Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis

Review information

Review number: MCA871

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What's new

Date / Event	Description
01 November 2016 Updated	This review was updated in October 2016. The search identified no new studies to be included. Unless new evidence emerges this review will no longer be updated.

History

Date / Event	Description
20 September 2010 Amended	Contact details updated.
11 February 2009 New citation: conclusions not changed	Review updated Apirl 2008
31 August 2008 Updated	Searches updated 21 April 2008. No new studies found. Review amended. Risk of bias tables and two new figures added. Search strategies moved to appendices.
29 April 2008 Amended	Converted to new review format.
23 August 2005 New citation: conclusions changed	Substantive amendment

Abstract

Background

Endometriosis is a common gynaecological condition that affects women and can lead to painful symptoms and infertility. It greatly affects women's quality of life, impacting on their careers, everyday activities, sexual and non-sexual relationships, and fertility. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used first-line treatment for endometriosis pain.

Objectives

To assess the effects of NSAIDs used for the management of pain in women with endometriosis compared to placebo, other NSAIDs, other pain management drugs, or no treatment.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (October 2016) published in the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE (January 2008 to October 2016), EMBASE (date limited from 01 January 2016 to 19 October 2016 as all earlier references are included in the CENTRAL output due to the Embase project), and the reference lists from relevant publications. No new randomised controlled trials were identified. Unless new evidence is identified in the future, this review will not be updated.

Selection criteria

We included all randomised controlled trials (RCTs) describing the use of NSAIDs in the treatment of endometriosis in women of all ages.

Data collection and analysis

In the 2009 update of this review, two review authors (CA and SH) independently read and extracted data from each of the included studies. Crossover trials were analysed using the inverse variance method in RevMan to calculate the odds ratio for binary outcomes.

Main results

No new trials were identified in the 2016 update. This review includes two trials but only one trial, with 24 women, was included in the analysis.

The overall risk of bias was unclear due to a lack of methodological detail. Using GRADE methodology the quality of the evidence was judged to be very low. Evidence was downgraded for risk of bias and for imprecision (wide confidence intervals and evidence based on a single small trial).

Comparing NSAIDs (naproxen) to placebo, there was no evidence of a positive effect on pain relief (odds ratio (OR) 3.27, 95% CI 0.61 to 17.69; one trial, 24 women; *very low quality evidence*) in women with endometriosis. There was also inconclusive evidence to indicate whether women taking NSAIDs (naproxen) were less likely to require additional analgesia (OR 0.12, 95% CI 0.01 to 1.29; one trial, 24 women; *very low quality evidence*) or to experience side effects (OR 0.46, 95% CI 0.09 to 2.47; one trial, 24 women; *very low quality evidence*) when compared to placebo.

No data were reported for quality of life, effect on daily activities, absence from work or school, women requiring more invasive treatment or participant satisfaction with treatment.

Authors' conclusions

Due to a lack of high quality evidence and lack of reporting of outcomes of interest for this review, we cannot make any judgement as to whether or not NSAIDs (naproxen) are effective in managing pain caused by endometriosis. There is no evidence on whether any individual NSAID is more effective than another. As shown in other Cochrane reviews, women using NSAIDs need to be aware of the possibility that these drugs may cause unintended effects.

Plain language summary

Non-steroidal anti-inflammatory drugs for treatment of pain in women with endometriosis

What is the issue?

Endometriosis is a common gynaecological condition that affects women of childbearing age. It can lead to painful symptoms, including painful periods, pain during or after sexual intercourse, pelvic and lower abdominal pain, and infertility. It can greatly affect women's quality of life by impacting on their careers, everyday activities, sexual and non-sexual relationships, and fertility. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used first-line treatment for endometriosis because they have few side-effects and many are available over the counter.

Why is this important?

Endometriosis is very common, but the diagnosis of it is difficult. In 2015, there were 1.8 billion women (aged 15 to 49 years) in the world. It is estimated that up to 60% of women with painful periods have endometriosis, Endometriosis greatly affects women's quality of life, impacting on their careers, everyday activities, sexual and non-sexual relationships, and fertility. An unpublished survey conducted by a patient support organization in the United Kingdom, Endometriosis UK (www.endometriosis-uk.org/), found that 65% of women with endometriosis reported that their condition had negatively affected their employment. Ten per cent of women had to reduce their hours of work and 30% had not been able to continue in the same employment. As many as 16% of women were unable to continue in any employment and 6% needed to claim state benefits; thus, in addition to their feelings of loss as contributors to society, they became dependent upon others. This increased their feelings of low self-esteem. Endometriosis is seen as a significant public health issue because of the large number of women affected and the significant illnesses associated with this disease.

Non steroidal anti-inflammatory drugs are a form of pain relief readily available without prescription. They work

by preventing or slowing down the production of prostaglandins which helps to relieve the painful cramps associated with endometriosis. However, a Cochrane Review on the use of NSAIDs for women with painful periods found a higher risk of stomach upsets (such as nausea and diarrhoea) or other side effects (for example headache, drowsiness, dizziness, and dryness of the mouth), The purpose of this review was to compare all NSAIDs used in the treatment of the painful symptoms caused by endometriosis with placebo, other pain management drugs, or no treatment in order to evaluate their effectiveness and safety.

What evidence did we find?

We searched for new evidence in October 2016. No new randomised controlled trials were identified.

From previous updates, this review found limited evidence on whether NSAIDs (specifically naproxen) are effective for the treatment of pain caused by endometriosis. This review is also limited as it only includes one study which involved 20 women.The evidence is of very low quality, mainly due to poor reporting of the methods, and lack of precision in the findings for overall pain relief, unintended side effects of treatment, and the need for extra pain relief. The included trial did not report on quality of life, effect on daily activities, absence from work or school or participant satisfaction with treatment.

What does this mean?

The available evidence does not allow us to conclude whether or not any individual NSAID is more effective than another. As shown in other Cochrane reviews, women using NSAIDs need to be aware that NSAIDs may cause adverse effects such as nausea, vomiting, headache, and drowsiness. Unless new evidence is identified in the future, this review will not be updated.

Background

Description of the condition

Endometriosis is defined as the presence of endometrial tissue (stromal and glandular) outside the normal uterine cavity (Barbieri 1990). Endometriosis is a common gynaecological condition which can lead to painful symptoms and infertility. Symptoms may include dysmenorrhoea (painful periods), dyspareunia (pain during or after sexual intercourse), and pelvic or lower abdominal pain. A less common symptom is cyclical pain in other sites relating to endometriosis (Prentice 2003). Endometriosis can be divided into four stages of severity (stage I: minimal disease; stage IV: severe disease) as defined by the American Fertility Society's classification system (Canavan 2000). Staging does not correlate with the degree or severity of symptoms; it quantifies the amount of disease visible at laparoscopy. The link between the pain experienced by women and the extent of endometriosis is not well understood, and the severity of pain experienced does not, therefore, always directly correlate with severity of the endometriosis (Kauppila 1985). Even when endometriosis is diagnosed, it may not be the cause of a woman's symptoms as the mechanism by which pain is caused is not fully understood.

Endometriosis greatly affects women's quality of life, impacting on their careers, everyday activities, sexual and non-sexual relationships, and fertility (Davies 2003; Jones 2002). An unpublished survey conducted by a patient support organization in the United Kingdom, Endometriosis UK (www.endometriosis-uk.org/), found that 65% of women with endometriosis reported that their condition had adversely affected their employment. Ten per cent of women had to reduce their hours of work and 30% had not been able to continue in the same employment. As many as 16% of women were unable to continue in any employment and 6% needed to claim state benefits; thus, in addition to their feelings of loss as contributors to society, they became dependent upon others. This increased their feelings of low self-esteem.

Prevalence

The exact prevalence of endometriosis is unknown. However, endometriosis is a significant problem for a great number of women and has high socio-economic costs (Prentice 2003). Endometriosis primarily affects

women of reproductive age (that is women who are menstruating). In women experiencing no symptoms, the prevalence of endometriosis has been estimated to be from 2% to 22% depending on the diagnostic criteria used and the populations studied. In women with painful periods, the prevalence of endometriosis ranges from 40% to 60%; and in women with subfertility, it is from 20 to 30%. The severity of symptoms and the probability of diagnosis increases with age, peaking at about 40 years old (Berube 1998; Vessy 1992). In the year 2000, there were 1.5 billion women (aged 15 to 49 years) in the world. A 1% prevalence means, therefore, that there could be 15 million women with endometriosis worldwide; assuming a 20% prevalence implies that there are 300 million women with endometriosis. The actual figure must lie somewhere in between but is unknown as studying the epidemiology of endometriosis is difficult (Kennedy 2003).

Diagnosis

Laparoscopy is considered the 'gold standard' for diagnosis of endometriosis (Canavan 2000; rAFS 1985). However, endometriosis may also be diagnosed (or presumed) based on a description of symptoms by the woman (and which may be suspected by the practitioner from the history, pelvic examination, and other tests such as ultrasound, magnetic resonance imaging (MRI), and the CA-125 blood test). However, examination, test findings, and the presence or absence of a classic history and symptoms cannot either confirm or rule out endometriosis.

Description of the intervention

There are many ways to treat the symptoms of endometriosis but to treat the underlying disease often requires repeated medical or surgical interventions. Management of endometriosis is varied. Medical treatments for endometriosis include oral contraceptives, progestagens, testosterone derivatives, and gonadotrophin-releasing hormone (GnRH) agonists (Rice 2002). Surgical treatments include ablative techniques (destroying the endometriosis with energy such as laser or electricity) and excision (using scissors, electricity, or laser). This surgical approach aims to relieve symptoms whilst conserving reproductive function. More radical surgery in the form of hysterectomy, removal of the ovaries (oophorectomy), or both may also be performed. Conventional medical and surgical treatments for endometriosis aim to remove or decrease deposits of ectopic endometrium (tissue like the lining of the uterus but found outside the uterus) (Barbieri 1990). Non-steroidal anti-inflammatory drugs (NSAIDs) are most commonly used as a simple first-line treatment for endometriosis because they have few side-effects and many are available over the counter. They do not remove or decrease the deposits of ectopic endometrium. NSAIDs may also act on local cytokines within the actual endometriotic deposits, as well as acting as analgesics.

How the intervention might work

Non-steroidal anti-inflammatory drugs (NSAIDs) work by decreasing the amount of pain experienced by women. NSAIDs (including COX2 inhibitors) inhibit prostaglandin production. Prostaglandins are locally produced chemicals that are believed to be responsible for causing the pain of endometriosis. NSAIDs purchased over the counter may be taken in doses that are insufficient to relieve pain. However, NSAIDs taken in high doses have the potential to cause side-effects. A Cochrane review of 31 studies that compared NSAIDs versus placebo for primary dysmenorrhoea found a statistically significant increased risk of adverse effects in the gastrointestinal (for example nausea and diarrhoea) and nervous (for example headache, drowsiness, dizziness, and dryness of the mouth) systems (Marjoribanks 2015). NSAIDs are analgesics which inhibit the cyclo-oxygenase (COX) enzymes thereby inhibiting the production of prostaglandins and alleviating cramps (Dawood 1986; Marjoribanks 2015). The first of the drugs with this mode of action was aspirin (acetylsalicylic acid), which was introduced in 1899. However, the term NSAID was not used until the 1950s when phenylbutazone was developed. Since then NSAIDs have become more widely used (Hart 1984; Marjoribanks 2015).

Why it is important to do this review

Endometriosis is seen as a significant public health issue because of the large number of women affected and the significant illnesses associated with this disease (Murphy 2002). NSAIDs are widely used drugs that are

readily available (both over the counter and on prescription). The purpose of this review was to compare all NSAIDs used in the treatment of the painful symptoms caused by endometriosis with placebo, other pain management drugs, or no treatment in order to evaluate their effectiveness and safety.

Objectives

To assess the effects of NSAIDs (of any type, dose, or duration) used for the management of pain in women with endometriosis compared with placebo, other NSAIDs, other pain management drugs, or no treatment.

Methods

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials describing the use of NSAIDs in the treatment of endometriosis in women of all ages. Crossover trials were included, as the crossover is a valid design in this context.

Types of participants

We included women with any stage or severity of endometriosis. Endometriosis was diagnosed by visualisation (for example laparoscopy or laparotomy) or was a suspected diagnosis based on the history and pelvic examination and other tests such as ultrasound, MRI, and the CA-125 blood test. We excluded women with chronic pelvic pain which was known to be due to causes other than endometriosis.

Types of interventions

We included all randomised controlled trials involving NSAIDs as a treatment for pain for women with endometriosis versus placebo, other NSAIDs, other drug pain management approaches, or no treatment. We considered randomised controlled trials describing NSAIDs of any type and administered at any dose, frequency, treatment duration, or by any type of administration.

Types of outcome measures

Data on each of the following outcomes were recorded from included trials, where available.

Primary outcomes

- Pain relief (measured either by visual analogue scale (VAS), other validated scales, or as a dichotomous outcome, for example improved or not improved)
- Unintended effects from treatment (incidence and duration of total side-effects, and type of side-effects)

Secondary outcomes

- Quality of life (measured using a validated scale, for example the SF36)
- Effect on daily activities (measured as proportion of women who reported activity restriction)
- Absence from work or school (measured as proportion of women reporting absences from work or school, and also as hours or days of absence as a more selective measure)
- Number of women requiring more invasive treatment (for example laparoscopic surgery), and length of follow up
- Requirements for additional medication (measured as proportion of women requiring analgesics (not NSAIDs) additional to their assigned treatment)
- Participant satisfaction with treatment (measured as proportion of women who reported improvements and satisfaction with their treatment)

Search methods for identification of studies

We searched for all published and unpublished RCTs of the use of NSAIDs for the treatment of pain in women with endometriosis, without language restriction and in consultation with the Gynaecology and Fertility Group (CGF) Information Specialist.

Electronic searches

We searched the Cochrane Gynaecology and Fertility Group (CGF) Specialised Register of Controlled Trials (October 2016), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, and CINAHL to identify all publications which described, or might describe, randomised trials of any NSAID in the treatment of endometriosis. Search strategies are outlined in the appendices (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6).

No new randomised controlled trials were identified.

Searching other resources

The World Health Organization International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/network/en/index.html), and the US National Institute of Health trial register Clinicaltrials.gov (http://www.clinicaltrials.gov) were also searched for ongoing studies using the terms 'endometriosis' AND 'non steroidal anti inflammatory', OR 'NSAIDs'. No ongoing trials were identified that were relevant to this review. References in relevant reports were checked to identify additional studies.

Data collection and analysis

Selection of studies

In 2016 support staff from the Cochrane Gynaecology and Fertility Group screened the titles and abstracts of all retrieved records to identify possible trials for inclusion in the review. Full copies of the reports were obtained for each of the records not rejected. No new studies for inclusion were identified.

Data extraction and management

In previous updates, data extraction was performed independently by two review authors (CA and SH) using a prespecified data extraction form. Any disagreements were resolved by discussion. Information was extracted from each included trial on:
(1) characteristics of trial participants (including age, stage and severity of disease, and method of diagnosis), and the trial's inclusion and exclusion criteria;
(2) type of intervention (including type, dose, duration, and frequency of the NSAID versus placebo; the type, dose, duration, and frequency of another NSAID; another pain management drug; or no treatment);
(3) type of outcome measure (including the level of pain reduction, improvement in quality of life score (using a validated scale), effect on daily activities, absence from work or school, length of follow up, unintended effects of treatment, number of women requiring more invasive treatment, and length of follow up).

Where data for a trial were insufficient or missing, we sought information from the named contact author of the trial. We attempted to contact Dr Kauppila but have been unable to elicit a response.

Assessment of risk of bias in included studies

In previous updates, two review authors independently assessed the included studies for risk of bias using the Cochrane risk of bias tool (Higgins 2011) to assess:

- Selection (random sequence generation and allocation concealment)

- Pefromance (blinding of participants and personnel)
- Detection (blinding of outcome assessors)
- Attrition (incomplete outcome data)
- Reporting (selective reporting)
- Other bias

Judgements were assigned as recommended in the Cochrane Handbook section 8.5 (Higgins 2011) Disagreements were resolved by discussion. We described all judgements and presented the conclusions in the Risk of Bias table.

Measures of treatment effect

Both of the trials identified for inclusion in this review were crossover trials. Only one trial (Kauppila 1985) contained sufficient information to be included in a meta-analysis. This trial was analysed using the method described by Elbourne and colleagues (Elbourne 2002), analysing information from both parts of the two-period, two-treatment crossover trial. For each binary outcome the log odds ratio, as a measure of the different effects of the two treatments, was calculated with its corresponding standard error. This information was then applied in the meta-analysis using the inverse variance method available in RevMan.

Unit of analysis issues

Statistical advice was sought regarding the analysis of crossover trials, to facilitate the appropriate inclusion of crossover data in meta-analysis.

Dealing with missing data

We analysed the data on an intention-to-treat basis as far as possible (i.e. including all randomised participants in analysis, in the groups to which they were randomised. Attempts were made to obtain missing data from the original trialists but these were unobtainable.

Assessment of heterogeneity

We intended to consider whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We intended to assess statistical heterogeneity by the measure of the I^2, with an I^2 measurement greater than 50% taken to indicate substantial heterogeneity (Higgins 2011)

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If ten or more studies had been included in the analysis, we would have used a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses, by analysing women with endometriosis and type of NSAID or type of diagnosis (by direct visualisation or just presumed), were not conducted as there were insufficient data. The decision about whether or not to combine the results of individual trials was dependent on an assessment of heterogeneity. In the first instance the trials were assessed for clinical and methodological homogeneity. Where trials were judged to be sufficiently homogeneous, it had been decided that a meta-analysis of these trials would be carried out and statistical heterogeneity investigated. In the event, this was not carried out.

Sensitivity analysis

We intended conducting sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding the eligibility and analysis. However, there was insufficient data to enable sensitivity analysis to be conducted.

Results

Description of studies

Results of the search

In earlier updates of this review, searches identified 53 citations. Of these, full papers were obtained for eight possibly relevant trials. Only two trials were identified which met the inclusion criteria for this review. One trial was identified which was potentially relevant but was then excluded. The other five possibly relevant trials were of naproxen used specifically for dysmenorrhoea, not endometriosis. No ongoing trials were identified.

Included studies

The first trial (Kauppila 1979) was a two-period, four-treatment crossover trial comparing indomethacin (25 mg, three times per day), acetylsalicylic acid (500 mg, three times per day), tolfenamic acid (200 mg, three times per day), and placebo (three times per day) in 24 women with symptomatic endometriosis (stage and severity were not described). Each woman received each of the four drugs for two menstrual cycles each but it was not clear how the women were randomised. Women were diagnosed with endometriosis by laparoscopy or pelvic examination.

The second trial (Kauppila 1985) was a two-period, two-treatment crossover trial comparing naproxen sodium (275 mg, four times per day) with placebo (four times per day) in 24 women with endometriosis as classified by the American Fertility Society (mild endometriosis, n = 7; moderate endometriosis, n = 8; severe endometriosis, n = 6). Women were diagnosed by pelvic examination, history of menstrual distress, or by direct visualisation of pelvic regions at laparoscopy or laparotomy. Each woman received either naproxen sodium for two menstrual cycles followed by placebo for two menstrual cycles, or placebo for two menstrual cycles followed by naproxen sodium for two menstrual cycles.

Excluded studies

The excluded trial (Cobellis 2004) assessed the use of the COX2-specific inhibitor (rofecoxib) for the management of pain related to endometriosis. However, this drug was withdrawn from the marketplace in November 2004 on the grounds of safety and, therefore, it is inappropriate to assess the efficacy of the product in this review. If the drug is re-launched then this decision will be reviewed when the review is updated.

Risk of bias in included studies

Information on potential risk of bias for each of the included studies is summarised in a risk of bias table and an overall summary provided in Figure 1; and Figure 2.

Allocation (selection bias)

Neither of the trials (Kauppila 1979; Kauppila 1985) provided information about the method of randomisation or concealment of allocation sequence. One trial (Kauppila 1985) described how each woman received either naproxen sodium for two menstrual cycles followed by placebo for two menstrual cycles, or placebo for two menstrual cycles followed by naproxen sodium for two menstrual cycles. In Kauppila 1979 each woman received each of four drugs (indomethacin, acetylsalicylic acid, tolfenamic acid, and placebo) for two menstrual cycles each, but it was not clear how the women were randomised.

Blinding (performance bias and detection bias)

Both of the trials (Kauppila 1979; Kauppila 1985) were described as double blind and one trial (Kauppila 1985) specifically mentioned the drugs being dispensed in identical capsules. No information was provided about the blinding of the outcome assessors or data analysers for either trial.

Incomplete outcome data (attrition bias)

In the trial Kauppila 1979, 24 women were randomised but only 18 were included in the analysis. The reasons for loss to follow up were not given. In the trial, Kauppila 1985, 24 women were randomised and only 20 were included in the analysis. The reasons given for loss to follow up included pregnancy (n = 1), psychiatric problems (n = 1), and unknown reasons (n = 2).

In the trial Kauppila 1979, data were presented graphically for each menstrual cycle (144 cycles) and not per woman in the trial. It was, therefore, not possible to link each of the menstrual cycles from one treatment against the corresponding menstrual cycle from an alternative treatment. It was also not possible to link the two menstrual cycles for each woman with each treatment. It appears as though the authors, in carrying out their analysis, did not take account of the pairing within each treatment group. For these reasons this trial was not included in the overall analysis.

Selective reporting (reporting bias)

Both included trials (Kauppila 1979; Kauppila 1985) were judged as having an unclear risk of bias because neither trial clearly prespecified primary and secondary outcomes.

Other potential sources of bias

The included trials were both judged as having an unclear risk of bias due to insufficient information to enable a judgement of low risk of bias.

Effects of interventions

Comparison of Naproxen Sodium versus Placebo.

Primary outcomes

1.1 Overall pain relief

One trial reported data on overall pain relief (Kauppila 1985). There was no evidence of a difference between naproxen sodium (275 mg, four times a day) and placebo in producing excellent to moderate relief of pain caused by endometriosis (Odds Ratio (OR) 3.27, 95% CI 0.61 to 17.69; 1 RCT, 24 women; *very low quality evidence*).

1.2 Unintended effects of treatment

One trial reported data on unintended effects of treatment (Kauppila 1985). This showed no evidence of a difference between women taking naproxen sodium and experiencing unintended effects of treatment compared to when they were taking placebo and experiencing unintended effects of treatment (OR 0.46, 95% CI 0.09 to 2.47; 1 RCT, 24 women; *very low quality evidence*). The unintended effects of treatment reported while taking naproxen sodium (n = 4) included fatigue, lightheadedness, eye lid swelling, and chest pain. The unintended effects of treatment reported while taking placebo (n = 7) included hypomenorrhoea (losing a small amount of menstrual blood but menstrual cycles still regular), diarrhoea, increased diuresis, headache, epigastric pain, nausea and vomiting, tremor, and dizziness.

Secondary outcomes

1.3 Requirement for additional medication

One trial (Kauppila 1985) provided data on the need for supplementary analgesia. This showed no evidence of a difference between women taking naproxen sodium and requiring supplementary analgesia compared to when they were taking placebo and requiring supplementary analgesia (OR 0.12, 95% CI 0.01 to 1.29; 1 RCT, 24 women) for pain caused by endometriosis.

The included trial did not report on the other secondary outcomes of this review (quality of life, effect on daily activities, absence from work or school, number of women requiring more invasive treatment, or participant satisfaction with treatment).

Discussion

Summary of main results

Despite rigorous searches, we only identified two randomised controlled trials comparing NSAIDs with placebo in the treatment of women with endometriosis. There was no evidence of a difference between NSAIDs and placebo for overall pain relief, unintended effects of treatment or requirement for additional medication (Summary of findings table 1). No data were report on the other secondary outcomes of this review (quality of life, effect on daily activities, absence from work or school, number of women requiring more invasive treatment, or participant satisfaction with treatment). The evidence is surprising given that NSAIDs are widely prescribed and are bought over the counter for the treatment of pain caused by endometriosis. In comparison, there is much literature suggesting the use of NSAIDs as a treatment for primary dysmenorrhoea. It is likely that prostaglandins are involved in pain causation in both groups of patients. A recent Cochrane review (Marjoribanks 2015) showed evidence that NSAIDs are an effective treatment for pain caused by primary dysmenorrhoea, although women using NSAIDs need to be aware of the risk of unintended effects of treatment.

Overall completeness and applicability of evidence

Due to the lack of randomised controlled trials in the area of NSAIDs as a treatment for endometriosis, we are unable to comment on many of the outcomes which are important to women who have endometriosis, such as quality of life, effect on daily activities, and absence from school or work. Only four NSAIDs (naproxen sodium, indomethacin, acetylsalicylic acid, and tolfenamic acid) were assessed for the treatment of endometriosis (Kauppila 1985; Kauppila 1979). One trial (Kauppila 1979) analysed three of these NSAIDs (indomethacin, acetylsalicylic acid, and tolfenamic acid) but was not analysed in this review as it had serious methodological flaws. However, there are many other prescribed and over-the-counter NSAIDs available. No evidence was found to support the use of these in controlling pain caused by endometriosis.

The one remaining trial (Kauppila 1985) included and analysed in this review showed no evidence of an effect when comparing NSAIDs (naproxen sodium) with placebo in the management of pain caused by endometriosis. There was inconclusive evidence to indicate whether or not women taking NSAIDs were less likely to take supplementary analgesia than those women taking placebo. We believe this is most likely because the trial was very small (randomising only 24 women) and, therefore, would recommend caution when applying these results to a larger population.

There was also inconclusive evidence to show whether or not women taking NSAIDs were more likely to experience unintended effects of treatment compared with women taking placebo. Four women experienced unintended effects of treatment whilst taking naproxen sodium compared with seven women while taking placebo. It is possible that the unintended effects reported when women were randomised to placebo could have been related to the pain caused by endometriosis rather than to the placebo itself. However, the small number of women included in this trial make it difficult to draw any firm conclusions.

Quality of the evidence

The risk of bias was judged to be unclear due to lack of methodological detail. The overall quality of the evidence using GRADE methodology was judged to be of *very low quality* due to unclear risk of bias, imprecision with wide confidence intervals and evidence being based on a single small study (Summary of findings table 1).

Potential biases in the review process

The authors believe they have minimised the potential biases in the review process by searching published and unpublished literature with no restrictions on date of publication or language. We were unable to judge the potential effect of publication bias as less than ten trials were identified.

Agreements and disagreements with other studies or reviews

Despite the findings of this review, it is important to highlight the findings of another Cochrane review of NSAIDs for the management of pain caused by primary dysmenorrhoea (Marjoribanks 2015), which showed that there is insufficient evidence to determine which (if any) individual NSAID is the most safe and effective treatment.

Authors' conclusions

Implications for practice

There is inconclusive evidence to show whether non-steroidal anti-inflammatory drugs (NSAIDs) (naproxen sodium) are effective for the treatment of pain caused by endometriosis. There is no evidence to suggest whether any individual NSAID is more effective than others. As shown in other Cochrane reviews, women using NSAIDs need to be aware of the possibility that these drugs may cause unintended effects.

Implications for research

The two included studies were conducted in the late 1970s and mid 1980s, and both randomised small numbers of women. A systematic search of the literature has found no randomised controlled trials comparing NSAIDs with other treatments. One trial compared different types of NSAIDs; however, this had methodological limitations. More trials with larger numbers of women are needed, ensuring they are of a robust design and assessing and reporting the outcomes that are important to women with endometriosis (for example quality of life, effects on daily activities, absence from school or work, and need for a more invasive treatment).

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Contributions of authors

2016: There was no contribution by authors as no trials were identified by the editorial team.

Previous updates: CA, SH, and AP were involved in all aspects of the review. CA and SH were responsible for the first draft. AP gave feedback on three subsequent drafts. CA, SH, and AP considered and addressed referees' comments. CA, DG, SH, and AP were involved in updating the review.

Declarations of interest

One of the authors (CA) has endometriosis and is a member of Endometriosis UK. One of the authors (AP) was Chairman of Endometriosis UK at the time the review was originally written.

Differences between protocol and review

The original review had six primary outcomes. In 2016 these were reduced to two:

- Pain relief (measured either by visual analogue scale (VAS), other validated scales, or as a dichotomous outcome, for example improved or not improved)
- Unintended effects from treatment (incidence and duration of total side-effects, and type of side-effects)

The remaining primary outcomes became secondary outcomes.

Published notes

Characteristics of studies

Characteristics of included studies

Kauppila 1979

Methods	Trial design: 2-period, 4-treatment crossover trial
Participants	24 women randomised; 18 analysed. Mean age 33 (22-43) years Inclusion criteria: women with symptomatic endometriosis (stage and severity not described). Women were diagnosed by laparoscopy (n=13) and by pelvic examination (n=5) Exclusion criteria: not clear Setting: Finland Timing: Unclear
Interventions	Group 1 - indomethacin 25 mg given 3 x daily for 2 menstrual cycles then crossover to acetylsalicylic acid, tolfenamic acid, and placebo for 2 menstrual cycles each (n = 6) Group 2 - acetylsalicylic acid 500 mg given 3 x daily for 2 menstrual cycles then crossover to tolfenamic acid, placebo, and indomethacin for 2 menstrual cycles each (n = 6). Group 3 - tolfenamic acid 200 mg given 3 x daily for 2 menstrual cycles then crossover to placebo, indomethacin, and acetylsalicylic acid for 2 menstrual cycles each (n = 6) Group 4 - placebo was given 3 x daily for 2 menstrual cycles then crossover to

	indomethacin, acetylsalicylic acid, and tolfenamic acid for 2 menstrual cycles each (n = 6)
Outcomes	These were self reported using a questionnaire completed by the patient immediately after each menstrual cycle Pain relief: pelvic pain, lower back pain, pain in walking, dyspareunia, pain on defecation, headache; number not reported but described more common with placebo and indomethacin Quality of life: not reported Effect on daily activities: not reported Absence from work or school: not reported Unintended effects from treatment: gastro-intestinal complaints (nausea and vomiting), number not reported but described as more common with indomethacin; psychic complaints (insomnia and nervousness), number not reported but described as more common with indomethacin No. of women requiring more invasive treatment: not reported Requirements for additional medication: not reported Patient satisfaction with treatment: not reported
Notes	Drugs for use in the trial were provided by Medica Ltd, Helsinki, Finland. "The authors wish to thank Medica Ltd, Helsinki, Finland for the drugs."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Unclear risk	"placebo-controlled double-blind trial"
Incomplete outcome data (attrition bias)	Low risk	"Twenty-four patients...volunteered for this study. Eighteen women completed the trial; the remaining six terminated treatment for a variety of personal reasons."
Selective reporting (reporting bias)	Unclear risk	Prespecified primary and secondary outcomes were not clearly defined.
Other bias	Unclear risk	Insufficient information provided to enable a judgement of low risk of bias.

Kauppila 1985

Methods	Trial design: 2-period, 2-treatment crossover trial
Participants	24 women randomised; 20 analysed. Mean age Group 1 32 years, Group 2 35 years. Inclusion criteria: women with endometriosis classified by the American Fertility Society (mild endometriosis n=7; moderate endometriosis n=8; severe endometriosis n=6) Women were diagnosed by pelvic examination, history of

	menstrual distress, and by direct visualisation of pelvic regions at laparoscopy or laparotomy Exclusion criteria: not clear Setting: Finland Timing: Unclear
Interventions	Group 1 - naproxen sodium (NSAID) 275 mg (102 tablets) 4 x daily for 2 menstrual cycles, then crossover to placebo for 2 menstrual cycles (n = 12) Additional interventions: additional analgesia was allowed if no relief after the first two doses of NSAID Group 2 - placebo was given for 2 menstrual cycles, then crossover to naproxen sodium (NSAID) for 2 menstrual cycles (n = 12). Additional interventions: additional analgesia was allowed if no relief after first two doses
Outcomes	These were all self reported using a questionnaire completed by the patient immediately after each menstrual cycle Pain relief: measured after each menstrual cycle (score 3 to -1) Quality of life: not reported Effect on daily activities: activity of patient (score 4 to 0) Absence from work or school: not reported Unintended effects from treatment: fatigue, lightheadedness, eye lid edema, and chest pain (n=4 while taking naproxen sodium); hypomenorrhoea, diarrhoea, increased diuresis, headache, epigastric pain, nausea and vomiting, tremor, and dizziness (n=7 while taking placebo) No. of women requiring more invasive treatment: not reported Requirements for additional medication: supplemental analgesia was more common in the placebo group (14) than in the NSAID group (2) Patient satisfaction with treatment: not reported
Notes	Drugs used in the trial were supplied by Syntex Research, Maidenhead, England. "The study drugs were kindly supplied by Syntex Research, Maidenhead, England."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Low risk	"The study was conducted according to a randomized, double-blind, four-period crossover design."
Incomplete outcome data (attrition bias)	Low risk	"Twenty-four patients...entered the present study...One patient became pregnant before the first treatment, one patient had psychiatric problems that rendered her responses unreliable, and two patients were lost to follow-up for unknown reasons during the trial."
Selective reporting (reporting bias)	Unclear risk	Prespecified primary and secondary outcomes were not clearly defined.

Other bias	Unclear risk	Insufficient information provided to enable a judgement of low risk of bias.

Footnotes

Characteristics of excluded studies

Cobellis 2004

Reason for exclusion	This trial assessed the use of the COX2-specific inhibitor (rofecoxib) for the management of pain related to endometriosis. However this drug was withdrawn from the marketplace in November 2004 on safety grounds and therefore it is inappropriate to assess the efficacy of the product in this review. If the drug is re launched this decision will be reviewed when the review is updated.

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 NSAID compared to placebo for pain in women with endometriosis

NSAID compared to placebo for pain in women with endometriosis

Patient or population: Women with endometriosis
Setting: Finland
Intervention: Non-steroidal anti-inflammatory drugs (NSAIDs)
Comparison: placebo

Outcomes	Anticipated absolute effects * (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with NSAID				
Pain relief assessed with: Overall pain relief score follow up: median 2 months	50 per 100	77 per 100 (38 to 95)	OR 3.27 (0.61 to 17.69)	24 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1] [2]	
Unintended effects from treatment	58 per 100	39 per 100 (11 to 78)	OR 0.46 (0.09 to 2.47)	24 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1] [2]	

Quality of life - not reported	-	-	-	-	-	
Effect on daily activities - not reported	-	-	-	-	-	
Absence from work or school - not reported	-	-	-	-	-	
Number of women requiring more invasive treatment - not reported	-	-	-	-	-	
Requirements for additional medication	83 per 100	38 per 100 (5 to 87)	OR 0.12 (0.01 to 1.29)	24 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1] [2]	
Participant satisfaction with treatment - not reported						

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Downgraded one level due to overall unclear risk of bias for included trial.

[2] Downgraded two levels for imprecision because confidence interval is wide, consistent with benefit and harm and evidence based on a single small trial.

Additional tables

References to studies

Included studies

Kauppila 1979

[CRSSTD: 2750617]

* Kauppila A, Puolakka J, Ylikorkala O. Prostaglandin biosynthesis inhibitors and endometriosis. Prostaglandins 1979;18(4):655-61. [CRSREF: 2750618]

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Kauppila 1985

[CRSSTD: 2750620]

Kauppila A, Ronnberg L. Naproxen sodium in dysmenorrhoea secondary to endometriosis. Obstetrics and Gynaecology 1985;65(3):379-83. [CRSREF: 2750621]

Excluded studies

Cobellis 2004

[CRSSTD: 2750622]

Cobellis L, Razzi S, De Simone S, Sartini A, Fave A, Danero S et al. The treatment with a COX-2 specific inhibitor is effective in the management of pain related to endometriosis. European Journal of Obstetrics, Gynecology, and Reproductive Biology 2004;116:100-2. [CRSREF: 2750623]

Studies awaiting classification

Ongoing studies

Other references

Additional references

Barbieri 1990

Barbieri RL. Endometriosis 1990 - current treatment approaches. Drugs 1990;39(4):502-10.

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Murphy AA. Clinical aspects of endometriosis. Annals of the New York Academy of Sciences 2002;955:1-10, Discussion 34-6, 396-406.

Prentice 2003

Prentice A, Deary AJ, Bland E. Progestagens and anti-progestagens for pain associated with endometriosis (Cochrane Review). Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD002122. DOI: 10.1002/14651858.CD002122.

rAFS 1985

Revised American Fertility Society classification of endometriosis. Revised American Fertility Society classification of endometriosis. Fertility and Sterility 1985;43:351-2.

RevMan 2014

Review Manager (RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. [Computer program].

Rice 2002

Rice VM. Conventional medical therapies for endometriosis. Annals of the New York Academy of Sciences 2002;955:343-52, Discussion 389-93, 396-406.

Vessy 1992

Vessey MP, Villard-Mackintosh L, Painter R. Epidemiology of endometriosis in women attending family planning clinics. BMJ 1992;306(6871):182-4.

Other published versions of this review

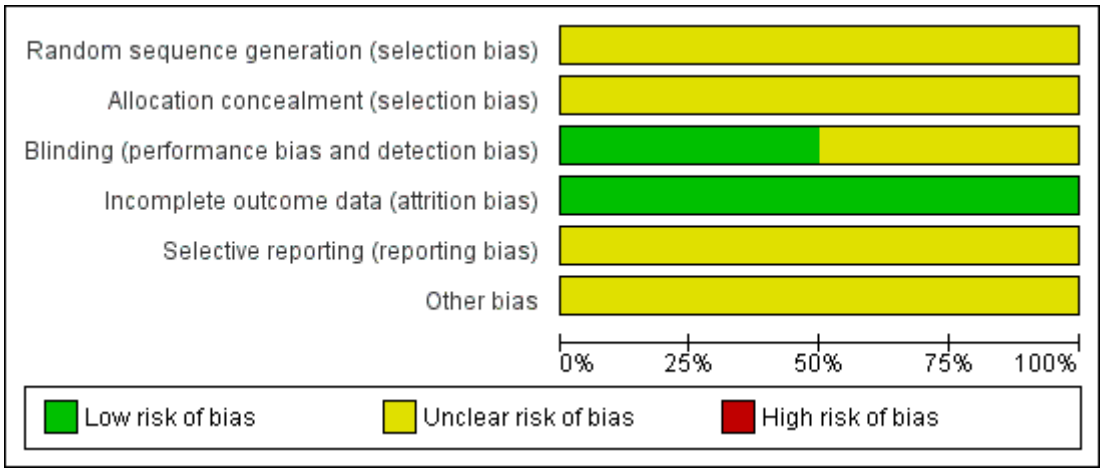
Data and analyses

1 NSAID versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Overall pain relief	1		odds ratio (IV, Fixed, 95% CI)	3.27 [0.61, 17.69]
1.2 Unintended effects of treatment	1		odds ratio (IV, Fixed, 95% CI)	0.46 [0.09, 2.47]
1.3 Requirements for additional medication	1		odds ratio (IV, Fixed, 95% CI)	0.12 [0.01, 1.29]

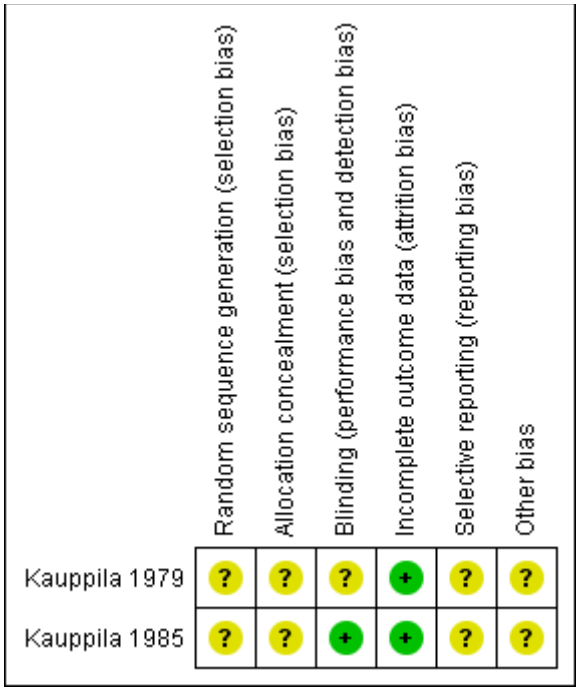
Figures

Figure 1



Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 2



Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Sources of support

Internal sources

- Cochrane Collaboration Secretariat, UK
- UK Cochrane Centre, NHS R & D Programme, UK
- University of Cambridge, UK

External sources

- No sources of support provided

Feedback

Appendices

1 Cochrane Gynaecology and Fertility Group search strategy

From inception to 19 October 2016

Procite platform

Keywords CONTAINS "endometriosis" or "endometriosis scores" or "pelvic pain" or "dyschezia" or "dyspareunia" or Title CONTAINS "endometriosis" or "endometriosis scores" or "pelvic pain" or "dyschezia" or "dyspareunia"

AND

Keywords CONTAINS "nonsteroidal" or "NSAID" or "NSAIDs" or "mefenamic acid" or "Naprosyn" or "naproxen" or "Ibuprofen" or "Flurbiprofen " or "Meclofenamic Acid" or "Meclofenamate" or "diclofenac" or "acetylsalicylic" or "Aspirin" or "indomeixin" or "indometacin" or "indomethacin"or "Ketoprofen" or "Piroxicam" or "Flufenamic Acid" or "nimesulide"or "COX-2 inhibitors" or "cyclooxygenase" or Title CONTAINS "nonsteroidal" or "NSAID" or "NSAIDs" or "mefenamic acid" or "Naprosyn" or "naproxen" or "Ibuprofen" or

"Flurbiprofen " or "Meclofenamic Acid" or "Meclofenamate" or "diclofenac" or "acetylsalicylic" or "Aspirin" or "indomeixin" or "indometacin" or "indomethacin"or "Ketoprofen" or "Piroxicam" or "Flufenamic Acid" or "nimesulide"or "COX-2 inhibitors" or "cyclooxygenase" (31 hits)

2 CENTRAL CRSO search strategy

From inception to 19 October 2016

CRSO web platform

#1 MESH DESCRIPTOR Endometriosis EXPLODE ALL TREES 509

#2 Endometriosis:TI,AB,KY 1127

#3 dyspareunia*:TI,AB,KY 483

#4 dyschezia:TI,AB,KY 18

#5 (pelvic adj2 pain):TI,AB,KY 840

#6 #1 OR #2 OR #3 OR #4 OR #5 2111

#7 MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL TREES 14868

#8 MESH DESCRIPTOR Cyclooxygenase 2 Inhibitors EXPLODE ALL TREES 887

#9 (nonsteroidal* or non steroidal*):TI,AB,KY 8816

#10 nsaid*:TI,AB,KY 2886

#11 (COX 2 or COX-2 or COX2):TI,AB,KY 896

#12 (diclofenac or flurbiprofen or ibuprofen or meclofenamic acid or mefenamic acid or naproxen or aspirin):TI,AB,KY 16304

#13 (etoricoxib* or lumiracoxib* or parecoxib*):TI,AB,KY 542

#14 (rofecoxib* or valdecoxib*):TI,AB,KY 509

#15 (acemetacin or celecoxib or dexibuprofen or dexketoprofen or indometacin or ketoprofen):TI,AB,KY 2744

#16 (ponstan or voltaren):TI,AB,KY 223

#17 (cyclooxygenase inhibitor* or cyclooxygenase 2 inhibitor*):TI,AB,KY 1665

#18 (sulphonanilide* or flufenamic or nimesulide):TI,AB,KY 386

#19 (salicylate* or sulindac or acetylsalicylic):TI,AB,KY 6178

#20 piroxicam:TI,AB,KY 1051

#21 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 30354

#22 #6 AND #21 89

3 MEDLINE search strategy

From 1946 to 19 October 2016

Ovid platform

1 exp Endometriosis/ (18905)
2 Endometriosis.tw. (18913)

3 dyspareuni$.tw. (3086)
4 (pelvic adj2 pain).tw. (7661)
5 dyschezia.tw. (220)
6 or/1-5 (31643)
7 exp anti-inflammatory agents, non-steroidal/ or exp aspirin/ or exp diclofenac/ or exp flurbiprofen/ or exp ibuprofen/ or exp indomethacin/ or exp ketoprofen/ or exp meclofenamic acid/ or exp mefenamic acid/ or exp naproxen/ or exp piroxicam/ or exp cyclooxygenase inhibitors/ or exp cyclooxygenase 2 inhibitors/ (177771)
8 nonsteroidal$.tw. (20990)
9 non-steroidal$.tw. (16588)
10 nsaid$.tw. (21016)
11 (COX 2 or COX-2 or COX2).tw. (27740)
12 (diclofenac or flurbiprofen or ibuprofen or meclofenamic acid or mefenamic acid or naproxen or aspirin).tw. (65356)
13 (etoricoxib$ or lumiracoxib$ or parecoxib$).tw. (1135)
14 (rofecoxib$ or valdecoxib$).tw. (2313)
15 (acemetacin or celecoxib or dexibuprofen or dexketoprofen or indometacin or ketoprofen).tw. (9277)
16 (ponstan or voltaren).tw. (406)
17 (cyclooxygenase inhibitor$ or cyclooxygenase 2 inhibitor$).tw. (6591)
18 (sulphonanilide$ or flufenamic or nimesulide).tw. (2422)
19 (salicylate$ or sulindac or acetylsalicylic).tw. (19959)
20 piroxicam.tw. (2765)
21 or/7-20 (242543)
22 6 and 21 (515)
23 randomized controlled trial.pt. (432907)
24 controlled clinical trial.pt. (91818)
25 randomized.ab. (373304)
26 placebo.tw. (185009)
27 clinical trials as topic.sh. (180215)
28 randomly.ab. (265279)
29 trial.ti. (163329)
30 (crossover or cross-over or cross over).tw. (71501)
31 or/23-30 (1098911)
32 exp animals/ not humans.sh. (4325953)
33 31 not 32 (1011983)
34 22 and 33 (86)

4 EMBASE search strategy

From 1974 to 19 October 2016

Ovid Platform

1 exp ENDOMETRIOSIS/ (30469)
2 endometriosis.tw. (25587)
3 (pelv$ adj2 pain).tw. (11770)
4 dyschezia.tw. (417)
5 dyspareunia.tw. (5383)
6 or/1-5 (44542)
7 exp nonsteroid antiinflammatory agent/ (507110)
8 exp acetylsalicylic acid/ (183969)
9 exp CELECOXIB/ (18678)
10 exp DICLOFENAC/ (34108)

11 exp ETORICOXIB/ (2430)
12 exp FLURBIPROFEN/ (7048)
13 exp ibuprofen/ or exp ketoprofen/ or exp ketorolac/ or exp mefenamic acid/ or exp naproxen/ or exp piroxicam/ or exp rofecoxib/ or exp salicylic acid/ or exp valdecoxib/ (100090)
14 nonsteroidal$.tw. (24626)
15 non-steroidal$.tw. (22681)
16 nsaid$.tw. (33773)
17 exp prostaglandin synthase inhibitor/ or exp cyclooxygenase 2 inhibitor/ (474499)
18 (COX 2 or COX-2 or COX2).tw. (36253)
19 (acetylsalicylic acid or celecoxib or diclofenac or etoricoxib).tw. (31334)
20 (flurbiprofen or ibuprofen or ketoprofen or ketorolac).tw. (24017)
21 (mefenamic acid or naproxen or piroxicam or rofecoxib or salicylic or valdecoxib).tw. (25457)
22 (sulphonanilide$ or flufenamic or nimesulide).tw. (3217)
23 (ponstan or voltaren).tw. (2942)
24 (acemetacin or dexibuprofen or dexketoprofen or indometacin).tw. (1861)
25 (cyclooxygenase inhibitor$ or cyclooxygenase 2 inhibitor$).tw. (7200)
26 or/7-25 (574498)
27 6 and 26 (1737)
28 Clinical Trial/ (978910)
29 Randomized Controlled Trial/ (454730)
30 exp randomization/ (83085)
31 Single Blind Procedure/ (26186)
32 Double Blind Procedure/ (135680)
33 Crossover Procedure/ (53307)
34 Placebo/ (319417)
35 Randomi?ed controlled trial$.tw. (146931)
36 Rct.tw. (21980)
37 random allocation.tw. (1611)
38 randomly allocated.tw. (26329)
39 allocated randomly.tw. (2198)
40 (allocated adj2 random).tw. (842)
41 Single blind$.tw. (18462)
42 Double blind$.tw. (171618)
43 ((treble or triple) adj blind$).tw. (626)
44 placebo$.tw. (245414)
45 prospective study/ (380568)
46 or/28-45 (1749996)
47 case study/ (91637)
48 case report.tw. (320145)
49 abstract report/ or letter/ (980824)
50 or/47-49 (1383573)
51 46 not 50 (1700346)
52 27 and 51 (481)

5 PsycINFO search strategy

From 1806 to 19 October 2016

Ovid Platform

1 exp Gynecological Disorders/ (1613)
2 endometriosis.tw. (206)

3 (pelv$ adj2 pain).tw. (517)
4 dyspareunia.tw. (527)
5 or/1-4 (2611)
6 exp Aspirin/ (438)
7 exp Analgesic Drugs/ (17453)
8 (non?steroidal adj5 anti?inflammatory).tw. (86)
9 (non-steroidal$ adj5 anti-inflammatory).tw. (460)
10 nsaid$.tw. (799)
11 (COX 2 or COX-2).tw. (733)
12 (acetylsalicylic acid or celecoxib or diclofenac or etoricoxib).tw. (594)
13 (flurbiprofen or ibuprofen or ketoprofen or ketorolac).tw. (627)
14 (mefenamic acid or naproxen or piroxicam or rofecoxib or salicylic acid or valdecoxib).tw. (341)
15 aspirin.tw. (1033)
16 or/6-15 (20157)
17 5 and 16 (31)

6 CINAHL search strategy

From 1982 to 19 October 2016

Ebsco platform

#	Query	Results
S42	S29 AND S41	40
S41	S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40	1,081,306
S40	TX allocat* random*	5,281
S39	(MH "Quantitative Studies")	14,919
S38	(MH "Placebos")	9,827
S37	TX placebo*	39,650
S36	TX random* allocat*	5,281
S35	(MH "Random Assignment")	41,699
S34	TX randomi* control* trial*	110,746
S33	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	857,082
S32	TX clinic* n1 trial*	190,012
S31	PT Clinical trial	79,719
S30	(MH "Clinical Trials+")	203,397
S29	S6 AND S28	104
S28	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	30,886
S27	TX piroxicam	209
S26	TX(salicylate* or sulindac or acetylsalicylic)	1,237
S25	TX(sulphonanilide* or flufenamic or nimesulide)	100
S24	TX(cyclooxygenase inhibitor* or cyclooxygenase 2 inhibitor*)	801

S23	TX(ponstan or voltaren)	28
S22	TX(acemetacin or celecoxib or dexibuprofen or dexketoprofen or indometacin or ketoprofen)	1,030
S21	TX(rofecoxib* or valdecoxib*)	520
S20	TX(etoricoxib* or lumiracoxib* or parecoxib*)	316
S19	TX(diclofenac or flurbiprofen or ibuprofen or meclofenamic acid or mefenamic acid or naproxen or aspirin)	14,883
S18	TX (COX 2 or COX-2 or COX2)	5,065
S17	TX nsaid*	3,651
S16	TX nonsteroidal* or TX non steroidal*	12,754
S15	(MM "Cox-2 Inhibitors")	1,857
S14	(MM "Piroxicam")	104
S13	(MM "Naproxen")	269
S12	(MM "Ketorolac")	273
S11	(MM "Indomethacin")	450
S10	(MM "Ibuprofen")	798
S9	(MM "Diclofenac")	566
S8	(MM "Aspirin")	4,207
S7	(MM "Antiinflammatory Agents, Non-Steroidal+")	12,096
S6	S1 OR S2 OR S3 OR S4 OR S5	5,662
S5	TX (pelvic N2 pain)	2,557
S4	TX dyschezia	19
S3	TX dyspareuni*	916
S2	TX Endometriosis	2,764
S1	(MM "Endometriosis")	1,702