0.47	⟷	Not significant
[8] Systematic review	Women with primary dysmenorrhoea 2 RCTs in this analysis	**Gastrointestinal adverse effects** with aspirin with other NSAIDs (1 RCT fenoprofen, 1 RCT indomethacin) Absolute results not reported	OR 2.05 95% CI 0.84 to 4.96 P = 0.11	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[8] Systematic review	96 women Data from 1 RCT 4-armed trial; there were two arms with fenoprofen (higher- and lower-dose) For adverse effects the review pooled data for both arms; the remaining arm evaluated placebo	**Neurological adverse effects** with aspirin with fenoprofen Absolute results not reported	OR 3.20 95% CI 0.92 to 11.11 P = 0.067	⟷	Not significant

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

Paracetamol versus NSAIDs:

We found one systematic review (search date 2009; 3 RCTs), which compared paracetamol versus NSAIDs and pooled data. [8] All three included RCTs were crossover trials (12 women, 67 women, 117 women), and two were sponsored by pharmaceutical companies, while the third was unclear on this issue. The first RCT had unclear allocation concealment, the second RCT had unclear adequate sequence generation and allocation concealment, while the third RCT reported results for 98/117 (83%) women randomised.

Pain

Paracetamol compared with NSAIDs Paracetamol may be less effective than NSAIDs (analysis including ibuprofen and naproxen) 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					
[8] Systematic review	196 women 3 RCTs in this analysis 2 RCTs were 3-armed trials, in which the remaining arm evaluated placebo	**Pain relief binary data (numbers reporting good, excellent or complete pain relief; further individual definition not supplied)** with NSAIDs (2 RCTs ibuprofen, 1 RCT naproxen) with paracetamol Absolute results not reported	OR 1.89 95% CI 1.05 to 3.43 P = 0.035	●○○	NSAIDs

Daily activities and work

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

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[8]	67 women Data from 1 RCT	**All adverse effects** with ibuprofen	OR 0.85 95% CI 0.31 to 2.34	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Systematic review		with paracetamol Absolute results not reported	P = 0.75		
[8] Systematic review	117 women Data from 1 RCT 3-armed trial; other arm evaluated placebo	**Gastrointestinal adverse effects** with naproxen with paracetamol Absolute results not reported	OR 1.00 95% CI 0.06 to 16.62 P = 1.0	⟷	Not significant
[8] Systematic review	117 women Data from 1 RCT 3-armed trial; other arm evaluated placebo	**Neurological adverse effects** with naproxen with paracetamol Absolute results not reported	OR 1.54 95% CI 0.24 to 9.83 P = 0.65	⟷	Not significant

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

Further information on studies

[12] Most RCTs included in the systematic review were short (usually only one 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.

Comment: **Drug safety alert**
August 2013 (paracetamol [acetaminophen]) — The Food and Drug Administration (FDA) issued a drug safety alert on the risk of rare but serious skin reactions with paracetamol (acetaminophen). These skin reactions, known as Stevens–Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP), can be fatal.(www.fda.gov/)

OPTION CONTRACEPTIVES (COMBINED ORAL)

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 23 .
- 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.
- There may be an increased risk of adverse effects, irregular uterine bleeding, and nausea with low-dose combined oral contraceptive pill (ethinyl estradiol plus norethisterone) compared with placebo.

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. [13] Two RCTs examined low-dose oestrogen plus progestogen and four RCTs examined medium-dose oestrogen plus progestogen. [13] We found one subsequent RCT. [14]

Pain

Combined oral contraceptives compared with placebo Combined oral contraceptives may be more effective at reducing pain in women with primary dysmenorrhoea compared with placebo or no treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[13] Systematic review	497 women with primary dysmenorrhoea 6 RCTs in this analysis	**Proportion of women with pain improvement , after 2–6 cycles** 142/307 (46%) with combined oral contraceptives (COC) 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	●●○	COC
[14] RCT	115 women with primary dysmenorrhoea	**Reduction in Visual Analogue Scale score (scale not reported; measured 'the degree of dysmenorrhoea'; further details not supplied) , after 4 cycles** –36.0 with low-dose combined oral contraceptive pill (ethinyl estradiol plus norethisterone) –20.8 with placebo 107 women in this analysis Women were also allowed to use other analgesic agents	P = 0.001	○○○	COC

Daily activities and work

Combined oral contraceptives compared with placebo Combined oral contraceptives may be more effective at reducing a composite dysmenorrhoea score (including elements of ability to work but also usage of analgesia) in women with primary dysmenorrhoea compared with placebo. We found no evidence reporting directly on effect on daily activities or work (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Daily activities					
[14] RCT	115 women with primary dysmenorrhoea	**Reduction in total dysmenorrhoea score (composite measure of limited ability to work [score 0–3; from none/low efficacy to work to 1 or more day in bed] and need for analgesics [score 0–3; from none to taking analgesia for 3 or more days]) , after 4 cycles** –2.6 with low-dose combined oral contraceptive pill (ethinyl estradiol plus norethisterone) –1.4 with placebo 107 women in this analysis Women were also allowed to use other analgesic agents	P <0.001	○○○	COC

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

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] 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 36/78 (46%) with placebo or no treatment Adverse effects included nausea, headaches, and weight gain	OR 1.45 95% CI 0.71 to 2.94	⟷	Not significant
[14] RCT	115 women with primary dysmenorrhoea	**Irregular uterine bleeding** 63.2% with low-dose combined oral contraceptive pill (ethinyl estradiol plus norethisterone) 14.5% with placebo Absolute numbers not reported	Reported as significant difference P value not reported	○○○	placebo
[14] RCT	115 women with primary dysmenorrhoea	**Nausea** 14% with low-dose combined oral contraceptive pill (ethinyl estradiol plus norethisterone) 0% with placebo Absolute numbers not reported	Reported as significant difference P value not reported	○○○	placebo
[14] RCT	115 women with primary dysmenorrhoea	**Total adverse effects** 80.7% with low-dose combined oral contraceptive pill (ethinyl estradiol plus norethisterone) 40.0% with placebo Absolute numbers not reported	Reported as significant difference P value not reported	○○○	placebo

Further information on studies

[13] 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 PROGESTOGENS (INTRAUTERINE)

- For GRADE evaluation of interventions for Dysmenorrhoea, see table, p 23 .
- We found no direct evidence from RCTs about intrauterine progestogens compared with placebo or other listed interventions in this review in women with primary 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). [15]

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). [16]

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

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.

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.

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

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

Visual Analogue Scale (VAS) 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 0–10 cm or 0–100 mm.

SUBSTANTIVE CHANGES

Contraception (combined oral) New evidence added. [14] Categorisation unchanged (likely to be beneficial).

Non-steroidal anti-inflammatory drugs (NSAIDs) Existing review updated. [8] Categorisation unchanged (beneficial).

Simple analgesics (aspirin, paracetamol) Previous option restructured to include only aspirin and paracetamol. Existing review updated. [8] Categorisation unchanged (likely to be beneficial).

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Dysmenorrhoea

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Disclaimer

GRADE **Evaluation of interventions for Dysmenorrhoea.**

Important outcomes					Daily activities and work, Pain				
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of pharmacological treatments for primary dysmenorrhoea?									
at least 34 (at least 1319) [8] [9] [10]	Pain	NSAIDs versus placebo	4	–2	–1	0	+1	Low	Quality points deducted for incomplete reporting of results and weak methods; consistency point deducted for statistical heterogeneity; effect size point added for OR >2 and <0.5
at least 5 (at least 306) [8]	Daily activities and work	NSAIDs versus placebo	4	–2	0	–1	+1	Low	Quality points deducted for incomplete reporting of results and weak methods; effect size point added for OR <0.5; directness point deducted for inclusion of data on aspirin
unclear (unclear) [8]	Pain	Different NSAIDs versus each other	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, comparing single agent versus rest of group, and weak methods
at least 3 (unclear) [8]	Daily activities and work	Different NSAIDs versus each other	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, comparing single agent versus rest of group, and weak methods
6 (unclear) [8] [12]	Pain	Aspirin versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for weak methods and incomplete reporting of results; directness point deducted for different conclusions depending on the analysis performed
at least 3 (at least 203) [8] [12]	Daily activities and work	Aspirin versus placebo	4	–2	0	0	0	Low	Quality points deducted for weak methods and incomplete reporting of results
1 (30) [12]	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) [12]	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
3 (less than 175) [8] [12]	Pain	Aspirin versus NSAIDs	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods; directness point deducted for outcome data per cycle
1 (fewer than 96) [8]	Daily activities and work	Aspirin versus NSAIDs	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods
3 (fewer than 196) [8]	Pain	Paracetamol versus NSAIDs	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods
7 (604) [13] [14]	Pain	Combined oral contraceptives versus placebo/no treatment	4	–1	–1	0	0	Low	Quality point deducted for weak methods; consistency point deducted for statistical heterogeneity
1 (107) [14]	Daily activities and work	Combined oral contraceptives versus placebo/no treatment	4	–1	0	–2	0	Very low	Quality point deducted for sparse data; directness points deducted for use of composite measure (including function and pain), no ITT analysis, and small number of comparators

Important outcomes			Daily activities and work, Pain						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consisten-cy	Direct-ness	Effect size	GRADE	Comment
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.									