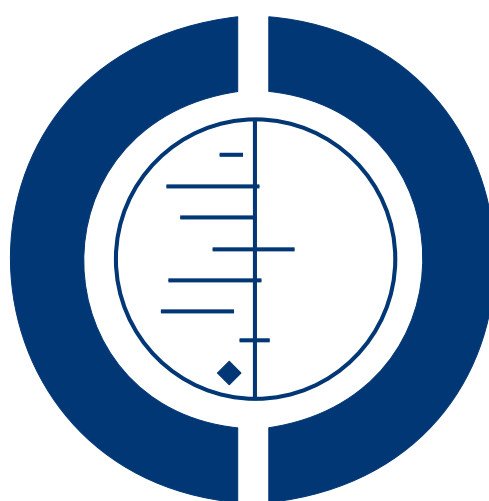


# Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use (Review)

Grimes DA, Hubacher D, Lopez LM, Schulz KF



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[Intervention Review]

# Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

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## ABSTRACT

### Background

Heavy bleeding and pain are the most common reasons why women discontinue IUDs. Non-steroidal anti-inflammatory drugs, which inhibit prostaglandin synthesis, have been shown to be effective in reducing menstrual bleeding and pain in women without IUDs.

### Objectives

This review summarizes all randomized controlled trials studying use of nonsteroidal anti-inflammatory drugs for treatment of bleeding or pain associated with IUD use. Trials of prophylactic use of these drugs around the time of IUD insertion were also included.

### Search strategy

We searched for relevant trials in PubMed, CENTRAL, POPLINE, EMBASE, LILACS, and CINAHL. We also searched for clinical trials in ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP). We wrote to the authors of trials identified to seek other published or unpublished trials.

### Selection criteria

We included all randomized controlled trials in any language that tested one or more nonsteroidal anti-inflammatory drugs for treatment or prevention of bleeding or pain associated with IUD insertion or use.

### Data collection and analysis

Two authors independently abstracted data from relevant trials, and we entered data into RevMan for analysis.

### Main results

We found 15 trials from 10 countries; the total number of participants was 2702. Nonsteroidal anti-inflammatory drugs (naproxen, suprofen, mefenamic acid, ibuprofen, indomethacin, flufenamic acid, alclofenac, and diclofenac) were effective in reducing menstrual blood loss associated with IUD use. This held true for women with and without complaints of heavy bleeding. Similarly, these drugs were effective in reducing pain associated with IUD use. In contrast, prophylactic use of nonsteroidal anti-inflammatory drugs had mixed results; studies with ibuprofen found no effect on pain after insertion on IUD discontinuation. No important differences emerged in the one trial comparing the effect of different NSAIDs on bleeding.

## Authors' conclusions

Nonsteroidal anti-inflammatory drugs reduce bleeding and pain associated with IUD use. NSAIDs should be considered first-line therapy; if NSAIDs are ineffective, tranexamic acid may be considered as second-line therapy. Prophylactic ibuprofen administration with the first six menses after insertion appears unwarranted.

## PLAIN LANGUAGE SUMMARY

### Pain relievers for bleeding and pain related to intrauterine devices used for birth control

Heavy menstrual bleeding and cramping are the most common reasons why women stop using an intrauterine device (IUD) for birth control. A class of drugs (nonsteroidal anti-inflammatory drugs, or NSAIDs) reduces menstrual bleeding and cramping in women who are not using an IUD. These drugs, such as naproxen and ibuprofen, are sold over-the-counter as pain relievers in many countries. Hence, researchers have studied whether these same drugs might reduce bleeding and pain associated with use of intrauterine devices. This might lead to more comfortable use of IUDs for longer periods of time.

We searched for and summarized all the randomized controlled trials that looked at using these drugs to treat bleeding or pain related to an IUD. We also included trials that studied the use of these drugs to prevent these problems.

We found 15 trials from 10 countries, with more than 2700 women studied. These drugs reduced both bleeding and pain with intrauterine device use. Whether one drug is better than another was not clear. Similarly, the best dosing was not clear. Preventive treatment with these drugs around the time of IUD insertion had mixed results. No serious problems were reported, but stomach upset and sleepiness can occur with this class of drugs. Because of their safety, low cost, and wide availability, these drugs are appropriate treatment for women who have troublesome bleeding or pain with IUD use.

## BACKGROUND

Abnormal uterine bleeding and pain are the most common medical reasons for premature discontinuation of the intrauterine device (IUD). The IUD is the most common method of reversible contraception worldwide (147 million current users) (United Nations 2003), so premature discontinuation affects large numbers of women. Each year, an estimated 40 million women have an IUD inserted. From 5% to 15% of women discontinue IUD use within one year because of bleeding or pain (Speroff 1996). In a large trial sponsored by the World Health Organization, the cumulative net probability of removal of a Copper T380A IUD for pain or bleeding over 12 years of use was 36 per 100 women (WHO 1997). The corresponding figure with the Copper TCu220C was 34 per 100 women.

Both non-medicated and copper-bearing devices increase menstrual blood loss. Early studies found that non-medicated devices, such as the Lippes Loop, caused more bleeding than did copper devices, such as the Copper 7 and Copper T (Gallegost 1978; Guillebaud 1976; Israel 1974). More recent studies with the Cop-

per T380A indicated a persistent increase in menstrual blood loss of about 55%. However, in Swedish women this did not lead to iron deficiency anemia (Milsom 1995). Some women view the increased bleeding as an annoyance. For others, increased bleeding may be unacceptable (Connell 2002). Although cramping is common in the early days after IUD insertion, this commonly resolves (Connell 2002; Speroff 1996). However, some women have an increase in dysmenorrhea (painful, difficult menses) with non-medicated and copper IUDs. In contrast, progestin-releasing devices alleviate dysmenorrhea for most women (Pakarinen 2001).

Excessive prostaglandin release in the endometrial cavity appears to play a role in both bleeding and pain related to IUDs (Ylikorkala 1994). For example, endometrial concentrations of some prostaglandin metabolites correlate with measured blood loss in IUD users. Prostacyclin (PGI<sub>2</sub>) causes vasodilation and inhibits platelet aggregation. Thromboxane exists in two forms: A<sub>2</sub> is active but unstable and is quickly converted into B<sub>2</sub>, which is inactive. Thromboxane causes vasoconstriction and blood clotting. Among Chinese women using a copper T IUD and hav-

ing bleeding greater than 80 mL per cycle, endometrial levels of 6-keto-PGF<sub>1α</sub> (a metabolite of prostacyclin) were significantly higher than those of women with either a levonorgestrel IUD or no IUD (Zhang 1992). In contrast, the endometrial thromboxane B<sub>2</sub> concentrations were significantly higher in women using the levonorgestrel IUD. The authors speculated that the imbalance between the prostacyclin and thromboxane A<sub>2</sub> may play a role in heavy bleeding with IUDs. Another Chinese study correlated increases in 6-keto-PGF<sub>1α</sub> with menstrual blood loss in IUD users (Zheng 1988).

Non-steroidal anti-inflammatory drugs (NSAIDs) are prostaglandin synthetase inhibitors. By decreasing production of endometrial prostaglandins, they can alleviate both heavy uterine bleeding (Lethaby 2007) and dysmenorrhea (Marjoribanks 2003). Since the discovery of this effect of NSAIDs in the mid-1970s, several different drugs in this class have been used to treat or prevent heavy uterine bleeding and pain associated with IUD use as well. This review summarizes the randomized controlled trials evaluating an NSAID for these purposes.

## OBJECTIVES

To review all randomized controlled trials that have evaluated an NSAID for treatment or prevention of heavy uterine bleeding or pain associated with IUD use.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included all randomized controlled trials in any language that compared any NSAID for treating heavy uterine bleeding or pain associated with any IUD use. We excluded cohort studies and before-after studies.

#### Types of participants

We included women of reproductive age of any gravidity and parity who were using an IUD.

#### Types of interventions

Any NSAID used for the treatment or prevention of heavy uterine bleeding or pain associated with IUD was included. Comparisons included a placebo, another NSAID, or other treatment, such as tranexamic acid or desmopressin.

### Types of outcome measures

Outcome measures for bleeding included quantitative measurements of blood loss (Hallberg 1964), semi-quantitative assessments of blood loss by pictorial blood assessment scores (Higham 1990; Reid 2000), or IUD discontinuation (Hubacher 2006). Participant perceptions of bleeding using categorical scales or menstrual diary cards could also be included. Level of pain was reported on several different Likert scales, ranging from none to extreme pain. We also examined harms of therapy when provided in trial reports.

### Search methods for identification of studies

#### Electronic searches

We searched the computerized databases of MEDLINE via PubMed, POPLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, LILACS, and CINAHL. In addition, we searched for recent clinical trials through ClinicalTrials.gov (National Institutes of Health, USA) and the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization. The strategies are given below.

#### MEDLINE via PubMed

(intrauterine devices OR intrauterine system\* OR IUD\* OR IUCD\* OR IUS) AND (NSAID\* OR anti inflammatory agents, nonsteroidal)

#### CENTRAL

contracept\* AND (non-steroidal anti-inflammatory OR NSAID\*) in Title, Abstract or Keywords

#### POPLINE

(iud\*/iucd\*/intrauterine device\*) & (NSAID\*/nonsteroidal anti inflammatory agent\*)

#### LILACS

intrauterine devices or intrauterine device or dispositivos intrauterinos or dispositivos Intra-uterinos OR IUD or iuds OR IUCD or iucds [Words] and bleeding or pain [Words]

#### EMBASE

(INTRAUTERINE CONTRACEPTIVE DEVICE or INTRAUTERINE(1N)DEVICE? or IUD? OR IUCD?) and (NONSTEROID ANTI INFLAMMATORY AGENT or NONSTEROID ANTI INFLAMMATORY DRUG or

NONSTEROID ANTIINFLAMMATORY AGENT or NON-  
STEROIDAL(1N)ANTI(1N)INFLAMMATORY(1N) AGENT  
or  
NON-  
TEROIDAL(1N)ANTI(1N)INFLAMMATORY(1N)DRUG or  
NONSTEROIDAL(1N)ANTIINFLAMMATORY(1N)AGENT?  
or  
NON-  
TEROIDAL(1N)ANTIINFLAMMATORY(1N)DRUG? or  
NSAID?)

### CINAHL

(intrauterine device\* or IUD\* or IUCD\*)

and

(non?steroidal anti?inflammatory agent? or non?steroidal anti?in-  
flammatory drug? or non?steroidal anti?inflammatory agent\* or  
non?steroidal anti?inflammatory drug\* or NSAID\*)

### ClinicalTrials.gov

Search terms: non-steroidal anti-inflammatory OR NSAID

Condition: contraceptive OR contraception

### ICTRP

Title or Intervention: non-steroidal anti-inflammatory OR  
NSAID

Condition: contraception OR contraceptive

### Searching other resources

We wrote to authors of published trial reports to solicit other  
published or unpublished trials that we may have missed. We also  
contacted trial-report authors as needed to supplement published  
information.

### Data collection and analysis

We assessed all titles and abstracts found for inclusion.

### Data extraction and management

Two authors (Grimes and Lopez) independently abstracted data  
from the studies identified to improve accuracy. One author en-  
tered data into RevMan 4.2, and a second confirmed correct data  
entry.

### Assessment of risk of bias in included studies

We evaluated the methodological quality of the trials for potential  
biases by qualitatively assessing the study design, randomization  
method, allocation concealment, blinding, premature discontin-  
uation rates, and loss to follow-up rates.

### Data synthesis

Peto odds ratios with 95% confidence intervals were used for di-  
chotomous outcomes, such as pregnancy. We reported weighted  
mean differences for measured blood loss. We did not perform  
subgroup analyses.

Since no important 'carryover' effect (Elbourne 2002; Higgins  
2005) of NSAIDs has been documented from one menstrual cycle  
to another (Lethaby 2007; Roy 1981), we combined all measure-  
ments from identical treatments in crossover trials. None of these  
trials was amenable to meta-analysis (Higgins 2005).

### Sensitivity analysis

Sensitivity analyses were not performed, because we were unable  
to aggregate these trials.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

We identified 15 randomized controlled trials that met our eli-  
gibility criteria. The total number of participants was 2702, al-  
though the number ranged widely in the individual trials, from 10  
(Hahn 1979) to 2019 participants (Hubacher 2006). Most trials  
were small: 12 had fewer than 100, and two had between 100 and  
200 participants. The trials came from 10 countries in Europe,  
the Middle East, North and South America, and Asia. Seven trials  
focused on prevention, while eight focused on treatment. The pre-  
vention trials gave NSAIDs to asymptomatic women as prophyl-  
axis. The treatment trials examined use of NSAIDs as therapy for  
heavy bleeding, pain, or both. Among the trials studying bleeding,  
some used quantitative (Hallberg 1964) and others qualitative as-  
sessments of blood loss, such as pictorial scores (Higham 1990;  
Reid 2000) or Likert scales.

### Prevention trials

Seven trials examined prophylactic use of NSAIDs (Hahn 1979;  
Hubacher 2006; Jensen 1998; Massey 1974; Roy 1981; Topozada  
1982; Ylikorkala 1978). Two of these studied bleeding (Hahn  
1979; Roy 1981), two focused on pain (Jensen 1998; Massey  
1974), and three studied both of these outcomes (Hubacher 2006;  
Topozada 1982; Ylikorkala 1978)

## Bleeding

Hahn 1979 studied the effects of aspirin and paracetamol on menstrual bleeding in a group of 37 Swedish women, 10 of whom were using copper IUDs. Women did not have to have heavy bleeding for inclusion. Each woman received aspirin, paracetamol, or placebo for one month; women then crossed over to alternative treatments, so that each woman received each regimen for one month. The outcome measure was menstrual blood loss as determined by the alkaline hematin method (Hallberg 1964). Paracetamol, also known as acetaminophen, has no anti-inflammatory properties and, unlike aspirin, is not an NSAID (Mayo Clinic 2005). Paracetamol will not be considered further.

A trial from Los Angeles examined the impact of ibuprofen on IUD users without heavy bleeding or other complaints (Roy 1981). The researchers recruited 20 women, 10 using a copper IUD and 10 using a Lippes Loop. Participants kept menstrual diaries and collected sanitary products for blood-loss measurement by the alkaline hematin method. Each woman provided three months of observation: one baseline month, one month using either ibuprofen 1600 mg per day or placebo, and one month crossed over to the alternative treatment. The ibuprofen or placebo was begun at the onset of bleeding and continued until the end of bleeding, or a maximum of seven days.

## Pain

A Danish trial evaluated ibuprofen 600 mg given before IUD insertion, four to six hours after insertion, then again within the first three days (Jensen 1998). Fifty-five women having either a Nova T or a Gyne T 380 Slimline were randomized to receive either the ibuprofen or a placebo. A 10-point Likert scale for rating pain was used; one was the least pain and ten was the most intense. An early U.S. trial compared prophylactic administration of naproxen with placebo for Dalkon Shield insertion (Massey 1974). Fifty women, mainly nulliparous (48), were enrolled and allocated to either naproxen or placebo. Treatment began at 2200 hours the evening before the insertion and continued with repeat doses of 300 mg 1.5 hours before insertion, two hours after insertion, and six hours after insertion. Paracervical block with lidocaine was routinely used, given the wide diameter of this device (24 mm) and the nulliparous status of most participants. Outcomes included the need for additional analgesia as well as a complex pain score (including a five-point Likert scale) developed for this trial.

## Both bleeding and pain

A recent trial from Chile examined the use of prophylactic ibuprofen after insertion of a copper T380A IUD (Hubacher 2006). This large trial enrolled 2019 women in Santiago, Chile, who had never had an IUD before. They were randomized to receive either ibuprofen 1200 mg per day in divided doses or placebo for a maximum of five days with each menses. This regimen was to continue

for six menstrual cycles after IUD insertion. The primary outcome measure was removal of the IUD by the 52-week follow up for any reason, although information was collected to document reasons due to both bleeding and pain.

A trial from Egypt compared three different NSAIDs in copper IUD users without a complaint of heavy bleeding (Toppozada 1982). Eighteen parous IUD users were recruited for the four-month study. Six women were randomized to three different treatment arms: indomethacin, flufenamic acid, or alclufenac. Half of the women in each treatment arm began with the active drug, and the other half started on a placebo. After two months, each woman was crossed over to the alternative placebo or assigned NSAID. Thus, each of the 18 participants used an NSAID for two months and a placebo for two months. Participants maintained diary cards to record bleeding and pain.

An early prevention trial was conducted in Finland (Ylikorkala 1978). In this trial, 160 women wanting to have a copper T200 inserted were enrolled in a trial comparing an NSAID (tolfenamic acid) with placebo. At the time of IUD insertion, participants were requested to begin taking either tolfenamic acid 600 mg per day in divided doses or a placebo in the same regimen. Treatment was to continue for seven days, and participants were requested to repeat this regimen starting with menses for the next three cycles. The outcomes of interest included both pain and bleeding, although blood loss was not quantified. Participants and investigators were kept unaware of treatment assignment by use of a placebo, with distribution of drug and placebo in coded vials.

## Treatment trials

Eight trials evaluated NSAIDs as treatment of bleeding, pain, or both (Buttram 1979; Davies 1981; Di Lieto 1987; Lalos 1983; Mercorio 2003; Wu 2000; Yarkoni 1984; Ylikorkala 1983). Four examined bleeding (Davies 1981; Mercorio 2003; Wu 2000; Yarkoni 1984), two studied pain (Buttram 1979; Lalos 1983), and two reported on both bleeding and pain (Di Lieto 1987; Ylikorkala 1983).

## Bleeding

Davies 1981 performed a randomized controlled trial with 48 participants in the U.K. Women had to have documented heavy bleeding (an average of at least 80 mL per cycle on two pre-treatment cycles) and a normal pelvic examination. The trial had three treatment arms: two different regimens of naproxen and a placebo. The higher naproxen regimen was 1250 mg daily in divided doses; the lower regimen was 1000 mg on the first day and 750 mg daily thereafter. Each woman received one of the treatments above for two menstrual cycles then switched to another regimen for two cycles. Hence, each participant used two of the three regimens over a total of four treatment cycles. The IUDs being used by the 34 participants analyzed included copper devices (12) and non-

medicated devices (22); the latter included Saf-T-Coil (11), Lippes Loop (six), and Dalkon Shield (five) IUDs.

A recent Italian trial (Mercorio 2003) compared a standard NSAID (mefenamic acid) to a newer treatment: desmopressin acetate. Desmopressin is an analog of vasopressin with longer activity. This drug enhances blood coagulation by mediating the release of von Willibrand factor from endogenous storage sites; this increases circulating Factor VIII and platelet adhesiveness. It also induces uterine contractions because of its similarity to oxytocin. The trial (Mercorio 2003) randomized 24 women judged by pictorial blood assessment scores (Higham 1990) to have bleeding more than 80 mL per cycle. All were wearing a copper IUD. Half the participants received desmopressin (300 mcg) as a nasal spray each morning for five days, starting on the first day of bleeding. Those assigned to mefenamic acid took 1500 mg per day in divided doses for five days, starting on the first day of bleeding. Participants were then followed for three months, with pictorial blood assessment scores as the primary outcome.

A Chinese trial compared indomethacin with a traditional Chinese medicine (Wu 2000). Women using copper IUDs and with complaints of heavy or prolonged bleeding were assigned to receive either indomethacin 50 mg per day in divided doses or Bao-fuxin, a granular preparation of plant products, 16 g per day in divided doses (dissolved in boiling water). The treatments started on the first day of bleeding and continued for seven and 10 days, respectively. Participants kept menstrual diaries for 90 days before the three-cycle treatment phase and for another 90 days after treatment ended. The outcome was menstrual bleeding patterns as recorded on menstrual diaries; neither bleeding nor spotting was defined.

An early trial from Israel (Yarkoni 1984) compared indomethacin 100 mg per day in divided doses versus placebo. Women with perceived heavy bleeding were invited to take part in baseline observations for a two-month period, during which menstrual blood loss was determined by the alkaline hematin method. Fifteen women had mean blood loss 100 mL or greater, and these were enrolled in the treatment phase. Participants were randomized to receive either indomethacin or placebo; a crossover to the other treatment occurred after two months. Over the course of the four-month trial, each participant received two months of each treatment.

### Pain

An early U.S. trial (Buttram 1979) randomized 35 women with new or worsened uterine pain associated with IUD insertion. The type of IUDs was not specified. Participants were allocated to receive either naproxen sodium (550 mg initially, then 275 mg every six hours as needed) versus a placebo (lactose) for three consecutive menstrual cycles. The primary outcome of interest was pain, assessed by a self-administered six-point Likert scale, with six being excellent relief and one being no relief.

A Swedish trial compared naproxen with placebo in a crossover trial

(Lalos 1983). Twenty-one women with primary dysmenorrhea and who noted increased pain after insertion of a copper IUD (either copper T or Cu-7) were enrolled. They were randomized to receive either naproxen or placebo for two menstrual cycles, after which they crossed over to receive the alternative treatment. The naproxen regimen was 500 mg initially and then 250 mg two to four times a day as needed. Follow up was sought after the second and fourth menstrual periods. Pain was assessed with a five-point Likert scale, and participants reported subjectively on their bleeding patterns.

### Both bleeding and pain

Di Lieto and colleagues in Italy reported a “double blind crossover study” among 28 women with reported “increased menstrual blood loss and pelvic pain” associated with IUD use (Di Lieto 1987). The trial compared suprofen and placebo. Each woman had one pre-treatment month of observation, one month on the active drug or placebo, then the final month on the alternative treatment. In this crossover design, each participant took the active drug for a month and the placebo for a month. The IUDs used by participants included the Gravigard (Copper 7) in 18 and the copper T in 10. No quantitative or semi-quantitative assessments of bleeding were used.

Another trial from Finland (Ylikorkala 1983) compared an antifibrinolytic drug (tranexamic acid) versus an NSAID (diclofenac sodium) versus a placebo. Thirty-one women complaining of heavy bleeding related to IUD use were screened by quantitative measurement of menstrual blood loss by the alkaline hematin method. Twenty-one were found to have loss greater than 70 mL, and 17 of these qualified as having menorrhagia (greater than 80 mL). Two participants were excluded from analysis (one had leiomyomas, and the other had her IUD removed during the trial). Participants were studied over five cycles: two months on each active treatment and one month on the placebo. The dose of tranexamic acid was 4.5 g per day in divided doses, starting on the first day of bleeding and continuing for five days. The dose of diclofenac sodium started with 150 mg on day one of bleeding and 75 mg per day on days two through five. Placebo was also given for the first five days of bleeding.

### Risk of bias in included studies

#### Prevention trials

#### Bleeding

Hahn and Petruson (Hahn 1979) did not explicitly state that participants were allocated by a random method. We infer this from

the description of “double-blind crossover technique.” Correspondence with the author indicated that allocation concealment was ensured by using sealed envelopes. The adequacy of treatment blinding with the placebo is unclear. Four of 37 (11%) of women enrolled in the study dropped out: two because of pregnancy and two for unspecified reasons. The sample size was one of convenience.

Correspondence with the author indicated that the Los Angeles trial (Roy 1981) used a computer-generated randomization scheme. Allocation concealment was provided by pharmacy distribution of the drug and placebo. Sample size was one of convenience. A placebo was used to keep participants and investigators unaware of treatment. No losses to follow up were reported.

### **Pain**

The Danish trial (Jensen 1998) of prophylactic ibuprofen around the time of insertion featured a computer-generated randomization scheme. Correspondence with the author revealed that allocation concealment was assured by having pharmacy-generated envelopes containing pills. A formal sample size calculation was done in advance. Participants had a stratified randomization by type of IUD inserted. Blinding was provided by use of a placebo. No participants were lost to follow up.

The U.S. trial of naproxen (Massey 1974) featured permuted block randomization with a block size of 10. Allocation concealment was not described. The allocation to method apparently occurred some time before the IUD insertion, since two women assigned to naproxen subsequently changed their minds and did not have the insertion done. Blinding of treatment appears to have been adequate, with identical-appearing capsules provided in sealed strips. The sample-size calculation was not provided. All participants who requested additional analgesia were dropped from the trial at that point, leading to considerable missing data.

### **Both bleeding and pain**

The trial from Chile (Hubacher 2006) was both the largest and most rigorous to date. Randomization was by random permuted blocks, and central pharmacy distribution ensured allocation concealment. Blinding of participants and investigators was provided by using an identical-appearing placebo. The sample size was determined in advance according to the anticipated reduction in IUD discontinuations by 52 weeks. Losses after randomization were low: 95% of women provided follow-up information at 52 weeks. Protocol violations were analyzed according to intention-to-treat analysis. More detailed analyses of bleeding and pain are in progress; only discontinuation is reported here as an outcome. The Egyptian trial (Toppozada 1982) described randomization by computer. Communication with the author indicated that the sequence was generated by the World Health Organization. WHO trials of that era generally provided allocation concealment by us-

ing envelopes that were opaque, sealed, and sequentially numbered. The sample size selection was not described. No losses to follow up were reported. A placebo was used to keep participants and investigators unaware of the treatment assignments.

The Finnish prophylactic NSAID trial (Ylikorkala 1978) did not describe the randomization method, allocation concealment, or sample size calculation. Blinding of participants and investigators as to treatment regimen was done by having the drug and placebo distributed in coded vials; whether the blinding was successful is unclear. Due to noncompliance, many participants were excluded from analysis after randomization. For example, 160 women were enrolled and randomized. However, only 122 took the drugs at insertion and with the next menses as requested. By the second menses, only 103 complied with the regimen. Only 85 took the assigned drugs at the third menses. Because of this attrition, determining the number of women portrayed in the results is difficult. The analysis used cycles, rather than participants, as the unit of measurement for some statistical tests, which was improper.

### **Treatment trials**

#### **Bleeding**

The U.K. trial by Davies and colleagues (Davies 1981) had a small sample size of 48 and a complex design, with three treatment arms and a crossover after two cycles. This led to data so sparse for some comparisons some planned analyses were abandoned. Fourteen of 48 (29%) of participants were lost or excluded after randomization. The method of randomization was not mentioned, and allocation concealment was not described. Although placebos were used to enable blinding of participants and investigators, whether this worked is unclear from the report, due to difference in numbers of pills taken.

The trial of Mercorio and colleagues in Italy (Mercorio 2003) reported randomization by “computer analysis” and allocation concealment by “envelopes.” No sample size calculation was provided. No losses after randomization were reported. Attempts to contact the lead author were unsuccessful.

The Chinese trial (Wu 2000) reported that it was “double blind,” yet no mention was made of a double dummy or other way to conceal the disparate treatments (one a bag of herbs, the other a capsule). The method of randomization was not specified, and no mention was made of allocation concealment. The sample size calculation was not provided. The lack of blinding likely biased the acceptability assessments of the treatments. Important losses to follow up after randomization appear likely; 90 participants were recruited to each treatment, but only 73 women in the Baofuxin group and 71 in the indomethacin group provided diary information. However, the report indicates that only one participant assigned to Baofuxin was lost to follow up.

The Israeli trial of indomethacin (Yarkoni 1984) had no mention of randomization method, description of allocation concealment,

or justification for sample size. Moreover, a large proportion of subjects discontinued the trial prematurely: of 15 enrolled, only 9 completed the planned observations. The report did not provide standard deviations for the mean blood losses observed, so these data were not entered into RevMan.

### **Pain**

The U.S. trial of naproxen sodium (Buttram 1979) for pain did not describe the method of randomization or allocation concealment. The sample size of 35 was not explained. Of 35 women initially enrolled, two dropped out for personal reasons. Six others did not use the assigned treatment for each of three menstrual cycles: three were unsatisfied with the pain relief provided, two had insufficient pain to warrant treatment, and one had her IUD removed. Overall, 23% of participants did not complete the trial as planned. Pain at baseline differed for the two treatment groups; those assigned to the placebo had less pain at baseline than those assigned to the NSAID ( $P = 0.02$ ), raising questions about selection bias. Blinding of the treatments was accomplished by use of a placebo; whether the placebo tablets were identical in appearance and taste is unclear.

The Swedish study of naproxen featured a placebo treatment and crossover design (Lalos 1983). Correspondence with the author indicated that randomization was done with a table of random numbers. Allocation concealment was not described. Blinding was achieved by distributing the drug and identical-appearing placebo in amber bottles. A sample size calculation was not provided. Although the trial had approval of an institutional review board, informed consent was verbal rather than written. One participant was inappropriately dropped from analysis because of an intervening operation. Primary presentation of data was in a figure, and raw data were no longer available from the author.

### **Both bleeding and pain**

Di Lieto 1987 did not explicitly state that they used random allocation to assign treatments, although we inferred from other descriptions that this was a randomized controlled trial. No method of allocation concealment was described. No sample size calculation was provided, and no objective measurement of bleeding was done. Of note, no losses of participants occurred. Attempts to contact the author were unsuccessful.

The Finnish trial (Ylikorkala 1983) comparing tranexamic acid and diclofenac versus placebo did not describe the method of randomization or when it was done in the enrollment sequence. No mention was made of allocation concealment or sample size determination. Two participants were apparently dropped after randomization. Otherwise, all 19 participants had complete data. One woman who discontinued diclofenac sodium because of edema was apparently kept in the group to which she was assigned. A double-dummy approach was used to maintain blinding as to treatment.

## **Effects of interventions**

### **Prevention trials**

#### **Bleeding**

Aspirin at a daily dose of 1500 mg had no notable effect on menstrual blood loss in asymptomatic copper-IUD users (Hahn 1979). In this small trial, mean menstrual blood loss for those receiving aspirin was 49 mL and for those receiving placebo 51 mL.

In contrast, use of ibuprofen in asymptomatic IUD users reduced menstrual bleeding (Roy 1981). The effect was stronger with the non-medicated Lippes Loop: mean menstrual blood loss was 30 mL less during ibuprofen use than during placebo use. For women using a copper device, the difference in bleeding was only 10 mL. No serious complications were reported, but one participant using ibuprofen developed edema around her mouth and eye, which resolved after drug discontinuation. Two women reported stomach cramps: one with ibuprofen and one with placebo. Another reported headache, dizziness, nausea, and hot flashes associated with placebo.

#### **Pain**

In the Danish trial, administration of ibuprofen around the time of IUD insertion had no effect on pain (Jensen 1998). Participants having three doses of ibuprofen 600 mg had median pain scores that were not significantly lower than those of women who received placebo; this held true at each of the three assessments. The median pain scores for the ibuprofen and placebo groups were 3.3 and 2.5 at insertion, 1.7 and 1.8 during the first four to six hours, and 1.1 and 1.1 on the third day after insertion, respectively. No important differences were seen in pain by type of IUD.

In an early U.S. trial, naproxen given around the time of Dalkon Shield insertion was more effective than placebo in managing pain (Massey 1974). Only seven of 24 women who received naproxen needed additional medication, in contrast to 17 of 26 assigned to placebo. Other analyses were not possible due to missing data. No "untoward effects" or laboratory abnormalities were related to administration of naproxen.

### **Both bleeding and pain**

Prophylactic administration of ibuprofen 1200 mg per day with the first six menses after IUD insertion had no impact on discontinuation rates (Hubacher 2006). For all reasons combined, 257 of 985 women assigned to ibuprofen discontinued IUD use with 52 weeks, compared with 246 of 977 who took placebo. These figures include spontaneous expulsion (113 and 125, respectively) and removals because of any pain or bleeding (112 and 91, respectively). At 26 weeks, removals for dysmenorrhea or increased

menstrual blood loss were 59 of 985 in the ibuprofen group and 61 of 977 women in the placebo group. These removals were related to problems during menses, which is when the women were taking the medication or placebo. The two groups were similar.

In asymptomatic Egyptian IUD users, each NSAID tested reduced measured blood loss as compared with a placebo (Toppozada 1982). The mean total blood loss over two months of placebo use and two months of indomethacin was 102.8 and 66.3 mL, respectively. The mean total blood loss over two months of placebo and two months of flufenamic acid was 101.1 and 59.6 mL, respectively. With alclofenac, the corresponding figures were 110.0 and 68.5 mL, respectively. Standard deviations for these means were not provided in the report. However, the authors aggregated all three groups versus placebo and provided standard deviations for these means, allowing for data entry in RevMan. All three NSAIDs decreased total bleeding as compared with placebo; differences between the NSAIDs were minor. Treatment did not shorten the duration of bleeding. Side effects were generally mild; four women assigned to indomethacin had complaints (including headache, nausea, and epigastric pain), one assigned to flufenamic acid had a headache, and two assigned to alclofenac had complaints (intestinal colic and dizziness). Pain was much lower during treatment cycles.

Prophylactic administration of tolfenamic acid (Ylikorkala 1978) offered subjective benefit over a placebo. Bleeding immediately after IUD insertion was shorter by about a day, and fewer sanitary pads were required for protection. With subsequent menses, about 15% fewer cycles were deemed heavier than normal with the active drug, and about one pad fewer on average was required. Clots and pain were both less frequent with the NSAID than with placebo. Side effects were noted in both treatment groups. Dyspepsia and diarrhea were reported by four women taking tolfenamic acid, and five taking placebo noted headache. Three participants taking placebo complained of depression and fatigue. Discontinuations because of side effects occurred in three participants in the tolfenamic acid group and two in the placebo group.

## Treatment trials

### Bleeding

Among women with documented heavy bleeding, naproxen in either of two regimens tested reduced measured blood loss as compared with the placebo (Davies 1981). In addition, the pooled results indicated a decline in blood loss from pre-treatment cycles with both doses of naproxen. The pooled mean pre-treatment blood loss was 127 mL; with the higher dose of naproxen, 93 mL; with the lower dose of naproxen, 89 mL; and with placebo, 129 mL. The one patient who dropped out of the trial because of nausea and vomiting of six day's duration had been taking the

placebo. No other side effects were reported. Individual responses to naproxen varied widely; some women experienced a 50% reduction in bleeding, while others had no benefit.

Mefenamic acid was comparable to desmopressin in reducing heaving bleeding associated with copper-IUD use (Mercorio 2003). Both treatments led to similar reductions (46% and 41%, respectively) in bleeding scores, compared with baseline. Treatment responses were variable, however. All participants given desmopressin had reduced bleeding; two women assigned to mefenamic acid had a negligible change in bleeding. No serious complications occurred, but three of 12 women assigned to desmopressin reported headache and insomnia.

The Chinese trial found indomethacin to be comparable to Baofuxin in reducing number of days of bleeding (Wu 2000). During the three-cycle treatment phase, the numbers of bleeding/spotting days were similar (mean 28.8 and 28.3, respectively). Likewise, the numbers of bleeding/spotting episodes were comparable (mean 3.4 and 3.3, respectively). The report noted more bleeding/spotting days after treatment with indomethacin than after Baofuxin (mean 30.2 versus 24.7, respectively). A total of 13 women assigned to indomethacin and 12 assigned to Baofuxin had their IUDs removed during the trial because of bleeding, and two others in the indomethacin group had their devices removed for other reasons, such as cramping or pregnancy.

The trial from Israel (Yarkoni 1984) found that indomethacin reduced menstrual bleeding by more than 50%. In the baseline cycles, the mean measured blood loss was 174.7 mL. In the placebo cycles, the mean was 159.9. In contrast, during treatment with indomethacin, the mean fell to 75.1 mL, a 57% reduction from baseline, which was statistically significant. No side effects were attributed to indomethacin or placebo.

### Pain

Naproxen sodium improved uterine pain associated with IUD use better than did placebo (Buttram 1979). Of 17 women who took naproxen sodium in one or more cycles, 14 reported "good" or "excellent" pain relief in at least one cycle. In contrast, of 16 participants who took placebo in one or more cycles, only 4 noted "good" or "excellent" relief in one or more cycles. Daily pain relief scores for the 27 women who completed all three cycles confirmed better pain relief with naproxen sodium. The highest relief score possible was 18 (Likert scale of six, added for each of three observation cycles). With naproxen, the mean relief score was 13.9 compared with 10.8 with placebo ( $P = 0.03$ ). Side effects or harms were not mentioned.

The Swedish trial of naproxen (Lalos 1983) found it superior to placebo for pain relief. Of the 20 women with pain assessments, 17 reported better pain relief with the NSAID than with the placebo; only three reported superior relief with the placebo. Calculation of mean pain scores for the two treatments was not possible from published data. Subjective reports of bleeding patterns revealed

little impact of naproxen on either amount or duration of flow. Side effects were similar for the two treatments: seven women reported side effects with naproxen, and five did with placebo. None was serious, and none led to trial discontinuation. Gastrointestinal side effects were noted in two and one women, respectively.

### Both bleeding and pain

Suprofen had powerful benefit on both bleeding and pain (Di Lieto 1987). Twenty-two of 28 women given this NSAID had moderate to “intense” decreases in bleeding, in contrast to none given the placebo. Similarly, with pain, 23 of 28 had moderate to “intense” relief of pain with suprofen, in contrast to only one of 28 with placebo. Three participants reported side effects (stomach cramps, one; nausea and headaches, two). The latter two participants were taking suprofen, but the regimen is not clear for the participant with stomach cramps.

The Finnish trial (Ylikorkala 1983) found the antifibrinolytic drug more effective than either the NSAID or placebo in reducing bleeding. The reduction in blood loss was more than 50% with tranexamic acid, compared with only about 20% with diclofenac sodium. Side effects varied by treatment. The most common complaints with tranexamic acid were gastrointestinal disturbances, headache, and sweating. Complaints with diclofenac sodium included sweating, fatigue, dry mouth, headache, itching, and edema; one participant discontinued treatment on the fourth day due to leg edema. Neither drug influenced the duration of bleeding or pelvic pain associated with menses.

## DISCUSSION

### Prevention trials

NSAIDs reduced bleeding in asymptomatic IUD users. Alclufenac, indomethacin, flufenamic acid, and tolfenamic acid all reduced bleeding when compared with a placebo (Topozada 1982; Ylikorkala 1978). In one trial, the reduction in bleeding was greater with non-medicated than with copper devices (Roy 1981). In contrast, aspirin had no effect on bleeding (Hahn 1979). Despite the well-documented reduction in IUD-related bleeding, prophylactic ibuprofen administration had no impact on IUD continuation rates over the first year in the large Chilean trial (Hubacher 2006). Thus, the objective reduction in bleeding may not appreciably influence the subjective acceptability of IUDs.

The impact of prophylactic use of NSAIDs on pain is less clear. A recent Danish trial found no benefit of prophylactic ibuprofen at IUD insertion (Jensen 1998), whereas a Finnish trial reported less pain after insertion with prophylactic use of tolfenamic acid

than with placebo (Ylikorkala 1978). Naproxen appeared beneficial with insertion of the Dalkon Shield, but the relevance of this observation to contemporary IUDs is limited (Massey 1974).

### Treatment trials

NSAIDs also reduced bleeding in IUD users with heavy blood loss; naproxen (Davies 1981), indomethacin (Yarkoni 1984), suprofen (Di Lieto 1987), and diclofenac sodium (Ylikorkala 1983) all proved superior to placebo. Mefenamic acid was comparable to desmopressin in reducing heavy bleeding (Mercorio 2003), but the greater cost and more frequent side effects argue against use of desmopressin. In contrast, tranexamic acid reduced bleeding more than did either diclofenac sodium or placebo, but it was associated with more unpleasant side effects (Ylikorkala 1983). The superiority of tranexamic acid over NSAIDs is consistent with the conclusion of trials with women not using IUDs (Lethaby 2007). Most trials found NSAIDs to be effective therapy for IUD-related pain. NSAIDs found superior to placebo included naproxen sodium and suprofen (Buttram 1979; Di Lieto 1987; Lalos 1983). In contrast, one trial found no benefit of diclofenac sodium on dysmenorrhea (Ylikorkala 1983).

Evidence is insufficient to recommend a specific NSAID or regimen. Few trials have compared one NSAID to another, and one trial (Topozada 1982) that compared several NSAIDs found no important differences in effect on bleeding. Similarly, for women with heavy bleeding unrelated to IUD use, naproxen and mefenamic acid appeared equally helpful (Lethaby 2007). Hence, the choice of an NSAID may be based on other concerns, such as cost, convenience, and side effects. For example, naproxen sodium requires twice daily dosing, in contrast to ibuprofen, which is taken four times daily. Another Cochrane review concluded that gastrointestinal side effects may be greater with naproxen than with mefenamic acid (Lethaby 2007). Similarly, for women not using an IUD, the preferred NSAID for treating dysmenorrhea (Marjoribanks 2003) remains unsettled as well. An alternative approach to managing bleeding and pain with IUD use is to switch to a levonorgestrel intrauterine system, which reduces both menstrual bleeding and dysmenorrhea (Lethaby 2005; Pakarinen 2001).

No serious harms were reported in these trials, although such reporting was incomplete (Ioannidis 2002), especially in reports published in the 1970s and 1980s. The anticipated gastrointestinal side effects of NSAIDs did not appear problematic in the regimens tested.

Trial reports varied widely in quality, but reporting of randomization method and allocation concealment was incomplete for most. Attempts to contact investigators were largely unproductive, due to the age of the reports. Subjective outcomes, lack of blinding, and losses after randomization likely biased the Chinese trial of Baofuxin (Wu 2000). The claim of double blinding appears to be incorrect. Moreover, the report suggested a lingering effect of

the traditional medicine for up to 90 days after discontinuation, which appears improbable.

If participants assigned to placebo took unauthorized, over-the-counter NSAIDs to compensate for their lack of treatment benefit, this would have biased the comparison toward the null. If this occurred, then the true differences between NSAID and placebo may be larger than reported.

## AUTHORS' CONCLUSIONS

### Implications for practice

NSAIDs should be considered as first-line therapy of bleeding and pain associated with IUD use. The optimal NSAID and regimen are unclear, so the choice of NSAID may be based on cost, convenience, or side effects instead. Should NSAID treatment not yield the desired improvement in bleeding, tranexamic acid, where available, could then be considered. Because of its high cost, desmopressin should not be used. Existing evidence does not support prophylactic ibuprofen administration with the first six menses after IUD insertion.

### Implications for research

Trials comparing leading NSAIDs with each other might help establish the best approach. However, since few important differences are evident between NSAIDs used as analgesics, comparative trials of effects on bleeding or pain associated with IUD use should not be a research priority.

## ACKNOWLEDGEMENTS

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Buttram 1979

Methods	Randomized controlled trial
Participants	35 women in the U.S. with either uterine pain starting after IUD insertion or prior menstrual pain exacerbated by IUD insertion. Inclusion criteria included a normal physical examination, and, if necessary for pain evaluation, normal laparoscopy. Women with cycle irregularities were excluded.
Interventions	Naproxen sodium 550 mg initially, then 275 mg every six hours as needed for uterine pain versus a placebo (lactose). Trial ran for three cycles.
Outcomes	Uterine pain as judged by six-point Likert scale.
Notes	Method of randomization not specified; no mention of allocation concealment. Sample size calculation not provided. Thirty-five women initially enrolled; two dropped out for personal reasons. Only 27 women used the assigned drugs for each of three menstrual cycles. Of the six who did not complete all planned treatments, three did not have satisfactory relief, two had no further pain, and one had her IUD removed.

#### *Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	No	D - Not used

#### Davies 1981

Methods	Randomized controlled trial with crossover
Participants	48 women of reproductive age using IUDs in England with measured menstrual blood loss averaging at least 80 mL per cycle over two pre-treatment cycles. Participants had regular cycles, were healthy, and had a normal pelvic examination.
Interventions	Three treatment arms: naproxen 1250 mg per day, naproxen 1000 mg on first day then 750 mg on subsequent days, or placebo. Each participant took two of the three treatments, each for two menstrual cycles. Each regimen was begun on the first day of menstrual bleeding and continued for a total of five days.
Outcomes	Volume of menstrual blood loss measured by alkaline hematin method; menstrual diaries kept by participants.
Notes	Complex design with small number of participants. Twenty-nine percent of participants were lost or excluded after randomization. Method of randomization not stated, and no mention of allocation concealment. No sample size calculation provided. Placebos used to blind participants and investigators, but whether this worked is unclear. One participant withdrew from the trial because of nausea and vomiting considered related to treatment.

Davies 1981 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Di Lieto 1987

Methods	Probably randomized controlled trial with crossover	
Participants	28 women, aged 21 to 33 years, in Italy using IUDs and who "suffered from increased menstrual blood loss and pelvic pain."	
Interventions	Suprofen 800 mg per day on day one, then 600 mg per day versus placebo. Each regimen was started at the first sign of bleeding and continued up to seven days maximum. Each participant had one pre-treatment month, one month with suprofen, then the next month with the placebo.	
Outcomes	Likert-like scale of subjective improvement of bleeding and pain.	
Notes	Method of randomization not specified; no mention of allocation concealment. Placebo used to enable blinding of participants and investigators; report does not indicate whether blinding was successful. No sample size calculation. No losses after randomization.	

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hahn 1979

Methods	Randomized controlled trial with crossover	
Participants	37 women aged 20 to 40 years in Sweden, 10 of whom were using copper IUDs	
Interventions	Aspirin 1500 mg per day versus paracetamol 1500 mg per day versus placebo. Each participant received each treatment arm for one month.	
Outcomes	Menstrual blood loss measured by alkaline hematin method	
Notes	Method of randomization not specified; authors reported using "double blind crossover technique." Communication with author indicated allocation concealment by "sealed envelopes." Sample size was one of convenience.	

*Risk of bias*

Item	Authors' judgement	Description
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**Hahn 1979** (Continued)

Allocation concealment?	Yes	A - Adequate
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**Hubacher 2006**

Methods	Randomized controlled trial
Participants	2019 women aged 18-49 yr. in Chile having a copper T380A IUD inserted. Inclusion criteria included literacy, no previous IUD use, more than six weeks postpartum if recently pregnant, and without contraindications to an IUD or ibuprofen.
Interventions	Ibuprofen 1200 mg per day versus placebo, to be taken with the first six menses after IUD insertion and for a maximum of 5 days at a time.
Outcomes	The primary outcome was IUD removal within 12 months of insertion. Participants were followed up at 6, 13, 26, and 52 weeks after insertion.
Notes	Randomization by random permuted blocks with block sizes of 20, 10, 4, and 2, with computer generation of sequence. Allocation concealment by pharmacy distribution of medicine bottles. Sample size was calculated to achieve 85% power to detect a reduction in discontinuation from 16% to 11% with an alpha of 0.025 (one-sided hypothesis) Fifty-seven women did not have an IUD inserted; these were excluded from the primary analysis. Thirty-five minor protocol violations occurred, but these women were analyzed within the groups to which they were initially assigned, according to intention-to-treat principles. 95% of participants provided 52-week follow-up information.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Jensen 1998**

Methods	Randomized controlled trial with four treatment groups
Participants	55 women in Denmark having insertion of either a Nova T or Gyne T 380 Slimline IUD inserted. Trial conducted from May 1994 to May 1995. Trial enrolled all Danish-speaking women in good health who requested an IUD in the investigators' clinic. Exclusion criteria included age <18 years, serious illness, allergy to NSAID or aspirin, and medication of any kind except for oral contraceptives.
Interventions	Ibuprofen 1800 mg in divided doses (before insertion, four to six hours after insertion, and next morning) versus placebo. The type of IUD to be inserted was randomly chosen.
Outcomes	Pain assessed by a 10-point scale, administered during insertion, four to six hours after insertion, and again during the first three days.

**Jensen 1998** (Continued)

Notes	Computer-generated randomization. Correspondence with author indicated that allocation concealment was achieved by central pharmacy packaging of drug in sealed envelopes. Randomization stratified by type of IUD inserted. Neither participants nor investigators were aware of treatment assignment. Tablets were of same size and shape, but taste may have differed. Formal a priori sample size calculation.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	A - Adequate

**Lalos 1983**

Methods	Randomized controlled trial with crossover.	
Participants	21 women in Sweden with primary dysmenorrhea aggravated by insertion of a copper IUD (either a T or the Cu-7). Inclusion criteria included severe dysmenorrhea, regular menstrual cycles, and normal gynecological examination.	
Interventions	Naproxen 500 mg followed by 250 mg two to four times a day, with a maximum of 1250 mg, versus placebo. The drug was started at the first sign of menstrual distress.	
Outcomes	Pain assessed by a five-point Likert scale.	
Notes	Communication with the investigators indicated that a table of random numbers was used to generate the random sequence. Allocation concealment was not described. Participants and investigators were blinded as to treatment by using identical-appearing placebo tablets that had the same taste as the naproxen; both the drug and the placebo were distributed in amber bottles. Sample-size calculation not provided. One participant excluded after randomization because of intervening operation. Informed consent was verbal, not written.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	A - Adequate

**Massey 1974**

Methods	Randomized controlled trial with blinding	
Participants	50 women in the US having a Dalkon Shield inserted. Inclusion criteria included normal physical examination and laboratory tests. Exclusion criteria included severe painful, menses or premenstrual tension. 48 women were nulliparous, and two were primiparous.	

**Massey 1974** (Continued)

Interventions	Naproxen 300 mg taken the evening before IUD insertion, 300 mg 1.5 hours before insertion, and 300 mg at two and four hours after insertion versus placebo.	
Outcomes	Requirement for additional analgesia plus complex pain scores created for the trial.	
Notes	Random permuted blocks with a block size of 10; source of the random sequence not specified. Allocation concealment not mentioned. Sample size not explained. Two women assigned to naproxen did not have IUD inserted and were replaced by another randomization, resulting in 24 assigned to naproxen and 26 to placebo. Blinding accomplished by providing four identical capsules in strips.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	B - Unclear

**Mercorio 2003**

Methods	Randomized controlled trial without blinding	
Participants	24 women aged 20 to 40 years with IUD-associated menorrhagia in Italy. Inclusion criteria included pictorial blood loss assessment for two treatment cycles indicating menorrhagia (score of 100 or greater); exclusion criteria included gynecological pathology, family or personal history of bleeding disorders, or prior use of study drugs.	
Interventions	Desmopressin 300 mcg intranasal spray each morning for the first five days after start of menses versus mefenamic acid 1500 mg per day for the first 5 days after the start of menses. Study duration of three months.	
Outcomes	Pictorial blood loss assessment charts	
Notes	Randomization done by "computer analysis" and allocation concealment by "envelope." Sample size calculation not provided. No participants discontinued the trial prematurely.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	A - Adequate

**Roy 1981**

Methods	Randomized controlled crossover trial with blinding of treatment for participants and investigators	
Participants	20 women in U.S.A. aged 18 to 33 years without bleeding or other complaints; ten used copper IUDs and ten used Lippes Loop. Inclusion criteria included having used the IUD for at least five months and being free of side effects. Exclusion criteria included previous salpingitis, undiagnosed bleeding, uterine	

**Roy 1981** (Continued)

	anomalies, multiple fibroids, and contraindications to ibuprofen.
Interventions	Ibuprofen 1600 mg per day starting with bleeding and continuing until end of bleeding or maximum of seven days. Each participant had one month of observation, one month on ibuprofen or placebo, and one month crossed over to the alternative treatment.
Outcomes	Menstrual blood loss measured by alkaline hematin method
Notes	Communication with investigator indicated computer-generated randomization sequence. Allocation concealment by pharmacy distribution of active drug and identical-appearing placebo. Sample size was based on feasibility rather than power calculation. Randomization was designed "to ensure equal and random patient distribution" to the two groups. Analysis was stratified by copper IUD versus Lippes Loop.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Topozada 1982**

Methods	Randomized controlled crossover trial without blinding
Participants	18 parous women in Egypt aged 20 to 35 years using a copper IUD. Inclusion criteria included regular menstruation and hemoglobin > 12 g%. Exclusion criteria included peptic ulcer disease, salpingitis, or "allergic" disease.
Interventions	Indomethacin 100 mg per day versus flufenamic acid 600 mg per day versus alclofenac 1500 mg per day. Treatment started on the first day of bleeding and was given for three days. Observation period ran four months. In each treatment arm, half started on active drug and half on placebo; after two months, crossover to the alternative occurred. Thus, each participant had two months on the assigned NSAID and two months on placebo.
Outcomes	Menstrual blood loss measured by alkaline hematin method
Notes	Communication with investigator indicated computer-generated randomization scheme; allocation concealment by sequentially-numbered, sealed, opaque envelopes provided by WHO. Sample size calculation not provided. No apparent losses to follow up after randomization.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Wu 2000**

Methods	Randomized controlled trial without blinding	
Participants	180 parous women in China. All had complaints of heavy or prolonged menses (more than seven days), good general health, a copper IUD for at least six months. Exclusion criteria included hemorrhagic illness or leiomyomas, unwillingness to avoid other medicines, and unwillingness to maintain a menstrual diary.	
Interventions	The NSAID regimen was indomethacin 50 mg daily in divided doses for 7 days, starting on the first day of menses. The alternative regimen was Baofuxin (a traditional Chinese medicine containing Tangshen, Radix Astragali seu Hedysari, Ass-hide Asafetida, Hairyein Agrimonia Herb, Indian Madder Root and other ingredients in a granular compound). The 8 g bag was dissolved in hot water and drunk twice daily for 10 days, starting on the first day of menses.	
Outcomes	Menstrual patterns as determined by diaries. Menstrual diaries were maintained for 90 days before, 3 menstrual cycles of treatment, and 90 days after stopping treatment.	
Notes	Method of randomization not specified; no mention of allocation concealment. Sample size calculation not provided. Lack of blinding likely influenced acceptability of traditional Chinese medicine. Report states “double-blind” trial, but no description of double dummy or other means to disguise treatment.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	B - Unclear

**Yarkoni 1984**

Methods	Randomized controlled trial with blinding and crossover	
Participants	15 Israeli women aged 24 to 36 years with Lippes Loop C who had mean measured blood loss of >100 mL by alkaline hematin method. Exclusion criteria included history of pelvic inflammatory disease, bleeding disorders, or leiomyomas. Those with contraindications to NSAIDs were excluded as well.	
Interventions	Indomethacin 100 mg daily for four days, starting on the first day of bleeding versus placebo. After two months of baseline measurements in 35 women, the 15 with mean losses > 100 mL were randomized. Each participant randomly received either indomethacin or placebo each month; each participant received two months of each regimen, not necessarily in sequence.	
Outcomes	Menstrual blood loss as measured by the alkaline hematin method	
Notes	Method of randomization not specified; allocation concealment not described. Sample size calculation not provided. High discontinuation proportion; only 9 of 15 women enrolled completed the study. Standard deviations not provided for mean blood loss.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>

**Yarkoni 1984** (Continued)

Allocation concealment?	Unclear	B - Unclear
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**Ylikorkala 1978**

Methods	Randomized controlled trial with blinding of participants and investigators
Participants	160 Finnish women of unspecified ages requesting insertion of a copper T200 IUD. Inclusion criteria included normal history and physical examination.
Interventions	Tolfenamic acid 600 mg per day starting at IUD insertion and continuing for seven days; this was to be repeated during the next three menses. Placebo given in same regimen.
Outcomes	Subjective reports of pain and bleeding patterns
Notes	Method of randomization not specified; no mention of allocation concealment. Sample size calculation not provided. Blinding of participants and investigators by using coded pill bottles with either tolfenamic acid of placebo; report does not state that placebo was identical in appearance and taste.

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Ylikorkala 1983**

Methods	Randomized controlled trial with blinding and crossover
Participants	19 Finnish women aged 25 to 44 years with measured mean menstrual blood loss >70 mL. 18 were using a copper IUD and one a non-medicated device. All had normal pelvic and general physical examinations.
Interventions	Tranexamic acid 4.5 g per day for five days versus diclofenac sodium 150 mg on day one then 75 mg per day on days two through four versus placebo. Over the five months of the trial, each participant received placebo for one month, two months of tranexamic acid, and two months of diclofenac sodium.
Outcomes	Menstrual blood loss
Notes	Method of randomization not specified; allocation concealment not described. No sample size calculation provided. Participants and investigators kept blinded as to treatment by use of double dummy.

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

### Characteristics of excluded studies *[ordered by study ID]*

Blum 1984	Not a randomized controlled trial.
Davies 1980	Not a randomized controlled trial.
Dreher 1980	Not a randomized controlled trial.
Guillebaud 1978	Before-after study.
Makarainen 1986	Participants allocated to treatment by odd-even year of birth.
Pedron 1982	Before-after study.
Pedron 1983	Before-after study.
Pizarro 1988	Correspondence with author revealed alternate assignment to treatment groups.
Sahmay 1987	Random allocation not specified in methods. Allocation of 43 participants to 79 cycles of proquazon and 50 cycles of placebo is unlikely to have occurred by simple randomization.
Topozada 1980	Methods did not specify random allocation to treatments.

### Characteristics of ongoing studies *[ordered by study ID]*

#### NCT00789802

Trial name or title	A randomized controlled trial of oral naproxen and transdermal estradiol for bleeding in LNG-IUC
Methods	RCT
Participants	114 women, 38 in each group
Interventions	Oral naproxen or transdermal estradiol or placebo for first 12 weeks of use
Outcomes	Number of bleeding and spotting days
Starting date	Nov 2008 (planned)
Contact information	TE Madden: madden@wustl.edu
Notes	Not yet open for participant recruitment

## DATA AND ANALYSES

### Comparison 1. Naproxen 1250 mg per day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Menstrual blood loss	1	47	Mean Difference (IV, Fixed, 95% CI)	-36.0 [-57.17, -14.83]

### Comparison 2. Naproxen 1000 mg (Day 1) then 750 mg per day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Menstrual blood loss	1	49	Mean Difference (IV, Fixed, 95% CI)	-40.0 [-55.40, -24.60]

### Comparison 3. Naproxen 1250 mg versus naproxen 1000 mg (Day 1) then 750 mg per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Menstrual blood loss	1	40	Mean Difference (IV, Fixed, 95% CI)	4.0 [-16.11, 24.11]

### Comparison 4. Suprofen 800 mg (Day 1) then 600 mg per day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderate or "intense" decrease in bleeding	1	56	Odds Ratio (M-H, Fixed, 95% CI)	197.31 [10.55, 3691.66]
2 Moderate or "intense" relief of pain	1	56	Odds Ratio (M-H, Fixed, 95% CI)	124.2 [13.52, 1141.14]

### Comparison 5. Aspirin 1500 mg per day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Menstrual blood loss	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-29.60, 26.60]

### Comparison 6. Ibuprofen 600 mg per day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Median pain values			Other data	No numeric data

### Comparison 7. Aspirin 1500 mg per day versus paracetamol 1500 mg per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Menstrual blood loss	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-26.16, 25.56]

### Comparison 8. Mefenamic acid 1500 mg per day versus desmopressin 300 mcg nasally per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pictorial blood loss assessment chart	1	24	Mean Difference (IV, Fixed, 95% CI)	Not estimable

### Comparison 9. Ibuprofen 1600 mg per day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Menstrual blood loss	1	40	Mean Difference (IV, Fixed, 95% CI)	-14.11 [-36.04, 7.82]
1.1 Copper IUD users	1	20	Mean Difference (IV, Fixed, 95% CI)	-9.47 [-34.46, 15.52]
1.2 Lippes Loop users	1	20	Mean Difference (IV, Fixed, 95% CI)	-29.68 [-75.44, 16.08]

**Comparison 10. Indomethacin 100 mg daily or flufenamic acid 600 mg daily or alclofenac 1500 mg daily versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Menstrual blood loss	1	36	Mean Difference (IV, Fixed, 95% CI)	-39.8 [-42.84, -36.76]
2 Severe or moderate pain	1	36	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

**Comparison 11. Indomethacin 50 mg per day versus Baofuxin 16 g per day**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleeding/spotting days	1	144	Mean Difference (IV, Fixed, 95% CI)	0.5 [-2.96, 3.96]
2 Bleeding/spotting episodes	1	144	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.38, 0.58]

**Comparison 12. Indomethacin 100 mg per day versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Menstrual blood loss	1	36	Mean Difference (IV, Fixed, 95% CI)	-85.22 [-119.27, -51.17]

**Comparison 13. Diclofenac sodium 150 mg then 75 mg versus tranexamic acid 4.5 mg per day**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Menstrual blood loss	1	38	Mean Difference (IV, Fixed, 95% CI)	42.70 [12.05, 73.35]

**Comparison 14. Diclofenac sodium 150 mg (Day 1) then 75 mg on days 2-5 versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Menstrual blood loss	1	38	Mean Difference (IV, Fixed, 95% CI)	-26.20 [-66.77, 14.37]

**Comparison 15. Tolfenamic acid 600 mg per day versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of bleeding after IUD insertion	1	122	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.51, 0.31]
2 Number of sanitary pads used for bleeding immediately after IUD insertion	1	122	Mean Difference (IV, Fixed, 95% CI)	-1.4 [-2.06, -0.74]
3 Next menses more abundant than normal	1	310	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.34, 0.85]
4 Clots in menstrual blood with subsequent menses	1	310	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.27, 0.68]
5 Subsequent menses more painful than normal	1	310	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.44, 1.14]

**Comparison 16. Naproxen sodium 550 mg then 275 mg every 6 hr as needed versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 "Good" or "excellent" relief of uterine pain in one or more cycles	1	33	Odds Ratio (M-H, Fixed, 95% CI)	14.0 [2.60, 75.41]
2 Mean daily pain relief scores	1	27	Mean Difference (IV, Fixed, 95% CI)	3.10 [0.27, 5.93]

### Comparison 17. Naproxen 500 mg initially then additional doses of 250 mg up to 1250 mg per day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain relief rated better than alternative treatment	1	40	Odds Ratio (M-H, Fixed, 95% CI)	32.11 [5.66, 182.18]

### Comparison 18. Naproxen 1200 mg per day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Need for additional analgesia after IUD insertion	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.07, 0.72]

### Comparison 19. Ibuprofen 1200 mg per day versus placebo with 6 menses after IUD insertion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IUD removal by 26 weeks for dysmenorrhea or increased menstrual blood loss	1	1962	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.66, 1.38]
2 IUD removal by 52 weeks	1	1962	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.86, 1.28]

#### Analysis 1.1. Comparison 1 Naproxen 1250 mg per day versus placebo, Outcome 1 Menstrual blood loss.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 1 Naproxen 1250 mg per day versus placebo

Outcome: 1 Menstrual blood loss

Study or subgroup	Naproxen		Placebo		Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)			
Davies 1981	19	93 (39)	28	129 (32)		100.0 %	-36.00 [-57.17, -14.83]
<b>Total (95% CI)</b>	<b>19</b>		<b>28</b>			<b>100.0 %</b>	<b>-36.00 [-57.17, -14.83]</b>

Heterogeneity: not applicable  
Test for overall effect: Z = 3.33 (P = 0.00086)

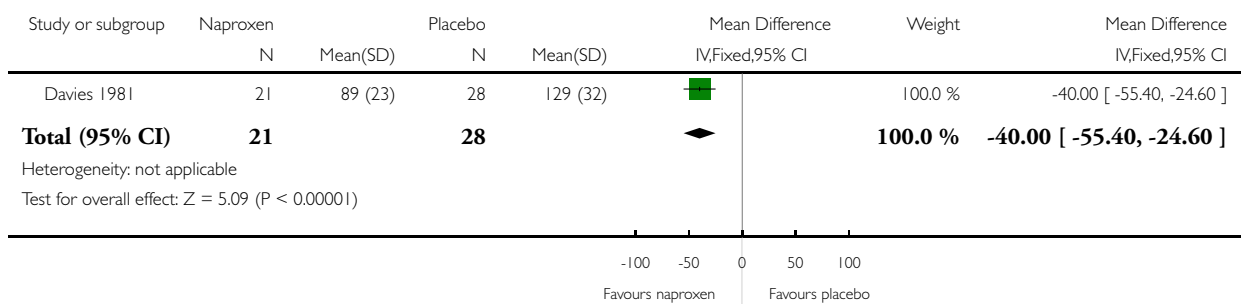
-100   -50   0   50   100  
Favours naproxen   Favours placebo

**Analysis 2.1. Comparison 2 Naproxen 1000 mg (Day 1) then 750 mg per day versus placebo, Outcome 1 Menstrual blood loss.**

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 2 Naproxen 1000 mg (Day 1) then 750 mg per day versus placebo

Outcome: 1 Menstrual blood loss



**Analysis 3.1. Comparison 3 Naproxen 1250 mg versus naproxen 1000 mg (Day 1) then 750 mg per day, Outcome 1 Menstrual blood loss.**

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 3 Naproxen 1250 mg versus naproxen 1000 mg (Day 1) then 750 mg per day

Outcome: 1 Menstrual blood loss

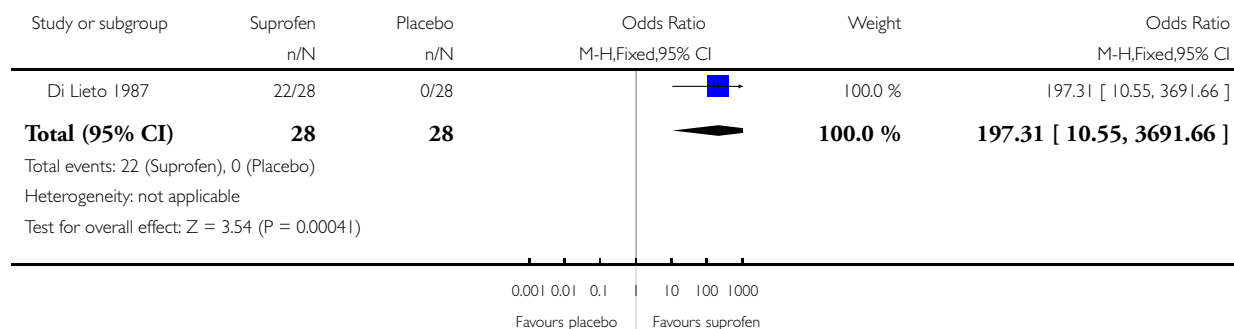


### Analysis 4.1. Comparison 4 Suprofen 800 mg (Day 1) then 600 mg per day versus placebo, Outcome 1 Moderate or "intense" decrease in bleeding.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 4 Suprofen 800 mg (Day 1) then 600 mg per day versus placebo

Outcome: 1 Moderate or "intense" decrease in bleeding

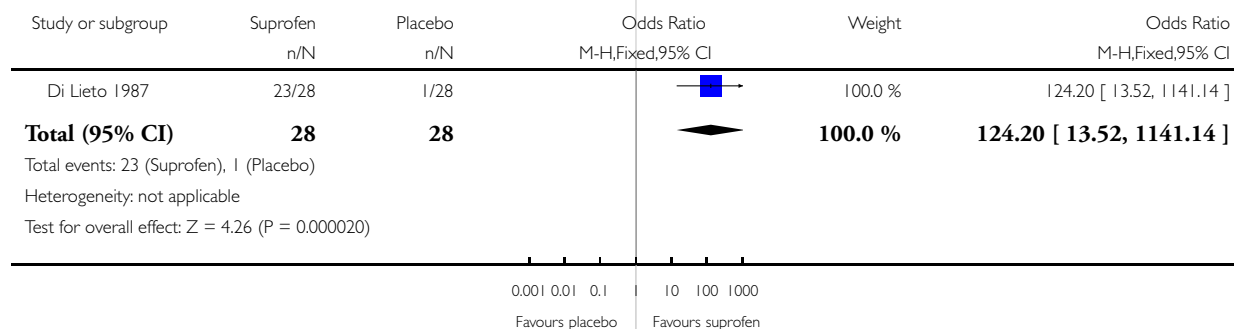


### Analysis 4.2. Comparison 4 Suprofen 800 mg (Day 1) then 600 mg per day versus placebo, Outcome 2 Moderate or "intense" relief of pain.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 4 Suprofen 800 mg (Day 1) then 600 mg per day versus placebo

Outcome: 2 Moderate or "intense" relief of pain

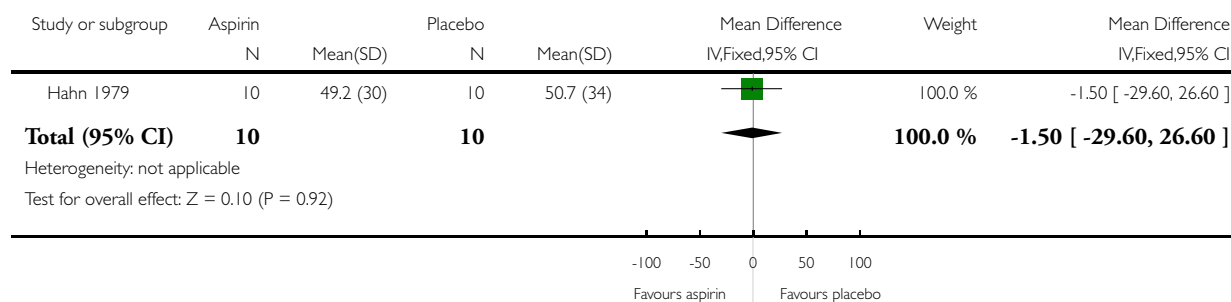


### Analysis 5.1. Comparison 5 Aspirin 1500 mg per day versus placebo, Outcome 1 Menstrual blood loss.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 5 Aspirin 1500 mg per day versus placebo

Outcome: 1 Menstrual blood loss



### Analysis 6.1. Comparison 6 Ibuprofen 600 mg per day versus placebo, Outcome 1 Median pain values.

#### Median pain values

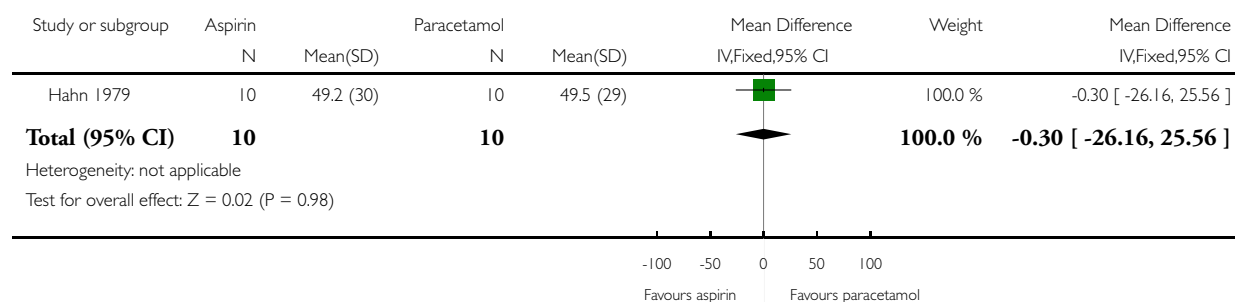
Jensen 1998	at insertion	3.3	2.5
Jensen 1998	first 4 to 6 hours	1.7	1.8
Jensen 1998	first day after insertion	1.4	1.3
Jensen 1998	second day after insertion	1.3	1.1
Jensen 1998	third day after insertion	1.1	1.1
Jensen 1998			

### Analysis 7.1. Comparison 7 Aspirin 1500 mg per day versus paracetamol 1500 mg per day, Outcome 1 Menstrual blood loss.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 7 Aspirin 1500 mg per day versus paracetamol 1500 mg per day

Outcome: 1 Menstrual blood loss



### Analysis 8.1. Comparison 8 Mefenamic acid 1500 mg per day versus desmopressin 300 mcg nasally per day, Outcome 1 Pictorial blood loss assessment chart.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 8 Mefenamic acid 1500 mg per day versus desmopressin 300 mcg nasally per day

Outcome: 1 Pictorial blood loss assessment chart

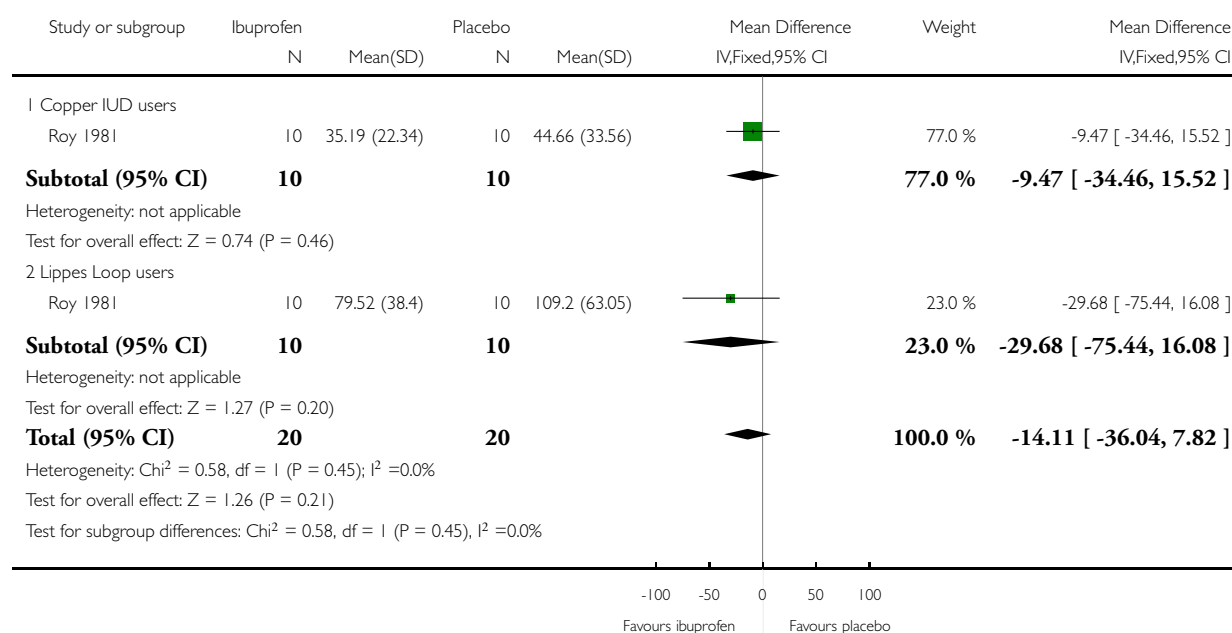


### Analysis 9.1. Comparison 9 Ibuprofen 1600 mg per day versus placebo, Outcome 1 Menstrual blood loss.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 9 Ibuprofen 1600 mg per day versus placebo

Outcome: 1 Menstrual blood loss

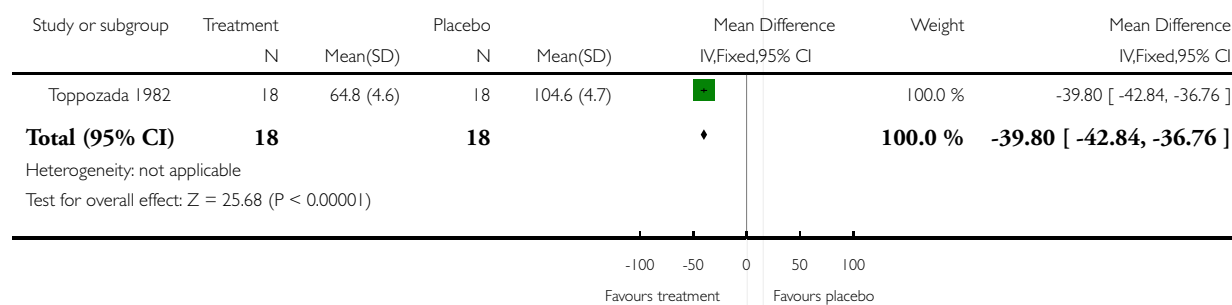


### Analysis 10.1. Comparison 10 Indomethacin 100 mg daily or flufenamic acid 600 mg daily or alclofenac 1500 mg daily versus placebo, Outcome 1 Menstrual blood loss.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 10 Indomethacin 100 mg daily or flufenamic acid 600 mg daily or alclofenac 1500 mg daily versus placebo

Outcome: 1 Menstrual blood loss

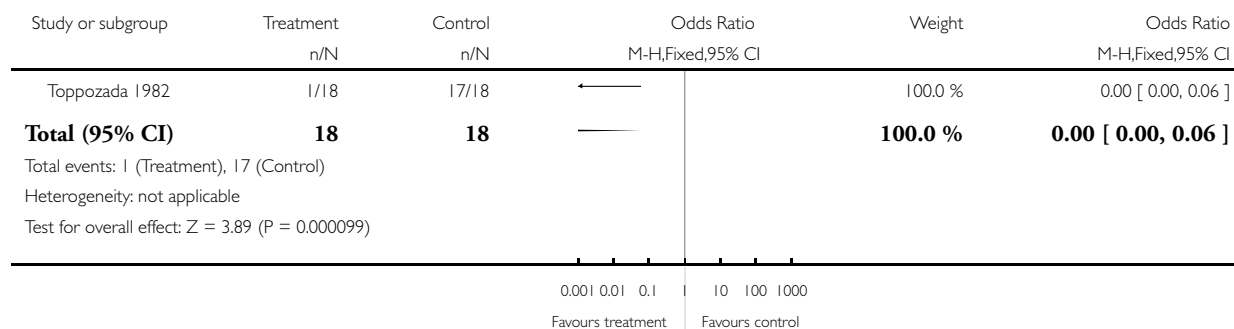


**Analysis 10.2. Comparison 10 Indomethacin 100 mg daily or flufenamic acid 600 mg daily or alclofenac 1500 mg daily versus placebo, Outcome 2 Severe or moderate pain.**

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 10 Indomethacin 100 mg daily or flufenamic acid 600 mg daily or alclofenac 1500 mg daily versus placebo

Outcome: 2 Severe or moderate pain

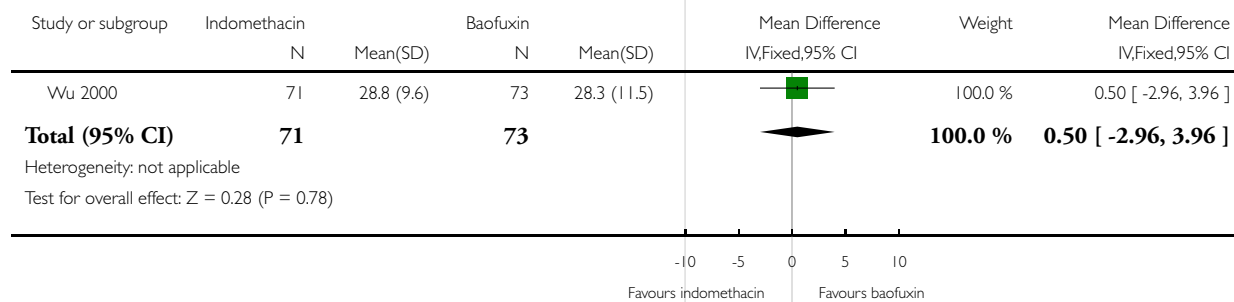


**Analysis 11.1. Comparison 11 Indomethacin 50 mg per day versus Baofuxin 16 g per day, Outcome 1 Bleeding/spotting days.**

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 11 Indomethacin 50 mg per day versus Baofuxin 16 g per day

Outcome: 1 Bleeding/spotting days

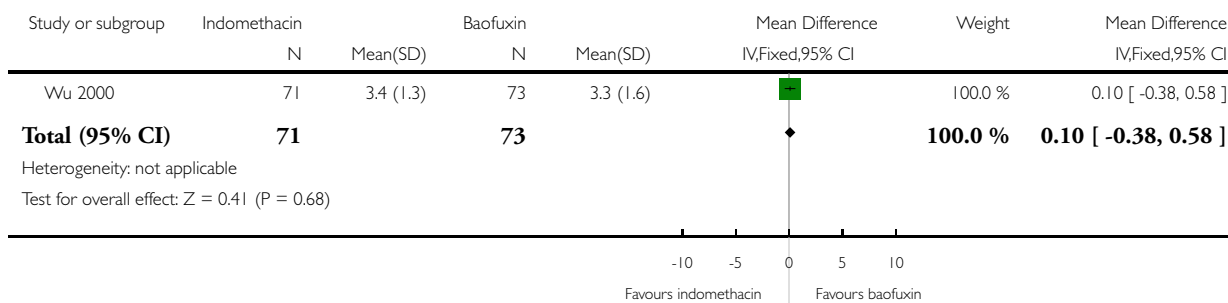


### Analysis 11.2. Comparison 11 Indomethacin 50 mg per day versus Baofuxin 16 g per day, Outcome 2 Bleeding/spotting episodes.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 11 Indomethacin 50 mg per day versus Baofuxin 16 g per day

Outcome: 2 Bleeding/spotting episodes

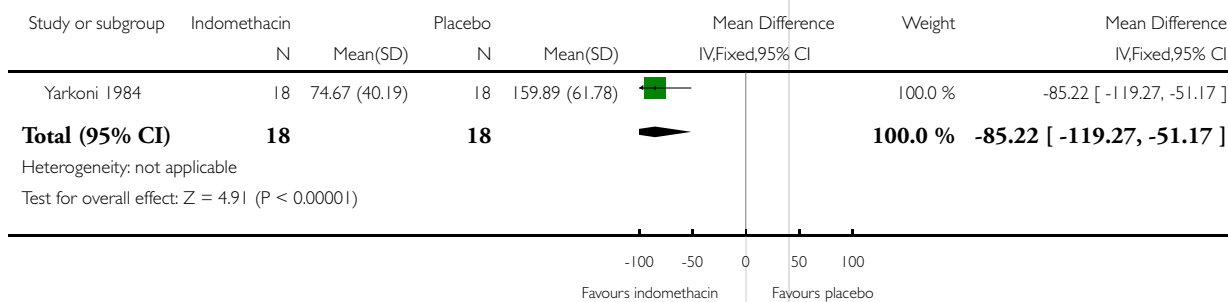


### Analysis 12.1. Comparison 12 Indomethacin 100 mg per day versus placebo, Outcome 1 Menstrual blood loss.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 12 Indomethacin 100 mg per day versus placebo

Outcome: 1 Menstrual blood loss

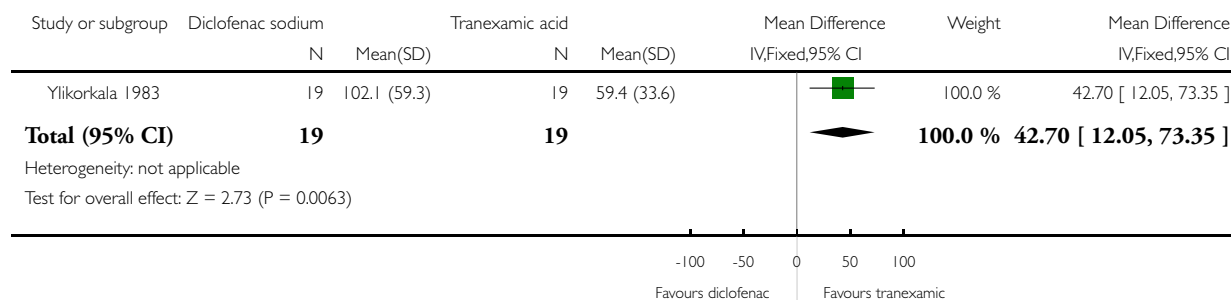


### Analysis 13.1. Comparison 13 Diclofenac sodium 150 mg then 75 mg versus tranexamic acid 4.5 mg per day, Outcome 1 Menstrual blood loss.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 13 Diclofenac sodium 150 mg then 75 mg versus tranexamic acid 4.5 mg per day

Outcome: 1 Menstrual blood loss

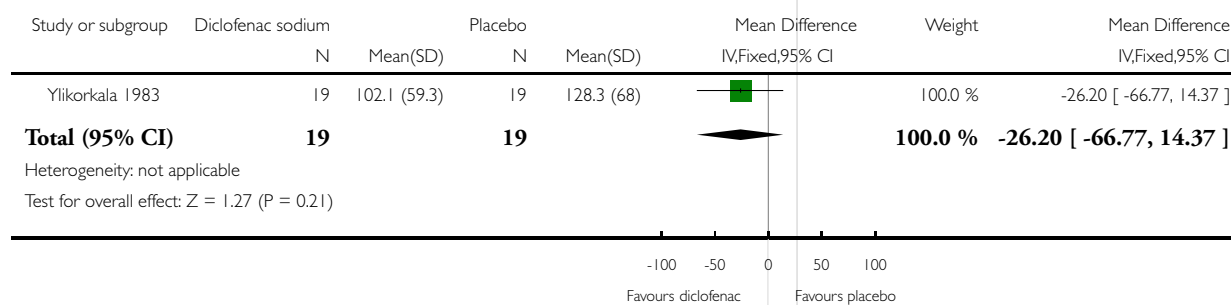


### Analysis 14.1. Comparison 14 Diclofenac sodium 150 mg (Day 1) then 75 mg on days 2-5 versus placebo, Outcome 1 Menstrual blood loss.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 14 Diclofenac sodium 150 mg (Day 1) then 75 mg on days 2-5 versus placebo

Outcome: 1 Menstrual blood loss

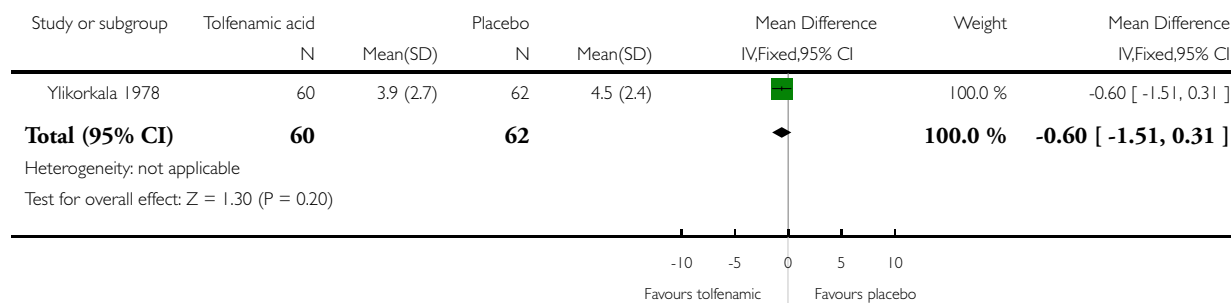


### Analysis 15.1. Comparison 15 Tolfenamic acid 600 mg per day versus placebo, Outcome 1 Duration of bleeding after IUD insertion.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 15 Tolfenamic acid 600 mg per day versus placebo

Outcome: 1 Duration of bleeding after IUD insertion

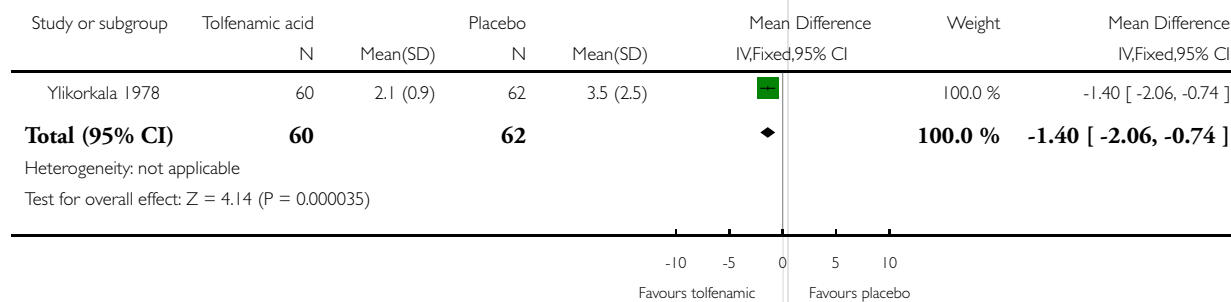


### Analysis 15.2. Comparison 15 Tolfenamic acid 600 mg per day versus placebo, Outcome 2 Number of sanitary pads used for bleeding immediately after IUD insertion.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 15 Tolfenamic acid 600 mg per day versus placebo

Outcome: 2 Number of sanitary pads used for bleeding immediately after IUD insertion

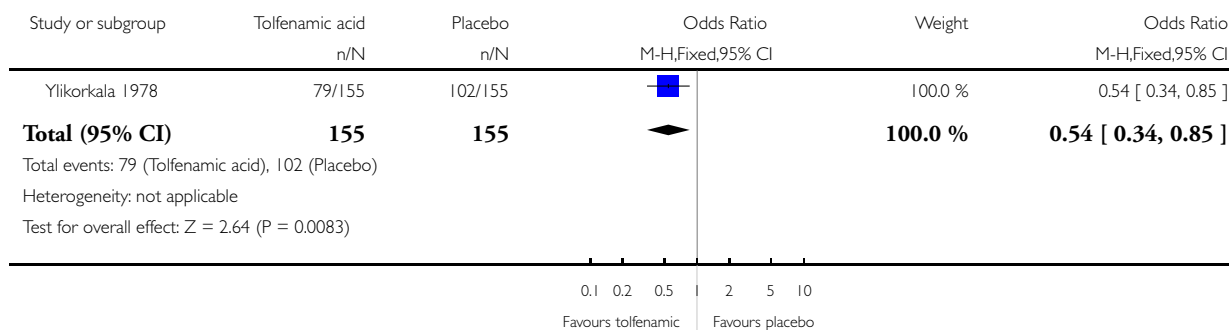


### Analysis 15.3. Comparison 15 Tolfenamic acid 600 mg per day versus placebo, Outcome 3 Next menses more abundant than normal.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 15 Tolfenamic acid 600 mg per day versus placebo

Outcome: 3 Next menses more abundant than normal

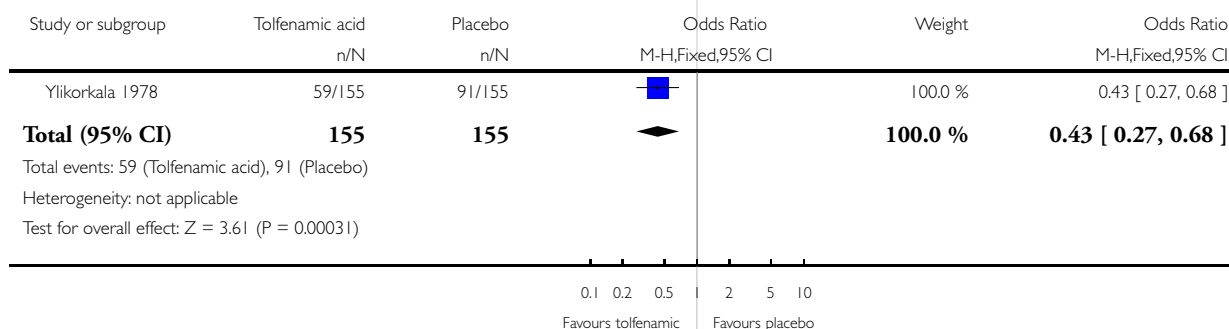


### Analysis 15.4. Comparison 15 Tolfenamic acid 600 mg per day versus placebo, Outcome 4 Clots in menstrual blood with subsequent menses.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 15 Tolfenamic acid 600 mg per day versus placebo

Outcome: 4 Clots in menstrual blood with subsequent menses

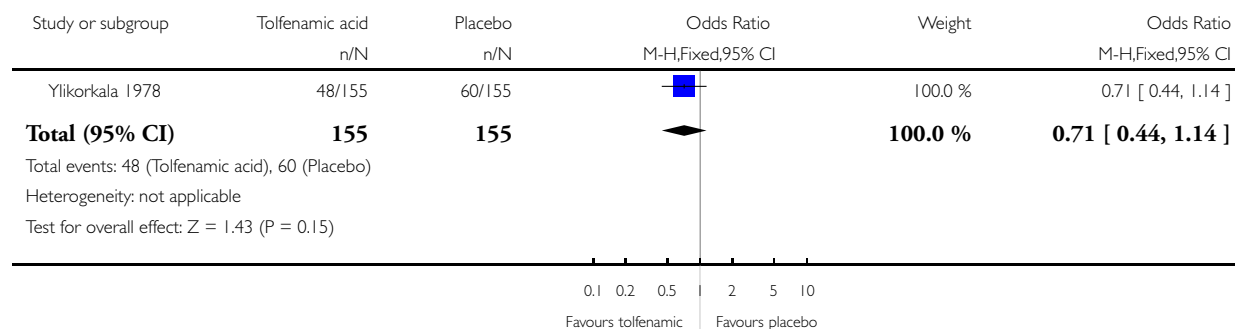


### Analysis 15.5. Comparison 15 Tolfenamic acid 600 mg per day versus placebo, Outcome 5 Subsequent menses more painful than normal.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 15 Tolfenamic acid 600 mg per day versus placebo

Outcome: 5 Subsequent menses more painful than normal

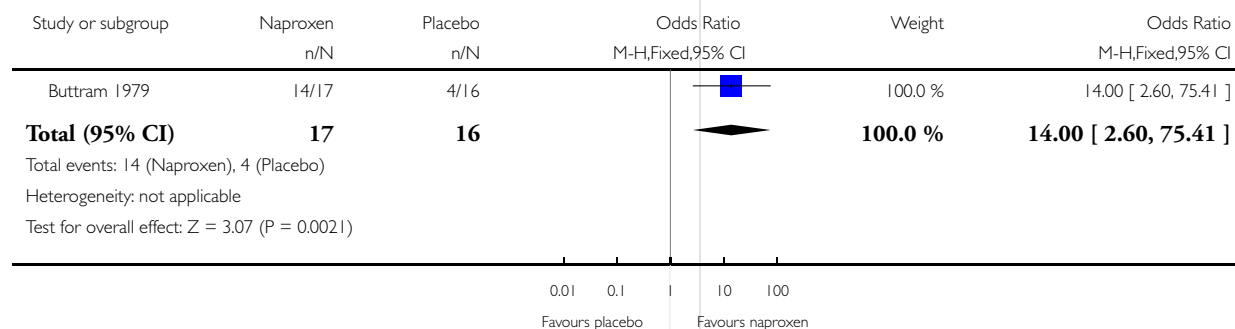


### Analysis 16.1. Comparison 16 Naproxen sodium 550 mg then 275 mg every 6 hr as needed versus placebo, Outcome 1 "Good" or "excellent" relief of uterine pain in one or more cycles.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 16 Naproxen sodium 550 mg then 275 mg every 6 hr as needed versus placebo

Outcome: 1 "Good" or "excellent" relief of uterine pain in one or more cycles

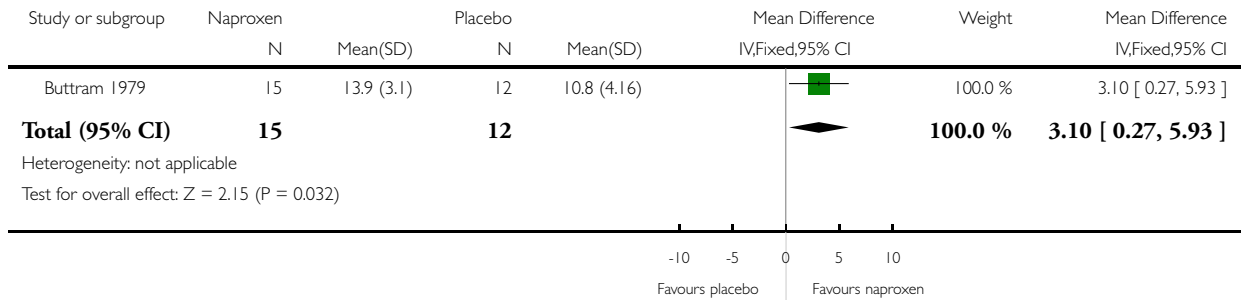


**Analysis 16.2. Comparison 16 Naproxen sodium 550 mg then 275 mg every 6 hr as needed versus placebo, Outcome 2 Mean daily pain relief scores.**

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 16 Naproxen sodium 550 mg then 275 mg every 6 hr as needed versus placebo

Outcome: 2 Mean daily pain relief scores

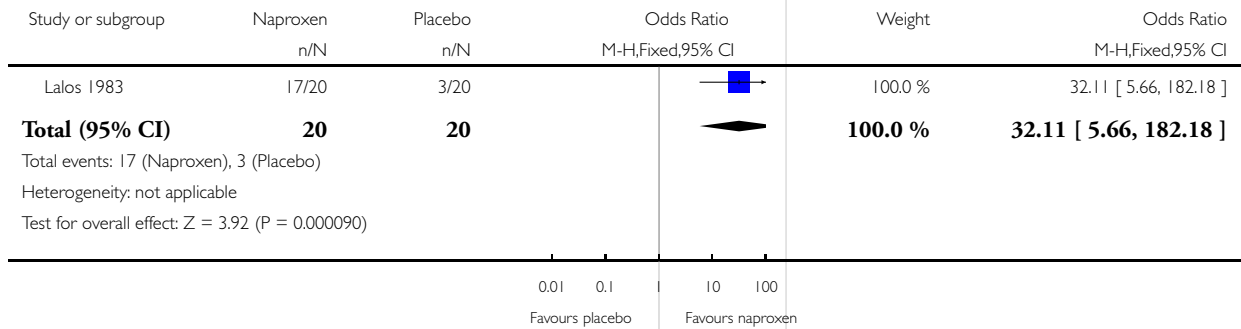


**Analysis 17.1. Comparison 17 Naproxen 500 mg initially then additional doses of 250 mg up to 1250 mg per day versus placebo, Outcome 1 Pain relief rated better than alternative treatment.**

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 17 Naproxen 500 mg initially then additional doses of 250 mg up to 1250 mg per day versus placebo

Outcome: 1 Pain relief rated better than alternative treatment

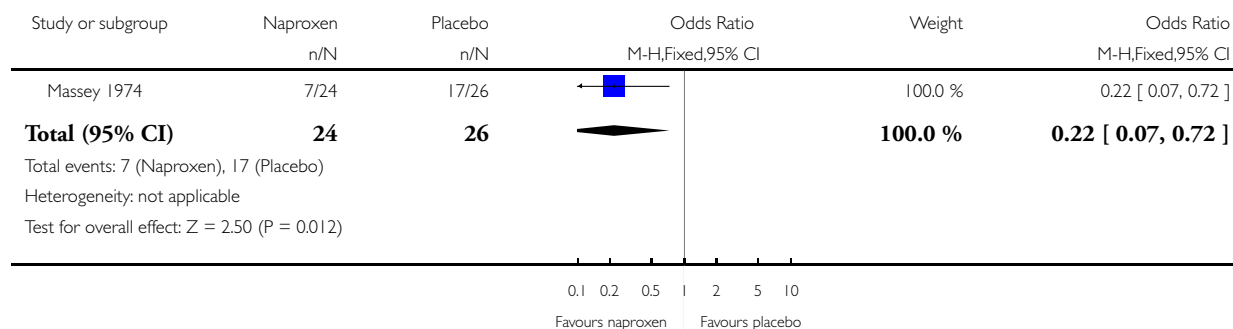


### Analysis 18.1. Comparison 18 Naproxen 1200 mg per day versus placebo, Outcome 1 Need for additional analgesia after IUD insertion.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 18 Naproxen 1200 mg per day versus placebo

Outcome: 1 Need for additional analgesia after IUD insertion

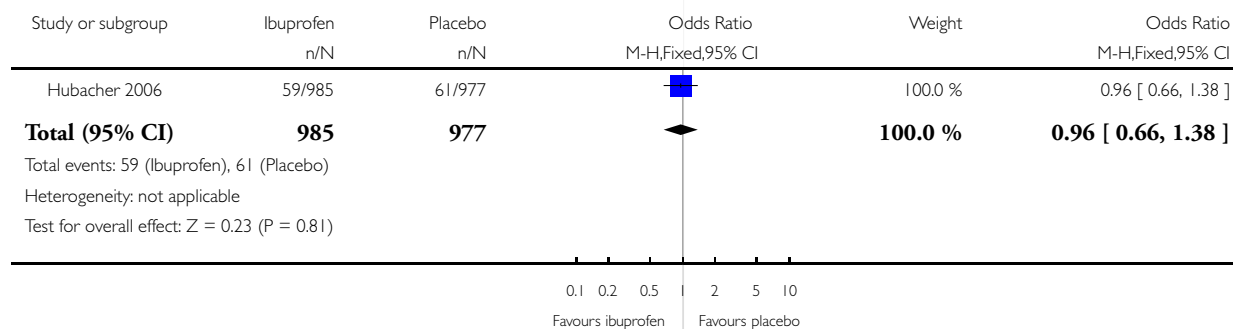


### Analysis 19.1. Comparison 19 Ibuprofen 1200 mg per day versus placebo with 6 menses after IUD insertion, Outcome 1 IUD removal by 26 weeks for dysmenorrhea or increased menstrual blood loss.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 19 Ibuprofen 1200 mg per day versus placebo with 6 menses after IUD insertion

Outcome: 1 IUD removal by 26 weeks for dysmenorrhea or increased menstrual blood loss

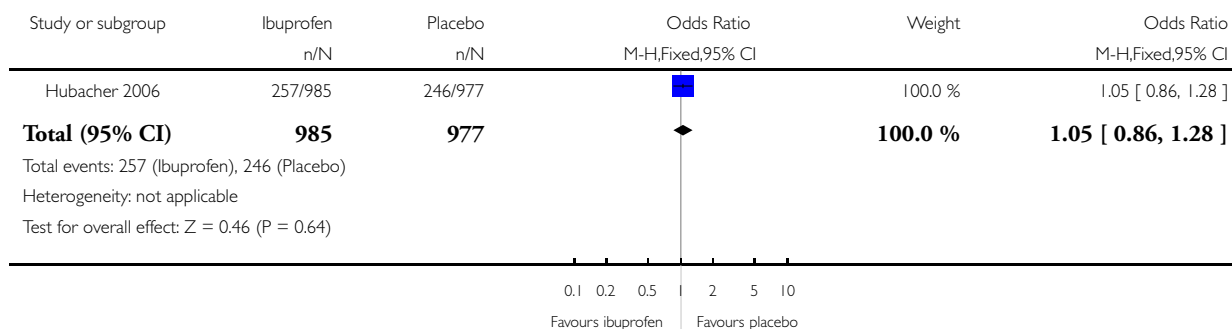


## Analysis 19.2. Comparison 19 Ibuprofen 1200 mg per day versus placebo with 6 menses after IUD insertion, Outcome 2 IUD removal by 52 weeks.

Review: Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use

Comparison: 19 Ibuprofen 1200 mg per day versus placebo with 6 menses after IUD insertion

Outcome: 2 IUD removal by 52 weeks



## WHAT'S NEW

Last assessed as up-to-date: 22 February 2009.

20 February 2009	New search has been performed	Searches were updated; searches of clinical trials databases were added. A trial was added to 'ongoing studies' that had not yet begun enrollment.
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## HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 4, 2006

15 April 2008	Amended	Converted to new review format.
30 September 2006	New citation required and conclusions have changed	Substantive amendment

## CONTRIBUTIONS OF AUTHORS

Dr Grimes developed the idea, registered the topic, and drafted the protocol and review. Dr Hubacher edited the protocol and assisted with the literature search and with writing and editing the review. Dr Lopez edited the protocol, performed an independent data extraction, and helped write the review. Dr Schulz edited the review and provided statistical oversight.

## DECLARATIONS OF INTEREST

Dr Grimes has served on the speakers' bureau for Berlex, Inc., and FEI Women's Health, LLC, which distribute IUDs. Dr Hubacher was the Principal Investigator for one of the trials included.

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- U. S. Agency for International Development, USA.
- National Institute of Child Health and Human Development, USA.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [\*therapeutic use]; Dysmenorrhea [\*drug therapy; etiology]; Intrauterine Devices [\*adverse effects]; Menorrhagia [\*drug therapy; etiology]; Randomized Controlled Trials as Topic

### MeSH check words

Female; Humans