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Danazol for heavy menstrual bleeding (Review)

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[Intervention Review]

Danazol for heavy menstrual bleeding

Heather H Beaumont¹, Cristina Augood², Kirsten Duckitt³, Anne Lethaby⁴

¹not applicable, not applicable, Birmingham, UK. ²Department of Epidemiology & Population Sciences,, London School of Hygiene and Tropical Medicine, London, UK. ³Prince George Regional Hospital, Prince George, Canada. ⁴Section of Epidemiology & Biostatistics, School of Population Health, University of Auckland, Auckland, New Zealand

Contact address: Heather H Beaumont, not applicable, not applicable, 59 Grosvenor Road, Harborne, Birmingham, England, B17 9AL, UK. heather_beaumont@hotmail.com.

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ABSTRACT

Background

Heavy menstrual bleeding (HMB) is an important cause of ill health in pre menopausal women. Medical therapy, with the avoidance of possibly unnecessary surgery is an attractive treatment option, but there is considerable variation in practice and uncertainty about the most effective therapy. Danazol is a synthetic steroid with anti-oestrogenic and anti progestogenic activity, and weak androgenic properties. Danazol suppresses oestrogen and progesterone receptors in the endometrium, leading to endometrial atrophy (thinning of the lining of the uterus) and reduced menstrual loss and to amenorrhoea in some women.

Objectives

To determine the effectiveness and tolerability of Danazol when used for heavy menstrual bleeding in women of reproductive years.

Search methods

We searched the Menstrual Disorders and Subfertility Group's Specialised Register (April 2007). We also searched the Cochrane Controlled Trials Register (Cochrane Library, Issue 2, 2007), MEDLINE (1966 to April 2007), EMBASE (1980 to April 2007), CINAHL (1982 to April 2007). Attempts were also made to identify trials from citation lists of included trials and relevant review articles.

Selection criteria

Randomised controlled trials of Danazol versus placebo, any other medical (non-surgical) therapy or Danazol in different dosages for heavy menstrual bleeding in women of reproductive age with regular HMB measured either subjectively or objectively. Trials that included women with post menopausal bleeding, intermenstrual bleeding and pathological causes of heavy menstrual bleeding were excluded.

Data collection and analysis

Nine RCTs, with 353 women, were identified that fulfilled the inclusion criteria. Quality assessment and data extraction were performed independently by two reviewers. The main outcomes were menstrual blood loss, the number of women experiencing adverse effects, weight gain, withdrawals due to adverse effects and dysmenorrhoea. If data could not be extracted in a form suitable for meta-analysis, they were presented in a descriptive format.

Main results

Most data were not in a form suitable for meta analysis, and the results are based on a small number of trials, all of which are under-powered. Danazol appears to be more effective than placebo, progestogens, NSAIDs and the OCP at reducing MBL, but confidence intervals were wide. Treatment with Danazol caused more adverse events than NSAIDs (OR 7.0; 95% CI 1.7 to 28.2) and progestogens (OR 4.05, 95% CI 1.6 to 10.2). Danazol was shown to significantly lower the duration of menses when compared with NSAIDs (WMD -1.0; 95% CI -1.8 to -0.3)

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and a progesterone releasing IUD (WMD -6.0; 95% CI -7.3 to -4.8). There were no randomised trials comparing Danazol with tranexamic acid or the levonorgestrel-releasing intrauterine system.

Authors' conclusions

Danazol appears to be an effective treatment for heavy menstrual bleeding compared to other medical treatments. The use of Danazol may be limited by its side effect profile, its acceptability to women and the need for continuing treatment. The small number of trials, and the small sample sizes of the included trials limit the recommendations for clinical care. Further studies are unlikely in the future and this review will not be updated unless further studies are identified.

PLAIN LANGUAGE SUMMARY

Danazol is an effective treatment for the reduction of heavy menstrual bleeding, but the adverse effects may be unacceptable to women

Options to help avoid surgery can be important for many women who are having problems with heavy menstrual bleeding. One of the drug options is Danazol. Danazol suppresses the hormones that increase the endometrium (the lining of the uterus that is shed during menstruation). However, Danazol can also produce male characteristics and some menopause-like symptoms, as well as weight gain and acne. The review found that although Danazol is effective at reducing menstrual blood loss there are not enough trials to show whether this treatment is acceptable to women with heavy menstrual bleeding.

BACKGROUND

Heavy menstrual bleeding (menorrhagia) can have a significant impact on women's lives. In the UK, one in 20 women aged 30 to 49 consult their general practitioner each year with heavy menstrual bleeding (Vessey 1992) and it accounts for 12% of all gynaecological referrals (Bradlow 1992). Once referred to a gynaecologist, surgical intervention is highly likely (Coulter 1991).

Heavy menstrual bleeding (HMB) or menorrhagia is clinically defined as greater than or equal to 80 ml blood loss per menstrual cycle (Hallberg 1966; Cole 1971). It is, however, the woman's perception of her own menstrual loss which is the key determinant in a referral and, indeed, subsequent treatment. The main aim of the treatment of menorrhagia is to reduce blood loss in order to improve quality of life and prevent anaemia.

Many factors can cause HMB for example coagulation disorders, endocrine disorders, uterine abnormalities and other pelvic pathology. These disorders should be excluded before decisions are made about treatment as they may require different management. However, in most cases, there is no pathological cause of the heavy bleeding, and the condition is labelled dysfunctional uterine bleeding (EHCB 1995). Eighty percent of women treated for menorrhagia have no uterine abnormality and over a third of the women undergoing hysterectomies for HMB have a normal uterus removed (Gath 1982; Clarke 1995). Although patient satisfaction with hysterectomies is high (Coulter 1994), there are complications and occasional death associated with hysterectomy (Dicker 1982). Complications are more likely when the hysterectomy is performed by the open abdominal route, as is usually the case (Hospital 1995). Effective medical therapy, that avoids unnecessary surgery, is therefore an attractive alternative.

A wide variety of medications are available to reduce HMB but their effectiveness has been questioned (Coulter 1995). The aim of this review is to see if Danazol is an effective therapy for HMB. Danazol is chemically derived from testosterone (a naturally occurring hormone). It inhibits ovulation and reduces oestrogen levels. It also causes endometrial atrophy (thinning of the lining of the uterus), reduced menstrual loss and leads to amenorrhoea (absence of periods) in some women (Chimbira 1980b). Danazol has a dramatic effect on increasing haemoglobin and serum ferritin levels and may therefore be valuable in women who need effective therapy to stop very heavy bleeding and restore their haemoglobin and iron status to normal (Ford 1994; Chimbira 1979). Danazol has androgenic properties (a tendency to cause male characteristics) which may result in acne, seborrhoea (greasy skin) and hirsutism (excessive hair growth). Other side effects include weight gain, irritability, musculoskeletal pains, hot flushes and breast atrophy (loss of breast tissue). Longer term treatment with Danazol may cause liver effects (including benign hepatic adenomas) in some women.

OBJECTIVES

To determine the effectiveness and tolerability of Danazol when given for heavy menstrual bleeding in women of reproductive years.

We wished to investigate:

1. Whether treatment with Danazol is more effective than placebo in reducing heavy menstrual blood loss.

2. Whether treatment with Danazol is more effective than other medical therapies (antifibrinolytics, NSAIDs, progestogens) in reducing heavy menstrual blood loss.
3. If effective, what is the optimum dosage of Danazol.
4. Whether treatment with Danazol leads to an improved quality of life for women with heavy menstrual blood loss.
5. Whether women tolerate treatment with Danazol and find it an acceptable treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled comparisons of Danazol versus placebo, any other medical (non-surgical) therapy or Danazol in different dosages when used to reduce heavy menstrual bleeding.

Types of participants

Inclusion criteria

1. Women of reproductive years
2. Regular (21-35 days cycle) heavy menstrual blood loss, subjectively or objectively defined (for example by alkaline haematin method (Hallberg 1964))
3. Recruitment from primary care, family planning or specialist clinic setting

Exclusion criteria

1. Post-menopausal bleeding
2. Irregular menses and intermenstrual bleeding
3. Pathological causes of heavy menstrual bleeding

Types of interventions

1. Danazol versus placebo
2. Danazol versus any other medical (non-surgical) therapy
3. Danazol versus Danazol (i.e. studies comparing different dosage regimens of Danazol)

Types of outcome measures

Primary outcomes

1. Reduction in objectively measured menstrual blood loss during intervention: in ml/cycle
2. Reduction in objectively measured menstrual blood loss after intervention: at 1 month and at 3 months, in ml/cycle
3. Reduction in menstrual blood loss as subjectively assessed by the woman
4. Quality of life: participant's perceived change in quality of life, provided this has been recorded in a reproducible and validated format
5. Presence of side effects of any degree reported either spontaneously by the woman or elicited from specific questioning
6. Presence of specific side effects: acne, hirsutism, weight gain, irritability, musculoskeletal pains, hot flushes, breast atrophy, voice changes.
7. Withdrawals due to side effects
8. Reduction in symptoms of dysmenorrhoea

Secondary outcomes

1. Weight gain
2. Subjective efficacy of intervention

3. Time to relapse, assessed subjectively (return of previous level of heavy bleeding)
4. Duration of periods
5. Resource use: women, general practitioner, hospital, health service

Search methods for identification of studies

Electronic searches

All publications which describe or might describe randomised controlled trials of Danazol for the treatment of heavy menstrual bleeding were obtained using search strategy see [Appendix 1](#).

Searching other resources

Citation lists of included trials and relevant review articles were also searched. For most of the included trials ([Cameron 1987](#); [Chimbira 1980a](#); [Higham 1993](#); [Lamb 1987](#); [Fraser 1991](#)), the first author was contacted to clarify issues related to data extraction.

Data collection and analysis

The review was undertaken by four reviewers (HB, AL, KD and CA), two of whom (KD, HB) have clinical expertise and one of whom has specific statistical expertise (AL).

Selection of trials for inclusion in the review was performed by the reviewers after employing the search strategy described previously.

Included trials were analysed for the following quality criteria and methodological details:

Trial characteristics

1. Method of randomisation
2. Presence or absence of blinding to treatment allocation
3. Quality of allocation concealment
4. Number of women randomised, excluded or lost to follow up
5. Whether an intention to treat analysis was done
6. Whether a power calculation was performed
7. Duration, timing and location of the study
8. Source of funding of the study

Characteristics of the study women

1. Age and any other recorded characteristics of women in the study
2. Other inclusion criteria
3. Exclusion criteria

Interventions used

1. Types of medical therapy used
2. Dose, duration and timing of administration of medical therapy

Outcomes

1. Methods used to measure menstrual blood loss after treatment
2. Methods used to evaluate adverse effects
3. Methods used to measure symptoms of dysmenorrhoea
4. Methods used to assess duration of menses
5. Methods used to evaluate efficacy of intervention
6. Methods used to assess acceptability of intervention
7. Methods used to assess quality of life measures
8. Methods used to measure time to relapse

All assessments of the quality of trials and data extraction were performed independently by two reviewers (HB and AL) using forms designed according to Cochrane guidelines. Discrepancies were resolved by discussion.

One of the included trials was published in Turkish ([Buyru 1995](#)). The methods, results and any associated tables or figures for this study were translated by Metin Gulmezoglu of the Cochrane Collaboration. Additional information was sought from the principal investigators of trials in which the methodology and/or original trial data was inadequately reported in the publication. Letters were sent to the authors of five of the included trials ([Cameron 1987](#); [Chimbira 1980a](#); [Fraser 1991](#); [Higham 1993](#); [Lamb 1987](#)) to request additional information. Replies were received from Dr IS Fraser, from the [Fraser 1991](#) study, and J Higham from the [Higham 1993](#) study, who both supplied individual participant data. A reply was also received from I Cameron of the [Cameron 1987](#) study, who was unable to supply any additional information. Replies were not received for the other studies.

One of the included studies was of a cross-over design ([Fraser 1991](#)). For each treatment, data from both arms of the cross-over were combined in the publication. It may not be valid to include the results after the cross-over because of potential carryover effects, and only data from before the cross-over were used in this review. Individual participant data were obtained from the principal author and the reviewers calculated means with their standard deviations for phase one data.

Allocation concealment was scored according to the categories used by the Cochrane Collaboration; allocation concealment was adequate (A), unclear (B), inadequate (C), or that allocation concealment was not used (D). Other aspects reported in the Methodological Quality section of the review are; method of randomisation, use of blinding, use of intention to treat analysis, baseline similarity of comparison groups, numbers lost to follow up and trial design and power. Details of any other important methodological issues are reported in the Table of Characteristics of included studies.

Three of the studies reported the number of pads used per day as one of the subjective measures of MBL. This outcome was not included in this review as it may be an inaccurate measure of MBL. There is no correlation between blood loss and the number of pads or tampons used ([Fraser 1984](#); [Chimbira 1980c](#)). Sanitary pad usage is based more on habit, convenience and individual personal hygiene than quantity of blood ([Chimbira 1980c](#)).

Quality of life measures were not assessed in a generic validated score in any of the trials. However, dysmenorrhoea was assessed by two authors and this outcome was added to the protocol. Both authors used a simple three point scoring system (where 1= mild pain and 3= severe pain). One author recorded scores for backache and abdominal pain ([Bonduelle 1991](#)) and the other recorded a score for dysmenorrhoea ([Dockeray 1989](#)).

Statistical analysis was performed in accordance with the guidelines for statistical analysis described in the Cochrane Handbook. Where possible, the outcomes were pooled statistically. For dichotomous data (for example proportion of women experiencing side effects), results for each study were expressed as an odds ratio with 95% confidence intervals and combined for meta analysis with Rev Man software using the fixed effects

Mantel-Haenszel model, unless there was significant heterogeneity in which case a random effects Der Simonian and Laird model was used. Continuous data were shown as a weighted mean difference (WMD) and 95% confidence interval. Heterogeneity between the results was examined by inspecting the scatter in the data plots and the overlap in their confidence intervals and more formally by checking the results of the Chi-squared tests. However, as some outcomes contained only one trial, it was not appropriate to look at heterogeneity for all outcomes.

Difficulties were encountered with the reporting of continuous outcomes. Meta-analysis with the Rev Man software offers a WMD option to combine outcomes and requires data to be presented as absolute values of means with their standard deviations. For many outcomes, particularly menstrual blood loss, the data are skewed and authors correctly presented their data as medians with a range. Where possible original data were obtained from the principal authors in order to calculate means with their standard deviations. This was done for one study (Higham 1993). Where only medians and ranges were available, as in the Cameron study, the data were inspected for skewness. If the distribution appeared to be skewed (median towards one end of the range), the results were reported in the Other Data section of the review. If there did not appear to be significant skewness, the median was taken as being the mean and an estimate of the standard deviation was roughly calculated from the range $((\text{range} \times 0.95)/4)$. For the Cameron study, means and standard deviations were estimated from the data for duration of menses, but the data for MBL (which showed skewness) were reported in the Other Data section.

For one study, standard errors were reported. These were converted to standard deviations (standard error $\times$ square root of n (where n = group size)) for the outcome of menstrual blood loss so that a WMD could be calculated (Chimbira 1980a).

When the mean was reported, but there was evidence of highly significant skewness ($\text{mean}/\text{SD} < 1$), the results were reported in the Other Data section of the review. Analyses based on means are only appropriate where the data is approximately normally distributed. A mean to standard deviation ratio of less than one indicates distinct evidence of a skewed distribution (Altman 1996) and it is not appropriate to use this data in a meta-analysis. The MBL data for three studies (Chimbira 1980a; Dunphy 1998; Fraser 1991) was reported in the Other Data section for this reason.

Where data could not be extracted in a form suitable for inclusion in the meta-analysis, for example where figures were inadequately reported in the publication, the data were reported in the Other data tables.

A priori it was planned to perform sensitivity analyses on results to assess the possible contribution of:

- Differences in adequacy of allocation concealment, clear concealment only compared to uncertain or inadequate concealment
 - Differences in methodological quality; trials of high quality only compared to all other trials
 - Differences in methods of defining menorrhagia and assessing menstrual blood loss, use of objectively determined (alkaline haematin method) menorrhagia compared to other methods
- However, such analyses were not possible as the number of studies included in the review was inadequate.

It is the intention of the reviewers that a new search for RCTs will be carried out annually and the review updated accordingly.

RESULTS

Description of studies

Eleven RCTs (reported in ten publications) comparing Danazol with either placebo, other medical treatments or other doses of Danazol in women with heavy menstrual bleeding were identified. Studies comparing Danazol with surgical treatments and studies comparing the effectiveness of various medical treatments as pre-operative agents for menorrhagia were excluded from this review.

Trials excluded from this review

Two trials were excluded from the review. One of them (Need 1992) was a study of 11 women with subjective and objective heavy menstrual bleeding who all received 200 mg Danazol per day for one month. The women were then split into four groups and given either Danazol 200 mg/day, Danazol 100 mg/day, Danazol 50 mg/day or placebo. There was concern that there was not a sufficient washout period between the induction and treatment phases of the trial. In addition the numbers randomised to each of the four arms of the trial were very small (only 2-3 women per arm), so that after withdrawals from the study some of the results became meaningless. The data from the initial induction phase of this trial could not be used as there was no control group- all the women received Danazol 200 mg/day. One publication reported on two trials, and one of these (Chimbira 1980b) was excluded from the review. It was a before-after treatment study of eight women- each participant took placebo followed by Danazol (the order the same for all women). This is likely to cause bias as there is no controlling for the time effect.

Trials included from this review

Nine RCTs met the inclusion criteria for this review. One trial compared Danazol with placebo (Lamb 1987), seven compared Danazol with other medical therapies (Bonduelle 1991; Buyru 1995; Cameron 1987; Dockeray 1989; Dunphy 1998; Fraser 1991; Higham 1993) and one study compared different doses of Danazol (Chimbira 1980a). Unpublished data were obtained for two of these trials to obtain separate figures for the group who had received Danazol before cross-over (Fraser 1991) and to try to obtain individual participant data for blood loss measurements (Higham 1993). The authors of two other studies (Chimbira 1980a; Lamb 1987) were contacted for additional data, but further clarification was not given.

women

The locations of the included studies were as follows: UK (five studies), Ireland, Australia, Turkey and Canada (one study for each). The review is based on studies that included a total of 353 women. The study women in the nine trials were pre menopausal women aged from 18 to 50 years, and all had a subjective complaint of heavy menstrual bleeding. Five of the studies required the women to have objectively determined (by the alkaline haematin method) heavy menstrual bleeding. However, the cut off point for this varied between trials. One study defined heavy MBL as greater than 50 ml per cycle (Cameron 1987), one used >60 ml per cycle, as the cut off point (Chimbira 1980a) and three studies defined heavy MBL as

greater than or equal to 80 ml/cycle (Dockeray 1989; Dunphy 1998; Higham 1993). In all of these studies women were randomised after the mean menstrual blood loss had been confirmed as meeting the criteria for the particular study. For one of these studies, MBL was measured for one month prior to starting treatment (Dunphy 1998). In the other four studies requiring women to have objectively determined HMB, MBL was measured for two months prior to starting treatment.

Most of the studies required the women to have regular (21 to 35 days cycle) menses, but the Higham trial included both ovulatory and anovulatory women. Pelvic pathology was an exclusion criteria in eight studies. Other exclusion criteria included pregnancy (two studies), hormone or anticoagulant treatment (two studies) and IUD use (two studies).

Interventions

The duration of treatment was two cycles in three studies (Cameron 1987; Dockeray 1989; Fraser 1991) and three cycles in the other six studies. Four of the included studies also had a three month follow up period after treatment was stopped (Chimbira 1980a; Dunphy 1998; Higham 1993; Lamb 1987).

Chimbira 1980a compared two different dosages of Danazol; 100 mg/ day and 200 mg/day. All the other studies (Bonduelle 1991; Buyru 1995; Cameron 1987; Dockeray 1989; Dunphy 1998; Fraser 1991; Higham 1993; Lamb 1987) used Danazol 200 mg/ day. In one of these studies (Dockeray 1989) Danazol was given twice daily as two 100 mg doses. In all the other studies 200 mg Danazol was given once daily. Danazol was given from day five of the cycle in one study (Fraser 1991), or throughout the cycle from the start of the menses, in all other studies.

Five studies compared Danazol with a progestogen. One of these (Dunphy 1998) compared Danazol with medroxyprogesterone, (10 mg on days 16-25 of the cycle), the other four compared Danazol with norethisterone (Bonduelle 1991; Buyru 1995; Cameron 1987; Higham 1993). In two of these studies, norethisterone was given as a dose of 5 mg three times daily on days 19-26 of the cycle (Bonduelle 1991; Higham 1993), and in the other two, it was given as 5 mg twice daily on days 15-25 of the cycle (Cameron 1987) and on days 16-25 of the cycle (Buyru 1995). In one of these studies (Dunphy 1998) women were given placebo for the other days of the cycle to ensure blinding.

In three trials Danazol was compared with a NSAID. Three studies compared Danazol with mefenamic acid (Cameron 1987; Dockeray 1989 and Fraser 1991) and the Fraser study also compared Danazol with naproxen. Where the comparison intervention was mefenamic acid, this was given in a dose of 500 mg three times daily for a maximum of five days per cycle. Naproxen, was given as an initial dose of 500 mg followed by 250 mg three to four times daily for a maximum of five days.

One study (Fraser 1991) compared Danazol with a low dose oral contraceptive pill (ethinyl oestradiol 30ug and levonorgestrel 150ug) for 21 out of every 28 days. In one study (Cameron 1987), one of the comparison interventions was a progesterone impregnated coil releasing 65ug progesterone daily.

Outcomes

For all of the trials MBL was a main outcome measure. In five trials menstrual blood loss was objectively measured by the alkaline haematin method (Cameron 1987; Chimbira 1980a; Dockeray 1989; Fraser 1991; Higham 1993). In the remaining four trials MBL was measured subjectively. The Dunphy study assessed MBL by using the pictorial chart method described by Higham (1990). In this study blood loss was recorded each month by women using the chart method and the total blood loss each month was recorded. The Bonduelle study used a scoring system, where heaviness of bleeding was rated on a scale and scored for each day of bleeding from 1 to 7 (where 1=spotting and 7= flooding). The daily values were combined to yield a menstrual bleeding intensity score for each period. Three studies assessed MBL by the number of pads used per day (Bonduelle 1991; Buyru 1995; Lamb 1987). This outcome was not included in the analysis, as it is an inaccurate measure of MBL. The MBL data in the Lamb (1987) trial could not be extracted as the paper gave no details on the type of score used or the information used to obtain a score. The author of this trial was contacted for further details, but no reply was received.

Two studies (Bonduelle 1991; Higham 1993) assessed the efficacy of treatment. Both assessed this subjectively, and the Higham study also assessed this objectively (the number of women with MBL <80 ml/cycle (measured by the alkaline haematin method) at the end of the intervention was reported). Three studies reported MBL after discontinuation of treatment. Dunphy 1998 and Chimbira 1980a measured MBL for three months after the intervention. The data from the Chimbira study could not be included in the analysis as the figures for one of the intervention groups were not reported. The Higham trial reported the recurrence rates of menorrhagia of the three groups during the placebo follow up phase. However this could not be included in the analysis as those who continued in the follow up phase were only a small subset of all the original women, and the numbers entering this stage of the trial were so small that some of the results were meaningless.

Seven studies reported on the effects of treatment on the duration of menses (Bonduelle 1991; Buyru 1995; Cameron 1987; Chimbira 1980a; Dockeray 1989; Higham 1993; Lamb 1987). Bonduelle (1991), Chimbira (1980a) and Dockeray (1989) reported the effects on dysmenorrhoea as one of the outcome measures. The Bonduelle (1991) trial used a scoring system for backache and abdominal pain and the other two studies assessed the numbers reporting an improvement in dysmenorrhoea.

Side effects were reported in a number of ways. Some studies reported numbers of women experiencing any adverse events, whereas others reported on specific adverse events (such as weight gain, hirsutism, nausea). Six studies reported on the total number of women experiencing any side effects from the treatment. Five studies looked at the number of women experiencing specific adverse events (Buyru 1995; Chimbira 1980a; Dockeray 1989; Higham 1993; Lamb 1987). However the results of these could not be included in the meta-analysis, as they were reported as frequency of events (rather than the number of women experiencing a particular side effect). Four trials (Bonduelle 1991; Buyru 1995; Dunphy 1998; Higham 1993) reported the number of withdrawals due to side effects and Dockeray (1989) assessed treatment acceptability.

Five studies assessed weight gain as one of the outcome measures. The way in which this was reported varied between trials. The trials by Chimbira (1980a) and Dunphy (1998) looked at the mean weight

gain for the different treatment groups. Two studies assessed the number of women with weight gain over a certain value. The Higham (1993) study reported on the number of women with a weight gain of less than 3 kg and the Bonduelle (1991) study reported the number of women with weight gain of less than 2 kg. Lamb (1987) compared the mean weight of the two groups after treatment.

Risk of bias in included studies

See Table 1

Randomisation and allocation concealment

Allocation to an intervention group was randomised in all of the included trials. All included studies were given an allocation score of B due to unclear details regarding the method of allocation and allocation concealment. In six trials, the authors stated that women were allocated at random to one of the interventions, but gave no further details. Higham (1993) described randomisation as "patients were allocated to the treatments in strict sequential order. Patients were stratified across treatment groups according to whether they were ovulatory or anovulatory and by their mean objectively measured menstrual loss during baseline". In the Dockeray (1989) trial, women were assigned to one of the two treatments according to a prepared randomisation code, but no other details were given. Dunphy (1988) also reported randomised allocation according to a random code.

Blinding

Blinding was uncertain in three of the studies (Buyru 1995; Chimbira 1980a; Fraser 1991). In the Cameron (1987) study, neither the treatment providers nor the women were blinded, as the study compared three medical treatments and a progesterone releasing intrauterine device, but it is unclear as to whether the outcome assessors were blinded. Two of the studies (Dunphy 1998 and Lamb 1987) were reported as being double blind and two were open studies with no blinding (Bonduelle 1991; Dockeray 1989). Two studies (Fraser 1991; Higham 1993) were single blind. In the Fraser (1991) study the laboratory staff who performed the MBL assays were blinded, but the treatment providers and women were not blinded. The Higham (1993) study was a single blind study, with the women not blind to the intervention.

Withdrawals, dropouts and intention to treat analysis

Withdrawal rates from randomisation to the end of the treatment phase ranged from 0 to 47% (14 out of the 30 randomised) in Bonduelle 1991. There were no reported drop outs or exclusions post randomisation in Buyru 1995 and Cameron 1987. In Chimbira 1980a it was unclear whether there were any withdrawals. Withdrawals after randomisation and prior to treatment included 20% (6 out of 30) in Bonduelle 1991, 9% (2 out of 23) in Dunphy 1998 and 5% (3 out of 57) in Higham 1993. Drop outs during the treatment phase were as follows: Bonduelle 1991, 27% (8 out of the 30 randomised); Higham 1993, 18% (10 of the 57 randomised); Fraser 1991, 16% (7 out of 45); Dunphy 1998, 13% (3 out of 23) and 3% (1 out of 40) in Dockeray 1989. Lamb 1987 reported 10 withdrawals out of 76 women (13%) between randomisation and the end of the first month of treatment. Reasons for withdrawal were usually due to side effects of treatment, unwillingness to continue, non-compliance or failure to meet some inclusion criteria. In the Higham

(1993) study, three women were excluded prior to treatment, two were excluded due to a pharmacy dispensing error and one due to menopausal symptoms.

Higham 1993 reported that an intention to treat analysis was performed, however three women who withdrew after randomisation were excluded from the intention to treat analysis. An intention to treat analysis was performed by default in two studies (Buyru 1995; Cameron 1987) where there were no reported withdrawals.

Baseline similarity of comparison groups

One study presented no information on the baseline similarity of the comparison groups (Chimbira 1980a). Dunphy 1998 and Fraser 1991 only presented data on pretreatment menstrual blood loss, and there was no significant difference between the treatment groups on this measure. Higham 1993 presented data on age, weight, duration of menses, cycle length, haemoglobin concentration and pretreatment menstrual blood loss. There was no significant difference between the three treatment groups on any of these measures. In the Dockeray 1989 study, the two groups did not significantly differ in terms of age, height, parity, menstrual blood loss measurements and numbers with dysmenorrhoea. Buyru 1995 reported no significant differences between the two groups in terms of age, weight, baseline haemoglobin and duration of menses.

In three trials (Bonduelle 1991; Cameron 1987; Lamb 1987) there were imbalances between the Danazol and comparison groups in potentially important baseline factors. In the Cameron 1987 study, the groups differed in terms of MBL at baseline, which was significantly higher in the Danazol group. There were however, no differences between the four groups in terms of age, height, weight, parity and duration of menses. Bonduelle 1991 presented data on age, gravidity, duration of menorrhagia, bleeding scores, backache scores and abdominal pain scores. Abdominal pain scores were significantly higher in the Danazol group, but the two groups were comparable on the other measures. Lamb 1987 reported no differences between the two groups in terms of weight, age, weight, blood pressure, parity and duration of symptoms. However there were differences between the groups for blood loss scores, with the Danazol group having higher blood loss scores.

Trial design

Fraser 1991 is a cross-over study. This trial did not have a sufficient washout period before women were crossed over to another treatment, and only the data from the first arm of the cross-over were used in this review. It is not valid to include the results from after the cross-over because of potential bias from carryover effects. The other eight trials were parallel in design (Bonduelle 1991; Buyru 1995; Cameron 1987; Chimbira 1980a; Dockeray 1989; Dunphy 1998; Higham 1993; Lamb 1987).

Trial size and power calculation

A statistical power calculation was included in the method of the Dunphy trial. The authors reported that 34 women would be needed for the study to have sufficient power. However the authors were only able to recruit 23 women, and only 18 of these women were included in the analysis.

Source of funding

For six of the included studies, the source of funding was a pharmaceutical company. One study was funded by a Birthright Research Grant, and two studies did not state any source of funding.

Effects of interventions

Overall nine studies compared the use of Danazol with placebo, other medical treatments or different doses of Danazol for the treatment of heavy menstrual bleeding. The studies contained a total of 353 women.

Danazol versus placebo

One study with 66 women compared Danazol 200 mg once daily with a matched placebo once daily for three months of treatment (Lamb 1987).

Menstrual blood loss (objective or subjective)

This study did not assess objective MBL, and subjective MBL was assessed using an unidentified scoring system. It was not possible to include data for the menstrual blood loss scores, as the type of scoring system used and the figures were poorly reported in the paper. The authors report no significant differences in blood loss scores for the placebo group when comparing before and after treatment scores. A significant difference in blood loss scores was reported for the Danazol group compared to the pre-treatment scores, but it is unclear how this was calculated.

Duration of menses

The data for duration of menses could not be included in this review as the figures were inadequately reported in the paper. The author reported no difference in duration of menses for the placebo group comparing pre and post treatment figures. A significant difference in duration of menses was reported for the Danazol group (when comparing before and after treatment figures), but the authors do not indicate how this was calculated.

Withdrawals due to side effects

The number of withdrawals due to side effects during the intervention did not significantly differ between the two groups (OR 2.06, 95% CI 0.18, 23.94).

Body weight

The trial reported data on the mean body weight for each group. After three months treatment the mean weight (kg) of the Danazol group was significantly greater than that of the placebo group (WMD 6.70, 95% CI 0.98, 12.42).

Danazol versus PROGESTOGENS

Five of the included studies involving a total of 131 women compared 200 mg Danazol with a progestogen. For four of the studies the comparison intervention was norethisterone, and in one study the progestogen was medroxyprogesterone acetate.

Menstrual blood loss (objective or subjective)

Four of the studies comparing Danazol with a progestogen reported data on MBL. In two trials MBL was measured objectively using

the alkaline haematin method. One small parallel trial comparing Danazol with norethindrone in the meta analysis (n=37) showed no significant difference between the two groups for menstrual blood loss after treatment (WMD -35.60, 95% CI -102.20 to 31.00) (Higham 1993). The other trial reporting objectively measured MBL, contained data which was not reported in a form suitable for pooling. This trial reported MBL as medians and ranges, rather than means and standard deviations and is included as descriptive data in the Other Data section (Cameron 1987). In this trial the groups were not comparable at baseline, and the study compared MBL after treatment to MBL at baseline for the different treatment groups. There was no significant difference between the before and after treatment values for the progestogen group ($p>0.05$), where as MBL after treatment was significantly lower than that at baseline for the Danazol group ($p<0.05$) (Cameron 1987).

Two studies comparing Danazol with a progestogen reported subjective measures of MBL. Both are included as descriptive data in the other data section due to skewing of the data in one (Dunphy 1998) and use of a non-standard bleeding scale in the other (Bonduelle 1991). One trial used the pictorial chart method described by Higham (1990) to record monthly blood loss and reported that MBL after three months treatment was significantly lower in the Danazol group compared to the medroxyprogesterone acetate group ($p=0.0128$) (Dunphy 1998). The other study used a seven point scoring system where daily bleeding scores were combined to give a score for each menstrual period. The trial compared bleeding scores after three months treatment and showed a significant difference between the two groups in favour of Danazol ($p<0.05$).

One study (n=18) included the outcome of MBL three months after the intervention. The trial showed that MBL (assessed by the pictorial chart method) was significantly lower in the progestogen group three months after treatment was stopped (WMD 203.00, 95%CI 25.65 to 380.35) (Dunphy 1998).

Side effects

Four trials reported the number of women in each of the two treatment groups experiencing side effects. The four studies in the meta analysis showed that significantly more women in the Danazol group experienced side effects compared to the progestogen group (OR 4.05, 95% CI 1.61 to 10.21) (Bonduelle 1991; Buyru 1995; Dunphy 1998; Higham 1993). Commonly reported side effects for Danazol treatment included acne, weight gain, headache, nausea and tiredness. One study found that adverse effects were reported with a similar frequency and were of a similar nature in both treatment groups (Bonduelle 1991). Commonly reported side effects in this study were weight gain, bloating, gastro-intestinal symptoms, skin changes, lethargy, depression and reduced concentration. Buyru 1995 found that headaches and muscle cramps were reported with similar frequency in both groups, but the Danazol group also complained of weight gain, acne, nausea and intermenstrual bleeding. The Higham (1993) study found that both groups reported the adverse effects of muscle cramps and depression with similar frequency. In this study, other commonly reported side effects amongst the Danazol group included headache, weight gain, nausea and vomiting and acne, where as other adverse effects reported amongst the progestogen group were premenstrual tension symptoms (Higham 1993).

Withdrawals due to side effects

Danazol for heavy menstrual bleeding (Review)

Four trials comparing Danazol with a progestogen reported the number of withdrawals due to side effects. Pooling of data from these studies showed that there was no significant difference between the two groups in terms of withdrawals due to side effects (OR 1.67, 95% CI 0.53 to 5.23).

Duration of menses

Four studies comparing Danazol with a progestogen assessed the duration of menses. The Chi square test for heterogeneity showed there is significant heterogeneity within the comparison (19.52, df=3, p=0.0002). To consider this heterogeneity, the data was analysed using a random effects model to take into account the variability between the studies when calculating the summary statistic. Pooling of data from these trials shows that there was no significant difference between the groups in the duration of menses after treatment (WMD -0.74, 95% CI -2.31, 0.82).

Dysmenorrhoea

One of the studies comparing Danazol with a progestogen reported this outcome (Bonduelle 1991). Abdominal pain and backache were assessed using a three point scoring system. The study compared before and after treatment scores for both measures of pain for the two groups. For the Danazol group there was no significant difference in the before and after treatment scores on either of these measures of dysmenorrhoea (p>0.05). The post treatment backache score was significantly lower than that at baseline for the norethisterone group (p<0.05), but there was no significant difference in the before and after treatment abdominal pain scores (p>0.05). This trial was included as descriptive data in the other data section due to the use of a non standard pain scale.

Weight gain

Three studies comparing Danazol with a progestogen reported weight gain as an outcome measure. One trial reported weight gain as mean weight gain, and showed that the mean weight gain was significantly higher in the Danazol group (WMD 2.80, 95% CI 1.60 to 4.00) (Dunphy 1998). One study reported the number of women with a weight gain of >2kg and the another reported the number of women with weight gain of less than 3kg. For weight gain as a dichotomous variable there was no significant difference between the Danazol and progestogen groups. Where the number of women with weight gain >2kg was assessed the OR was 2.86 (95% CI 0.48 to 17.11) (Higham 1993) and where the numbers with weight gain less than 3kg was reported the OR was 5.57 (95% CI 0.48 to 64.09) (Bonduelle 1991). But the reported results are imprecise with wide confidence intervals.

Efficacy of intervention

Three studies included this outcome. One study assessed this objectively, reporting the number in each group with MBL of <80 ml at the end of the intervention, and the other two studies assessed efficacy subjectively. The study assessing efficacy objectively showed a significant difference in favour of Danazol. Significantly more women in the Danazol group had a MBL of less than 80 ml at the end of the intervention (OR 7.20 95% CI 1.28 to 40.37) (Higham 1993).

For subjective efficacy of medication, where efficacy was measured as the number of women rating the treatment as highly or moderately effective, subjective efficacy was significantly better after Danazol treatment than after norethisterone (OR 4.33, 95% CI 1.09 to 17.17) (Higham 1993). Where efficacy was assessed by

the numbers rating their MBL as none or moderate, there was no significant difference between the two groups (OR 5.83, 95% CI 0.70 to 48.87) (Bonduelle 1991).

Danazol versus. NSAIDS

Three studies compared Danazol with a NSAID for the treatment of heavy menstrual bleeding. All three studies compared Danazol with mefenamic acid, but one trial also used naproxen as a comparison intervention.

Menstrual blood loss (objective/subjective)

All three studies reported this outcome, and all assessed MBL using the alkaline haematin method. One small parallel trial (n=39) in the meta-analysis showed that mean MBL after two months treatment was significantly lower in the Danazol group compared to the mefenamic acid group (WMD -96.70, 95% CI -138.80, -54.60) (Dockeray 1989). Two other trials are included as descriptive data in the other data section as one reported MBL in a form unsuitable for inclusion in the meta analysis and in the other the data showed significant skewness. One trial included in the other data section, compared Danazol with mefenamic acid and reported MBL as medians and ranges. In this trial the groups were not comparable at baseline and the study compared MBL after treatment to MBL at baseline for the different treatment groups, rather than comparing MBL across the groups. MBL after treatment was significantly lower than that at baseline for the Danazol group (p<0.05), but there was no significant difference between the before and after treatment MBL values for the mefenamic acid group (p>0.05) (Cameron 1987). The other trial was a cross-over trial which compared Danazol with both mefenamic acid and naproxen. When the mean and standard deviation were calculated from the individual participant data and put into the meta-analysis, mean MBL after two months treatment was significantly lower in the Danazol group compared to both the mefenamic acid group (p=0.001) and the naproxen group (p=0.02) (Fraser 1991). These figures refer to data prior to women crossing over to the other treatment.

Side effects

One study which compared Danazol with mefenamic acid reported this outcome. There were significantly more adverse effects in the Danazol group compared to the mefenamic acid group 75% compared to 30% (OR 7.00, 95% CI 1.74 to 28.17) (Dockeray 1989). The mefenamic acid group complained mainly of nausea, vomiting and diarrhoea; the Danazol group complained of more serious adverse effects such as musculoskeletal pains, dizziness, flushes, acne, behavioural changes, tiredness, breast atrophy, hirsutism and hoarseness.

Withdrawals due to side effects

None of the studies comparing Danazol with a NSAID reported this outcome.

Duration of menses

Two trials in both of which mefenamic acid was the comparison intervention assessed this outcome. Pooling of data from these trials showed the duration of menses was significantly shorter in the Danazol groups after two months of treatment (WMD -1.03; 95% CI -1.78 to -0.28).

Dysmenorrhoea

One parallel study reported this outcome. Dysmenorrhoea was assessed in two ways in the study; according to the number of women in each intervention group who reported an improvement

in dysmenorrhoea after two months treatment, and using a three point pain scale scoring system. The number reporting an improvement in dysmenorrhoea showed no significant difference between the two interventions (OR 1.20; 95% CI 0.20, 7.31). The dysmenorrhoea scores showed no significant difference between the two groups after two months of treatment ($p>0.05$) (Dockeray 1989). The data for the dysmenorrhoea scores was included in the Other Data section due to the use of a non-standard pain scale.

Acceptability of treatment

One study included the outcome of the numbers in each group unwilling to continue that particular treatment. This small parallel trial ($n=39$) compared Danazol with mefenamic acid and showed no significant difference between the two groups with regard to the number unwilling to continue the treatment (OR 1.11; 95% CI 0.32 to 3.90) (Dockeray 1989).

Danazol versus. ORAL CONTRACEPTIVE

One small cross-over study involving 12 women compared Danazol 200 mg with an oral contraceptive (ethinyl oestradiol 30ug and levonorgestrel 150ug) (Fraser 1991). Only the data prior to the crossover were included in the analysis.

Menstrual blood loss (objective or subjective)

Blood loss was measured objectively using the alkaline haematin method. After two months treatment mean MBL for the Danazol group was significantly lower than that for the oral contraceptive group ($p=0.02$). The trial was included in the Other Data section as descriptive data due to skewness of the data.

Other outcomes

The only trial comparing Danazol with an oral contraceptive did not report any other outcome measures.

Danazol versus PROGESTERONE RELEASING IUD

One trial with 14 women compared Danazol with a progesterone releasing intrauterine device (releasing 65ug progesterone daily) for two months treatment.

Menstrual blood loss (objective or subjective)

MBL was measured objectively using the alkaline haematin method. The study compared MBL after the intervention with that at baseline for each of the interventions, rather than making comparisons between the groups as the groups were not comparable at baseline. For both groups MBL after the intervention was significantly lower than that at baseline $p<0.05$ and $p<0.01$ for the Danazol and progesterone releasing IUD interventions respectively (Cameron 1987). The trial was included as descriptive data in the Other Data section as the data was not reported in a form suitable for inclusion in the meta-analysis.

Duration of menses

The one trial comparing Danazol with a progesterone releasing IUD reported data on the duration of menses after two months treatment compared with that at baseline for each group. The results show that the mean duration of menses was significantly shorter in the Danazol group (WMD -6.00; 95% CI -7.25 to -4.75).

Danazol 200 mg versus. Danazol 100 mg

One study involving 32 women compared Danazol 200 mg with Danazol 100 mg for the treatment of heavy menstrual bleeding (Chimbira 1980a).

Menstrual blood loss (objective or subjective)

MBL was reported objectively after three months treatment and compared with mean MBL at baseline for each group. For both groups mean MBL after three months treatment was significantly lower than mean MBL at baseline ($p<0.01$). There was no significant difference between the two groups after three months of treatment ($p=0.2$) (Chimbira 1980a). This trial was reported in the Other Data section as descriptive data as the data showed significant skewness.

Duration of menses

The mean duration of menses was included as one of the outcome measures in the study comparing Danazol 200 mg with Danazol 100 mg. The authors reported that the duration of menses after three months treatment with Danazol 200 mg was significantly less than that at baseline ($p<0.01$). There was no significant difference in the duration of menses after three months treatment with Danazol 100 mg compared to that at baseline ($p>0.05$). The trial was reported as descriptive data in the Other Data section as the figures were inadequately reported in the paper.

Dysmenorrhoea

The study assessed the outcome of the numbers in each group reporting an improvement in dysmenorrhoea after three months treatment. For this outcome there was no significant difference between the two groups (OR 0.68; 95% CI 0.12 to 3.83) (Chimbira 1980a).

Weight gain

The trial comparing Danazol 200 mg with Danazol 100 mg reported the mean gain in weight for the two groups, Danazol 200 mg (mean weight gain 2.3 kg after three months of treatment), Danazol 100 mg (mean of 2.1 kg) (Chimbira 1980a). No standard deviations were reported in the trial so a WMD could not be calculated.

Danazol 200 mg VERSUS REDUCING DOSE Danazol

One small parallel trial compared Danazol 200 mg with a reducing dose of Danazol for three months treatment. Thirty six women were involved in this comparison. The reducing dose Danazol was a regime of Danazol 200 mg/day for one month, 100 mg/day the next month and Danazol 50 mg/day for the third month.

Menstrual blood loss (objective or subjective)

Mean MBL was measured objectively after three months treatment, and there was no significant difference in mean MBL between the two groups (WMD 33.50; 95% CI -32.38 to 99.38) (Higham 1993).

Side effects

The number of women in each intervention group experiencing adverse effects was reported as an outcome measure. For this outcome there was no significant difference between the two groups (OR 1.13, 95% CI 0.14 to 9.07) (Higham 1993).

Withdrawals due to side effects

The number of withdrawals due to side effects showed no significant difference between the Danazol 200 mg group and the group taking a reducing dose of Danazol (OR 0.88, 0.15 to 5.05) (Higham 1993).

Weight gain

The study comparing Danazol 200 mg with a reducing dose of Danazol assessed the number of women in each group who had a weight gain of less than 2kg after three months treatment. There

was no significant difference between the two groups on this outcome measure (OR 0.32, 95% CI 0.08 to 1.28) (Higham 1993).

Duration of menses

The mean duration of menses for women in the two intervention groups was assessed after three months treatment. The only trial in the meta-analysis showed no significant difference between the two intervention groups (WMD 1.30, 95%CI -0.76 to 3.36) (Higham 1993).

Subjective efficacy of intervention

Subjective efficacy was measured as the number of women rating the treatment as highly or moderately effective in each of the intervention groups. There was no significant difference between the two groups after three months of daily treatment (OR 1.18, 95% CI 0.30 to 4.73) (Higham 1993).

DISCUSSION

The aim of this review was to assess the effectiveness and tolerability of Danazol for the treatment of heavy menstrual bleeding. Despite the fact that Danazol has been available for the treatment of menorrhagia for a considerable length of time, there is a general lack of well-designed research to evaluate the effectiveness and tolerability of this therapy. The results of this review are based on a small number of trials which are underpowered and with unclear allocation concealment.

The largest trial had 20 women in each arm. A power calculation for sample size based on a (alpha)=0.05 and b (beta)=0.80 where Danazol treatment is compared to either progestogen or NSAID therapy (the most common medical treatments) indicated that at least 30 women in each arm would be required to show an acceptable increase in benefit (30%) in the proportion of women having their menstrual bleeding reverting to normal (<80 mls/cycle). It was not feasible to consider a benefit of treatment in terms of the actual quantity of blood loss, mls/cycle, that women find satisfactory and no data were available to assess satisfaction with treatment. Therefore, where no differences between interventions are reported, it may be that the trials are too small to show any difference.

MENSTRUAL BLOOD LOSS: objective measurement

Danazol was shown to be no more effective than progestogens at reducing MBL by one trial included in the meta-analysis. If response to treatment is defined as reduction of menstrual blood loss to <80 ml/cycle, significantly more women in the Danazol group had their MBL reduced to below 80 ml/cycle. Another trial, included as descriptive data, suggested that Danazol may be more effective than progestogens at reducing MBL. One limitation of the studies comparing Danazol with a progestogen is that in all these studies, the progestogen was given in the luteal phase of the cycle (days 19-26). Progestogens given during the luteal phase of the cycle in women with ovulatory HMB may increase, rather than reduce menstrual blood loss (Preston 1995).

Danazol was shown to be more effective at reducing MBL than mefenamic acid by the one trial included in the meta-analysis and two other trials. Danazol was also shown to be more effective than naproxen at reducing MBL by one small trial included in the meta-analysis. Thus there is consistent evidence that Danazol is more effective than NSAIDs in reducing MBL.

Danazol was shown to be more effective at reducing MBL than the oral contraceptive pill by one small trial included as Other Data. The results of one trial included as descriptive data indicate Danazol is no more effective than a progestogen releasing IUD in reducing MBL.

On the available evidence, a 200 mg daily Danazol regime appears to be no more effective in reducing MBL compared to Danazol 100 mg or a reducing dose Danazol regimen. There are some limitations to this evidence. The results are based on one trial and small numbers of women for all comparisons and the data for some comparisons are heavily skewed.

It is possible that the differences found were underestimated. Trials were included in this review if women had a subjective complaint of heavy menstrual bleeding and/or if they had objectively determined heavy menstrual bleeding. In all of the included studies, women had a subjective complaint of heavy menstrual bleeding and in five studies, women had their MBL objectively measured by the alkaline haematin method. To comply with the definition of objectively defined menorrhagia, trials would have to include only women with MBL>80 ml/cycle. However in one study women were included if their objectively defined MBL was>50 ml/cycle (Cameron 1987) and another included women with a MBL of >60 ml/cycle. Menorrhagia was correctly defined as objectively determined MBL of >80 ml/cycle in three studies (Dockery 1989; Dunphy 1998; Higham 1993).

Many women who seek medical help for heavy menstrual bleeding have normal blood loss (Fraser 1984; Haynes 1977) and results from one RCT have suggested that there is little response to therapy in women with MBL <35 ml (Fraser 1981). Since a proportion of the study women with a complaint of heavy menstrual bleeding may have had normal menstrual blood loss, it is likely that some reported differences between treatment and placebo groups have been underestimated.

MENSTRUAL BLOOD LOSS: subjective measurement

Whilst the alkaline haematin extraction method is the most accurate method for assessment of blood loss and is used as the standard, a woman's own perception of her MBL is important in the evaluation of effectiveness of treatment on MBL. Therefore a woman's subjective assessment is an important outcome measure.

Three studies recorded MBL according to subjective measures. One trial compared Danazol 200 mg daily and a placebo and the authors reported that Danazol was significantly more effective after two months treatment. Danazol was shown to be significantly more effective than progestogens at reducing MBL by one study which used a pictorial bleeding chart method to assess MBL and by one study which used a bleeding intensity score to assess MBL.

The subjective assessment of MBL is an important outcome measure, as most diagnoses and interventions for heavy menstrual bleeding are based on clinical evidence, in the absence of objectively determined heavy menstrual bleeding. It is therefore important in practice that any intervention results in a significant improvement in the woman's own perceived cyclical loss.

MENSTRUAL BLOOD LOSS AFTER CESSATION OF THERAPY

It has been reported that Danazol has a significant 'carry-over' effect and many women have reduced MBL for up to four months after cessation of therapy (Shaw 1994), suggesting that Danazol

could be used intermittently. Danazol might be more acceptable in clinical use if it could be effectively used intermittently. There are no studies assessing intermittent Danazol use for HMB, but two of the included studies (Dunphy 1998; Lamb 1987) assessed whether Danazol has a significant 'carry-over' effect. Lamb (1987) reported that a reduction in blood loss score was maintained for four months after treatment ceased, but insufficient information was provided for these data to be included in the review. This finding was not confirmed in one study which compared Danazol with a progestogen, and found there to be no significant carry-over effect of Danazol 3 months after treatment was stopped (Dunphy 1998).

As Danazol has a rapid and significant effect on increasing haemoglobin and serum ferritin (Chimbira 1979; Ford 1994), it may be valuable in women who need a highly effective short term treatment to stop very heavy bleeding and restore their haemoglobin and iron status to normal. One of the potential short term uses of Danazol is to use it intermittently, however there is currently insufficient evidence to assess whether Danazol can be effectively used on an intermittent basis.

ADVERSE EVENTS

There were no significant differences in reported adverse effects with Danazol 200 mg in comparison with a reducing dose Danazol. No data are available for whether women treated with Danazol experience more adverse effects than those treated with the oral contraceptive or a progestogen releasing IUD. However, women treated with Danazol experienced significantly more adverse effects than those treated with a progestogen and those treated with mefenamic acid.

Danazol has weak androgenic properties, and hence can cause side effects related to this. These side effects spontaneously resolve after cessation of treatment. None of the included trials reported data on numbers experiencing specific adverse events in a suitable form for inclusion in this review, but commonly reported side effects for Danazol treatment included acne, weight gain, headache, nausea and tiredness. One study comparing Danazol with mefenamic acid, reported that women in the mefenamic acid group experienced mostly gastrointestinal side effects such as nausea/vomiting and diarrhoea, whereas women in the Danazol group experienced more serious side effects such as musculoskeletal pains, flushes, behavioural changes, lethargy, and androgenic effects such as acne, breast atrophy, hirsutism and hoarseness (Dockeray 1989).

Women using Danazol for heavy menstrual bleeding are likely to require long term treatment, so any adverse events which affect adherence to treatment or treatment safety are particularly important. One study reported that for the women treated with Danazol, the side effects of breast atrophy, hirsutism and hoarseness did not develop until the second month of treatment (Dockeray 1989). As the studies included in this review all involved two to three months treatment, data on the side effect profile of Danazol for longer term treatment with Danazol would be useful. A longer period of treatment would enable the longer term liver effects of Danazol to be assessed. These potential liver effects may be an important factor limiting the long term use of Danazol and they have not been evaluated by any of the studies.

WEIGHT GAIN

Weight gain is one of the androgenic side effects of Danazol which may limit its use (Irvine 1999), and is therefore an important outcome measure. When compared to placebo, the mean weight of the Danazol group was significantly greater than that of the placebo group after two months treatment. Three studies assessed weight gain for Danazol compared with a progestogen. The mean weight gain of the Danazol group was significantly greater than that of the progestogen group. However when weight gain was assessed in terms of the number of women with a weight gain of less than 2kg (Higham 1993) and the number of women with a weight gain of less than 3kg (Bonduelle 1991), there was no significant difference between the two interventions. There was no significant difference in terms of the number of women with weight gain of less than 2kg when Danazol 200mg was compared with a reducing dose of Danazol. However assessment of weight gain by a dichotomous outcome may not be sensitive to determine real differences between the groups. One study compared mean weight gain for Danazol 200mg versus 100 mg. There appears to be no difference in terms of mean weight gain between these regimens, however there is currently insufficient evidence to answer this question.

WITHDRAWALS DUE TO SIDE EFFECTS

There was no significant difference in withdrawals due to side effects when Danazol 200 mg daily was compared to placebo, progestogens or a reducing dose Danazol. However, due to the small number of women involved in the studies, there is insufficient evidence to evaluate this outcome adequately. It may be that the numbers are too small to reveal any differences between the groups. The large drop out rates of several trials (five studies had drop out rates of more than 10%) points towards the treatment being unacceptable to women. Some of these may be unreported withdrawals due to side effects.

DYSMENORRHOEA

There was no significant difference between Danazol 200 mg/day, NSAIDs and a reducing dose of Danazol in terms of the number of women reporting an improvement in dysmenorrhoea. There is insufficient evidence to determine whether there is any difference between Danazol and progestogens with regards to improvement in dysmenorrhoea. One study has evaluated this, and the results indicate that progestogens may produce a greater improvement in dysmenorrhoea (Bonduelle 1991).

DURATION OF MENSES

A significant reduction in the duration of menses in favour of Danazol is shown for those trials comparing Danazol with NSAIDs and a progesterone releasing IUD. The results of one trial indicate that the duration of menses may be shorter after treatment with a 200mg Danazol regimen when compared with a 100 mg regimen. Another study showed that the duration of menses is significantly shorter for women treated with a reducing dose of Danazol compared to those treated with Danazol 200 mg/day. There is no significant difference in the duration of menses when Danazol is compared to progestogens. The results from one trial comparing Danazol with a progestogen, indicate that Danazol may cause substantially more protracted bleeding in some women, whereas this is not the case for norethisterone (Higham 1993). The reason for this is unknown.

EFFICACY OF INTERVENTION

Two studies comparing Danazol with a progestogen evaluated subjective efficacy of treatment. One study showed subjective

efficacy was significantly greater for Danazol, where as the second found no difference between the two interventions.

ACCEPTABILITY OF INTERVENTION

One study comparing Danazol and mefenamic acid assessed the acceptability of treatment, and found there was no difference between the two treatments in terms of the number of women unwilling to continue treatment. However, it may be that too few women were included in the analysis to show any difference between the groups. The study reported that the reason women were unwilling to continue treatment differed between the two groups. For the mefenamic acid group, the reason most women gave for being unwilling to continue treatment was due to a lack of efficacy, whereas for women in the Danazol group it was largely due to side effects (Dockeray 1989).

DOSAGE

One of the objectives of this review is to determine the optimum dosage of Danazol as a treatment for HMB. Two small trials compared the standard dose of Danazol for HMB, 200 mg/day with a lower dose of 100 mg and a reducing dose regimen. No differences in effectiveness or frequency of adverse events were reported, but women treated with 200 mg/day had a shorter duration of menses when compared with a reducing dose regimen. Numbers of women in the trials were insufficient to adequately assess this outcome.

It is important to note that there are no studies comparing Danazol with tranexamic acid and the levonorgestrel-releasing intrauterine system (Mirena). These treatments may be as effective as Danazol, but an objective comparison has not been carried out.

No study has included changes in quality of life or resource cost as outcome measures. Danazol has a contraceptive effect in doses of above 200 mg/day, however it is not licensed for use as a contraceptive, and therefore women not wishing to conceive require additional contraception. This is particularly important with Danazol as it has a teratogenic effect and there is a risk of less than of a female fetus if exposure to Danazol is continued between 8 and 18 weeks of gestation. This means that the acceptability of Danazol to women, and quality of life outcomes are very important and they have not been properly addressed by any of the trials.

SUMMARY OF THESE RESULTS IN TERMS OF THE OBJECTIVES

1. Is Danazol more effective than placebo in reducing heavy menstrual blood loss?

One small trial assessed this outcome, and Danazol appears to be more effective than placebo, but the data are poorly reported.

2. Is Danazol more effective than other medical therapies?

Danazol is more effective than progestogens, NSAIDs and the OCP, although the results are imprecise with wide confidence intervals.

3. What is the optimum dosage of Danazol?

The standard dose of 200 mg/day of Danazol does not appear to differ in effectiveness and frequency of adverse events when compared to 100 mg/day or a reducing regimen. However these results are based on one small trial for each comparison.

4. Does treatment with Danazol lead to an improved quality of life for women with HMB?

The included trials only assessed improvement in dysmenorrhoea and there were insufficient data to address this outcome adequately.

5. Do women tolerate treatment with Danazol and find it acceptable?

There was an increased frequency of adverse events when Danazol was compared with other medical therapies. This did not appear to affect the acceptability of the treatment. However this comparison was only reported by one small study.

AUTHORS' CONCLUSIONS

Implications for practice

The results do not give clear indications for recommending Danazol as a treatment for heavy menstrual bleeding. Danazol appears to be an effective treatment for heavy menstrual bleeding when compared to other medical treatments, though it is uncertain whether it is acceptable to women. The use of Danazol may be limited by its side effect profile, its acceptability to women and the need for continuing treatment.

Implications for research

Additional well designed RCTs with sufficient power are needed to test the efficacy of Danazol compared to other medical therapies. Future trial design needs to include outcomes such as quality of life measures and a longer period of treatment (at least six months) to adequately evaluate adverse events and participant satisfaction. However, there may be difficulties in doing long term research because of the side effects of Danazol and the existence of more acceptable alternatives.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bonduelle 1991

Methods	Method of randomisation not given. Single centre "pilot study" with no blinding. 30 women randomised. Number of withdrawals: n=14. 6 withdrawals post randomisation (2 did not meet selection criteria, 4 lost to follow up) , 8 withdrawals during the course of the study due to adverse events (4 from each group) No power calculation performed and not intention to treat. No source of funding given
Participants	Women with a clinical diagnosis of menorrhagia. Based on complaint of MBL requiring >5 pads/tampons per day for longer than 6 days of cycle, the presence of clots or flooding on any day of the cycle,

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Bonduelle 1991 (Continued)

presence of secondary anaemia, excessive MBL proving socially and domestically disruptive. Exclusion criteria: underlying pathology. No other exclusion criteria reported. Mean age of participants 36.1 years (danazol group) and 39.2 years (norethisterone group). Women were recruited from the menstrual disorders clinic at Glasgow Royal Infirmary, UK.

Interventions	Danazol 200 mg once daily. Norethisterone 5 mg three times daily from days 19-26 of cycle. Duration: 3 cycles
Outcomes	Bleeding intensity score. (Daily bleeding scores (from 1 to 7, where 1=spotting and 7=flooding) were combined to yield a bleeding intensity score for each menstrual period), number of days of bleeding, backache score, abdominal pain score (pain scores from 1 to 3, 1=mild, 3=severe), improvement in MBL (participant perception), side effects.
Notes	Large number of losses to follow up. 14 out of the 30 participants recruited withdrew. (6 excluded after randomisation and 4 from each treatment group withdrew during the course of the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Buyru 1995

Methods	Randomisation method not given. Single centre study. 40 women randomised. No withdrawals reported. Intention to treat analysis performed (by default as no withdrawals). No power calculation made. Source of funding not reported.
Participants	Women attending Istanbul Medical School obstetric and Gynaecology outpatient department with a complaint of menorrhagia and a diagnosis of DUB were recruited. Inclusion criteria: women aged between 25-50, with a complaint of menorrhagia, reporting the use of >3 pads/day. Exclusion criteria: organic pathology.
Interventions	Danazol 200 mg/day, norethisterone 5 mg twice daily on days 16-25 of cycle. Duration: 3 cycles.
Outcomes	Duration of menses (days), side effects.
Notes	Paper in Turkish. Translated by Metin Gulmezoglu of the Pregnancy and childbirth and infectious diseases group. menorrhagia subjectively defined.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Cameron 1987

Methods	Method of randomisation not stated. Single centre un blinded study with 23 women randomised. Number of withdrawals: n=7. No Intention to treat analysis or power calculation performed. Source of funding: Birthright research grant.
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Cameron 1987 (Continued)

Participants	Women aged 29-50 with a subjective complaint of heavy menses were recruited from Edinburgh Royal Infirmary, UK. Inclusion criteria: MBL of >50 ml/ month. Exclusion criteria: pelvic pathology.
Interventions	Danazol 200 mg od, mefenamic acid 500 mg tds for 1st 5 days of menses, norethisterone 5 mg bd from day 15-25 of cycle, progesterone impregnated coil releasing 65 ug progesterone daily. Duration: 2 months
Outcomes	MBL (measured by alkaline haematin method), duration of menses (days).
Notes	Groups not comparable at baseline- higher initial blood loss in danazol group. Mean substituted from median and SD estimated from range.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Chimbira 1980a

Methods	Method of randomisation not stated. Single blinded study. Number of participants randomised: n=32. No withdrawals reported. No power calculation made and not intention to treat. Source of funding: pharmaceutical company (Sterling Winthrop Laboratories, UK).
Participants	Women, mostly aged 30-49 years complaining of heavy menstrual blood loss, but with regular cycles were recruited from gynaecology outpatients' clinic. Inclusion criteria: MBL >60 ml/cycle (measured by alkaline haematin method). Exclusion criteria: pelvic pathology, hormone treatment, IUD
Interventions	Danazol 100 mg daily and danazol 200 mg daily. Duration: 12 weeks.
Outcomes	MBL (measured by alkaline haematin method), duration of menses, side effects, weight gain, quality of life (dysmenorrhoea)
Notes	Data for duration of bleeding for 100 mg danazol group not given and SD for weight gain not reported. Author contacted for this data, but data not supplied.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Dockeray 1989

Methods	Randomisation by prepared randomisation codes. A single centre study with no blinding. 40 women randomised. One withdrawal from mefenamic acid group reported. No power calculation or intention to treat analysis. Source of funding: Pharmaceutical company (Parke Davis research laboratories). Danazol supplied by Winthrop Laboratories (pharmaceutical company).
Participants	Women aged 23-48 with a history of excessive MBL were recruited from St James's hospital in Dublin, Ireland. Inclusion criteria: subjective complaint of excessive MBL, MBL of >80 ml/cycle (measured by alkaline haematin method), normal pelvic organs and no endometrial pathology. No exclusion criteria stated.

Danazol for heavy menstrual bleeding (Review)

Dockeray 1989 (Continued)

Interventions	Danazol 100 mg bd for 60 days. Mefenamic acid 500 mg tds for 3-5 days per cycle. Duration:2 cycles.	
Outcomes	MBL (measured by alkaline haematin method), Duration of menses, subjective assessment of dysmenorrhoea, side effects, patient acceptability of treatment.	
Notes	Large SD of mean for MBL for the 2 groups.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Dunphy 1998

Methods	Randomisation by a code, but no other details of this given. Double blinded single centre study. Number of women randomised: n=23. 5 withdrawals reported. 2 withdrawals prior to commencing medication, 3 subjects withdrew during treatment phase because of side effects (2 from danazol group and 1 from medroxyprogesterone acetate group.) No intention to treat analysis. Power calculation to performed. 34 participants needed for study to have sufficient power. Study funded by pharmaceutical company (Sanofi Winthrop, Canada).	
Participants	Women aged 31-54 years with a MBL of 80 ml per cycle were recruited from Foothills Hospital, Calgary, Canada. Inclusion criteria: Age 18 years or greater, MBL>80 ml/cycle, willing to use barrier methods of contraception. Exclusion criteria: contraindications to treatment and pregnancy.	
Interventions	Danazol 200 mg once daily. Medroxyprogesterone 10 mg from days 16-25 of cycle, and placebo for other days. Duration: 3 months treatment, 3 months follow up.	
Outcomes	MBL (assessed by pictorial bleeding chart method) after 3 months treatment, and after 3 months follow up, side effects, withdrawals from side effects and weight after 3 months treatment and after 3 months follow up.	
Notes	The mean pre-treatment weight of the danazol group was significantly greater than that of the medroxyprogesterone acetate group. The authors calculated that 34 participants were needed for the study to have sufficient power, however only 18 participants were included in the analysis.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fraser 1991

Methods	Method of randomisation not given. Single blinded (outcome assessors blinded) cross-over trial. 45 women randomised, 7 withdrawals (not for treatment related reasons). Not intention to treat, no power calculation. Source of funding: Parke Davis Company, Sydney (Pharmaceutical company).	
Participants	Inclusion criteria: Women with a convincing clinical history of menorrhagia and regular periods. No exclusion criteria: pelvic and systemic causes of menorrhagia.	

Fraser 1991 (Continued)

Interventions	Danazol 200 mg od, mefenamic acid 500 mg three to four times daily for a maximum of 5 days, naproxen first dose 500 mg, then 250 mg 3-4 times daily for a maximum of 5 days, low dose OCP (ethinyl oestradiol 30 ug and levonorgestrel 150 ug) once daily for 21 out of every 28 days. Duration: 8 cycles.
Outcomes	MBL (measured objectively using alkaline haematin method).
Notes	Only data from before the crossover can be used in the review, original data produced by author. Menorrhagia not objectively defined. 14 of the 38 women had MBL of <80 ml.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Higham 1993

Methods	Randomised by allocation in sequential order according to blood loss and ovulatory status and stratified across the treatment groups. Single centre, single blinded, parallel study (participants were not blind). 54 women randomised. 3 withdrawals prior to treatment and 7 withdrawals during treatment phase mainly due to adverse events (3 from each of the 2 danazol groups and 2 from the norethisterone group). Intention to treat analysis performed. No power calculation done. Study funded by pharmaceutical company (Sanofi Winthrop Limited).
Participants	Women aged 26-28 years with unexplained menorrhagia were recruited from the Royal Free Hospital in London, UK. Inclusion criteria: Aged 20-50 years, mean MBL of at least 80 ml/cycle, regular cycle of length 21-35 days, weight 45-110 kg, endometrial sampling within the previous 3 years, no sensitivity to either danazol or norethisterone or ingestion of either in the 10 weeks prior, gave informed written consent. Exclusion criteria: underlying pathologic conditions, concomitant treatment with hormones, anti prostaglandins or anticoagulants, pregnancy, attempting pregnancy or lactating, perimenopausal women, concomitant significant disease, treatment with drugs which may have affected MBL, suffering from Dubin Johnson or rotor syndromes, history of idiopathic jaundice, severe pruritis or herpes gestationis in pregnancy, women with an IUCD.
Interventions	Danazol 200 mg daily, reducing dose danazol (danazol 200 mg/day for 1 cycle, 100 mg/day for one cycle and 50 mg/day for 1 cycle), norethindrone 5 mg tds on days 19-26 of cycle. Duration: 3 cycles.
Outcomes	MBL (measured by alkaline haematin method), subjective efficacy, duration of menses, side effects, withdrawal from treatment.
Notes	Authors reported an intention to treat analysis however they excluded 3 participants who withdrew prior to treatment. Original data supplied by author. MBL reported as median figure, SD estimated from range. Ovulatory and anovulatory women were combined as participants in the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lamb 1987

Methods	Randomisation method not given. A single centre double blind study. 76 women randomised, 10 excluded from analysis after initial assessment as lost from follow up or wished to stop treatment, 5 with-
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Danazol for heavy menstrual bleeding (Review)

Lamb 1987 (Continued)

drawals during treatment period and 39 withdrawals during follow up. No power calculation made and not intention to treat. Source of funding pharmaceutical company (Winthrop Laboratories, UK).

Participants	Women over 25 years of age with a clinical diagnosis of menorrhagia. Diagnostic criteria not given. Exclusion criteria were age ,25 years, weight less than 45 kg or greater than 110 kg, cardiac, hepatic or renal impairment, known hypersensitivity to danazol, on other hormone treatment or anticoagulants.
Interventions	Danazol 200 mg once daily. Placebo once daily. Duration: 3 months
Outcomes	MBL (subjective score) , duration of menstruation, weight at 3 months, side effects, withdrawals.
Notes	Groups not comparable at baseline. Blood loss scores greater in the danazol group. Author contacted for details of MBL score, the number of participants experiencing side effects (given as number of complaints in paper), actual figures for the blood loss scores and the number of days of bleeding. Large number of withdrawals especially during follow up period, only 22 women of the 76 recruited completed the study. Winthrop Laboratories who supplied the danazol, also conducted the statistical analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

MBL = menstrual blood loss (total monthly blood loss), mg= milligrammes, LFTs = liver function tests, IUCD= intrauterine coil device, OCP= oral contraceptive pill, DUB= dysfunctional uterine bleeding

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Chimbira 1980b	8 women were recruited in a placebo controlled trial, each patient took placebo for 2 cycles, followed by danazol for 2 cycles. This is likely to cause bias since there is no controlling for the time effect.
Need 1992	11 women were recruited for this study. Patients took danazol 200 mg/day for 1 month, patients were then split into 4 groups and given either danazol 200 mg/day, danazol 100 mg/day, danazol 50 mg/day or placebo. There was concern that there was no a sufficient washout period between the 2 phases of the trial, which is likely to cause bias. Also the numbers randomised to each of the 4 arms of the 2nd phase of the trial were very small, and some of the results became meaningless.

DATA AND ANALYSES
Comparison 1. Danazol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals due to side effects up to 3rd month	1	66	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.18, 23.94]
2 Weight after 3 months treatment	1	57	Mean Difference (IV, Fixed, 95% CI)	6.70 [0.98, 12.42]

Danazol for heavy menstrual bleeding (Review)

Analysis 1.1. Comparison 1 Danazol versus placebo, Outcome 1 Withdrawals due to side effects up to 3rd month.

Analysis 1.2. Comparison 1 Danazol versus placebo, Outcome 2 Weight after 3 months treatment.

Comparison 2. Danazol versus progestagens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MBL after treatment (descriptive data)			Other data	No numeric data
1.1 Median MBL after treatment (measured using alkaline haematin method)			Other data	No numeric data
1.2 Mean MBL after treatment (measured using pictorial chart method)			Other data	No numeric data
2 Subjective efficacy of medication	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Subjective efficacy of medication rated as highly or moderately	1	37	Odds Ratio (M-H, Fixed, 95% CI)	4.33 [1.09, 17.17]
2.2 Subjective efficacy of intervention (MBL rated as none or moderate)	1	17	Odds Ratio (M-H, Fixed, 95% CI)	5.83 [0.70, 48.87]
3 Number of women reporting adverse events	4	117	Odds Ratio (M-H, Fixed, 95% CI)	4.05 [1.61, 10.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Weight gain	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 weight gain >2kg	1	37	Odds Ratio (M-H, Fixed, 95% CI)	2.86 [0.48, 17.11]
4.2 Weight gain >3kg	1	24	Odds Ratio (M-H, Fixed, 95% CI)	5.57 [0.48, 64.09]
5 Duration of menses (days)	4	107	Mean Difference (IV, Random, 95% CI)	-0.74 [-2.31, 0.82]
6 Mean MBL	1	37	Mean Difference (IV, Fixed, 95% CI)	-35.60 [-102.20, 31.00]
7 Mean weight gain	1	18	Mean Difference (IV, Fixed, 95% CI)	2.8 [1.60, 4.00]
8 Mean MBL (pictorial chart method) after 3 months follow up	1	18	Mean Difference (IV, Fixed, 95% CI)	203.0 [25.65, 380.35]
9 Withdrawal from treatment because of side effects	4	122	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [0.53, 5.23]
10 Bleeding score (subjective severity of menorrhagia)			Other data	No numeric data
11 Severity of dysmenorrhoea			Other data	No numeric data
11.1 Backache score			Other data	No numeric data
11.2 Abdominal pain score			Other data	No numeric data
12 Objective efficacy of intervention (last MBL on treatment <80ml)	1	37	Odds Ratio (M-H, Fixed, 95% CI)	7.2 [1.28, 40.37]

Analysis 2.1. Comparison 2 Danazol versus progestagens, Outcome 1 MBL after treatment (descriptive data).

Study	MBL after treatment (descriptive data)	
	Danazol	Progestogen
Median MBL after treatment (measured using alkaline haematin method)		
Cameron 1987	Median= 54ml. Range= 30-347ml p<0.05, Wilcoxon rank sum test, comparing MBL at baseline and after treatment	Norethisterone: Median=106ml. Range= 24-216ml. Not significantly different from baseline.
Mean MBL after treatment (measured using pictorial chart method)		
Dunphy 1998	Mean MBL=72ml; SD=108. p=0.0128, Wilcoxon sign rank test comparing mean MBL on danazol at the end of the 3rd month of treatment with mean MBL on MPA at the end of the 3rd month of treatment.	Medroxyprogesterone acetate: MBL=568ml; SD=710

Analysis 2.2. Comparison 2 Danazol versus progestagens, Outcome 2 Subjective efficacy of medication.

Analysis 2.3. Comparison 2 Danazol versus progestagens, Outcome 3 Number of women reporting adverse events.

Analysis 2.4. Comparison 2 Danazol versus progestagens, Outcome 4 Weight gain.

Analysis 2.5. Comparison 2 Danazol versus progestagens, Outcome 5 Duration of menses (days).

Analysis 2.6. Comparison 2 Danazol versus progestagens, Outcome 6 Mean MBL.

Analysis 2.7. Comparison 2 Danazol versus progestagens, Outcome 7 Mean weight gain.

Analysis 2.8. Comparison 2 Danazol versus progestagens, Outcome 8 Mean MBL (pictorial chart method) after 3 months follow up.

Analysis 2.9. Comparison 2 Danazol versus progestagens, Outcome 9 Withdrawal from treatment because of side effects.

Analysis 2.10. Comparison 2 Danazol versus progestagens, Outcome 10 Bleeding score (subjective severity of menorrhagia).

Study	Bleeding score (subjective severity of menorrhagia)	
	Danazol	Norethisterone
Bonduelle 1991	Mean bleeding score after treatment=15.0; SD=9.4. N=6	Mean bleeding score after treatment= 23.6; SD= 9.6. N=10
	p<0.05, Wilcoxon 2 sample test (vs norethisterone) p<0.02, Wilcoxon matched pairs test (vs baseline)	

Analysis 2.11. Comparison 2 Danazol versus progestagens, Outcome 11 Severity of dysmenorrhoea.

Study	Severity of dysmenorrhoea	
	Danazol	Norethisterone
Backache score		
Bonduelle 1991	Mean score after treatment= 6.5; SD= 7.1. N=6	Mean score after treatment= 5.0; SD= 7.0. N=10
	p<0.05, Wilcoxon matched pairs test (vs baseline)	
Abdominal pain score		
Bonduelle 1991	Mean score after treatment= 3.0; SD=4.0. N= 6	Mean score after treatment= 4.2; SD=6.7. N=10

Analysis 2.12. Comparison 2 Danazol versus progestagens, Outcome 12 Objective efficacy of intervention (last MBL on treatment <80ml).

Comparison 3. Danazol 200mg versus reducing dose danazol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean MBL	1	36	Mean Difference (IV, Fixed, 95% CI)	33.50 [-32.38, 99.38]
2 Subjective efficacy of medication rated as moderate to highly	1	36	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.30, 4.73]
3 Number of women reporting adverse events	1	36	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.14, 9.07]
4 Withdrawal from treatment due to adverse events	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.15, 5.05]
5 Weight gain >2kg	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.08, 1.28]
6 Duration of menses (days)	1	36	Mean Difference (IV, Fixed, 95% CI)	1.30 [-0.76, 3.36]
7 Objective efficacy of intervention (last MBL on treatment <80ml)	1	36	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.27, 3.76]

Analysis 3.1. Comparison 3 Danazol 200mg versus reducing dose danazol, Outcome 1 Mean MBL.

Analysis 3.2. Comparison 3 Danazol 200mg versus reducing dose danazol, Outcome 2 Subjective efficacy of medication rated as moderate to highly.

Analysis 3.3. Comparison 3 Danazol 200mg versus reducing dose danazol, Outcome 3 Number of women reporting adverse events.

Analysis 3.4. Comparison 3 Danazol 200mg versus reducing dose danazol, Outcome 4 Withdrawal from treatment due to adverse events.

Analysis 3.5. Comparison 3 Danazol 200mg versus reducing dose danazol, Outcome 5 Weight gain >2kg.

Analysis 3.6. Comparison 3 Danazol 200mg versus reducing dose danazol, Outcome 6 Duration of menses (days).

Analysis 3.7. Comparison 3 Danazol 200mg versus reducing dose danazol, Outcome 7 Objective efficacy of intervention (last MBL on treatment <80ml).

Comparison 4. Danazol versus NSAID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MBL (descriptive data)			Other data	No numeric data
1.1 Danazol versus mefenamic acid			Other data	No numeric data
1.2 Danazol versus naproxen			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Duration of menses (days)	2	53	Mean Difference (IV, Fixed, 95% CI)	-1.03 [-1.78, -0.28]
3 Improvement in dysmenorrhoea	1	28	Odds Ratio (M-H, Fixed, 95% CI)	1.2 [0.20, 7.31]
4 Side effects	1	40	Odds Ratio (M-H, Fixed, 95% CI)	7.0 [1.74, 28.17]
5 Acceptability of treatment (number unwilling to continue treatment)	1	39	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.32, 3.90]
6 Mean MBL	1	39	Mean Difference (IV, Fixed, 95% CI)	-96.70 [-138.80, -54.60]
6.1 Danazol versus mefenamic acid	1	39	Mean Difference (IV, Fixed, 95% CI)	-96.70 [-138.80, -54.60]
7 Severity of dysmenorrhoea			Other data	No numeric data

Analysis 4.1. Comparison 4 Danazol versus NSAID, Outcome 1 MBL (descriptive data).

Study	MBL (descriptive data)	
	Danazol	NSAID
Danazol versus mefenamic acid		
Cameron 1987	Median MBL=54ml. Range= 30-347 n=6 P<0.05 Wilcoxon rank sum test comparing MBL at baseline and after treatment values.	Median MBL= 51. Range= 45-203 n=8
Fraser 1991	Mean MBL=19.6ml; SD= 35.6 WMD -73.2, 95%CI -118.20, -28.20. p=0.001 compared to mefenamic acid.	Mean MBL= 92.8ml; SD= 79.5
Danazol versus naproxen		
Fraser 1991	Mean MBL= 19.6ml; SD=35.6 WMD -42.7, 95%CI -78.84, -6.56. p=0.02 compared to naproxen.	Mean MBL= 62.3 ml; SD= 28.7

Analysis 4.2. Comparison 4 Danazol versus NSAID, Outcome 2 Duration of menses (days).

Study or subgroup	Danazol		NSAID		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Cameron 1987	6	4 (1)	8	5 (0.7)		69.41%	-1[-1.91,-0.09]
Dockeray 1989	20	4.8 (2.9)	19	5.9 (1.1)		30.59%	-1.1[-2.46,0.26]
Total ***	26		27			100%	-1.03[-1.78,-0.28]
Heterogeneity: Tau ² =0; Chi ² =0.01, df=1(P=0.9); I ² =0%							
Test for overall effect: Z=2.68(P=0.01)							
					Favours danazol	-10 -5 0 5 10	Favours NSAID

Analysis 4.3. Comparison 4 Danazol versus NSAID, Outcome 3 Improvement in dysmenorrhoea.

Analysis 4.4. Comparison 4 Danazol versus NSAID, Outcome 4 Side effects.

Analysis 4.5. Comparison 4 Danazol versus NSAID, Outcome 5 Acceptability of treatment (number unwilling to continue treatment).

Analysis 4.6. Comparison 4 Danazol versus NSAID, Outcome 6 Mean MBL.

Study or subgroup	Danazol		NSAID		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Total ***	20		19			100%	-96.7[-138.8,-54.6]
Heterogeneity: Not applicable							
Test for overall effect: Z=4.5(P<0.0001)							
<div style="display: flex; justify-content: space-between; align-items: center;"> Favours danazol -1000 -500 0 500 1000 Favours NSAID </div>							

Analysis 4.7. Comparison 4 Danazol versus NSAID, Outcome 7 Severity of dysmenorrhoea.

Study	Severity of dysmenorrhoea	
	Danazol	Mefenamic acid
Dockeray 1989	Mean score after treatment= 1.1; SD= 0.9	Mean score after treatment= 0.7; SD=1.1
No statistically significant difference between the two therapies (p>0.05)		

Comparison 5. Danazol versus oral contraceptive pill

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean MBL (descriptive data)			Other data	No numeric data

Analysis 5.1. Comparison 5 Danazol versus oral contraceptive pill, Outcome 1 Mean MBL (descriptive data).

Study	Mean MBL (descriptive data)	
	Danazol	Oral contraceptive
Fraser 1991	Mean MBL after treatment= 19.6ml; SD= 35.6	Mean MBL after treatment=72.2ml; SD= 41.1
WMD -52.6 95% CI -96.11, -9.09. p=0.02		

Comparison 6. Danazol versus progesterone releasing IUCD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Median MBL (ml)			Other data	No numeric data
2 Duration of menses (days)	1	14	Mean Difference (IV, Fixed, 95% CI)	-6.0 [-7.25, -4.75]

Analysis 6.1. Comparison 6 Danazol versus progesterone releasing IUCD, Outcome 1 Median MBL (ml).

Study	Median MBL (ml)	
	Danazol 200mg	IUCD
Cameron 1987	Median MBL at 2 months= 54ml; Range 30-347ml; n=6. p<0.05 Wilcoxon rank sum test, comparing MBL at baseline with MBL after treatment.	Median MBL at 2 months= 55ml; Range=31-75 ml; n=8 p<0.01 Wilcoxon rank sum test, comparing before and after treatment values.

Analysis 6.2. Comparison 6 Danazol versus progesterone releasing IUCD, Outcome 2 Duration of menses (days).

Comparison 7. Danazol 200mg versus danazol 100mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean MBL			Other data	No numeric data
2 Improvement in dysmenorrhoea	1	28	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.12, 3.83]
3 Weight gain			Other data	No numeric data
4 Duration of menses (descriptive data)			Other data	No numeric data

Analysis 7.1. Comparison 7 Danazol 200mg versus danazol 100mg, Outcome 1 Mean MBL.

Study	Mean MBL danazol 200mg	danazol 100mg
Chimbira 1980a	Mean MBL after treatment= 26 ml; SD=31 WMD -19.00, 95% CI -48.38, 10.38; p=0.2 comparing with danazol 100mg. P<0.01 Wilcoxon sign rank test comparing MBL at baseline with MBL after 3 months treatment.	Mean MBL after treatment=45ml; SD= 45. P<0.01 Wilcoxon sign rank test comparing MBL at baseline and MBL after 3 months treatment

Analysis 7.2. Comparison 7 Danazol 200mg versus danazol 100mg, Outcome 2 Improvement in dysmenorrhoea.

Analysis 7.3. Comparison 7 Danazol 200mg versus danazol 100mg, Outcome 3 Weight gain.

Study	Weight gain	
	Danazol 200mg	Danazol 100mg
Chimbira 1980a	Mean weight gain= 2.3 kg; SD not reported	Mean weight gain= 2.1 kg; SD not reported

Analysis 7.4. Comparison 7 Danazol 200mg versus danazol 100mg, Outcome 4 Duration of menses (descriptive data).

Study	Duration of menses (descriptive data)	
	Danazol 200mg	Danazol 100mg
Chimbira 1980a	Mean= 4.1 days. SD= 2.1. P<0.01 Wilcoxon sign rank test, comparing duration of menses at baseline with duration of menses after treatment.	Figures not given. Authors reported no significant effect on the duration of bleeding compared with baseline. (Wilcoxon rank sign test p>0.05)

ADDITIONAL TABLES

Table 1. Risk of bias

Study Name	Allocation concealed	Randomisation sequen	Dropouts	Intention to treat	Blinding
Bonduelle 1991	None	Not stated	Large numbers of losses to follow up with 14 of 30 withdrawing - equally distributed between the groups	No	None
Buyru 1995	Not stated	Not stated	No withdrawals reported	Yes	None
Cameron 1987	None	Not stated	7 withdrawals of 23 women	No	None
Chimbira 1980a	Not stated	Not stated	None	No	Single
Dockeray 1989	Not stated	Not stated	One withdrawal	No	None
Dunphy 1998	Not stated	Not stated	5 withdrawals of 23 women	No	Double
Fraser 1991	Not stated	Not stated	7 withdrawals of 45 women	No	Single (9 outcome assessors blind)
Higham 1993	Not stated	Not stated	10 withdrawals of 54 women	No	Single (participants were not blind)
Lamb 1987	Not stated	Not stated	15 withdrawals of losses from followup of 76 women	No	Double

APPENDICES

Appendix 1. Search strategy

MEDLINE(R) 1950 to April Week 3 2007

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1 menorrhagia/
2 menorrhag$.tw.
3 (menstrua$ adj5 (bleed$ or blood)).tw.
4 (heavy adj5 menstrua$).tw.
5 (dysfunctional adj5 uter$).tw.
6 hypermenorrh$.tw.
7 or/1-6
8 Danazol/ or Danazol.tw.
9 (azol or cyclomen or danatrol or danazant or danocrine or danol or danoval).tw.
10 or/8-9
11 7 and 10
12 randomized controlled trial.pt.
13 controlled clinical trial.pt.
14 Randomized Controlled Trials/
15 Random allocation/
16 Double-blind method/
17 Single-blind method/
18 or/12-17
19 clinical trial.pt.
20 exp clinical trials/
21 (clin$ adj25 trial$).ti,ab,sh.
22 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh.
23 Placebos/
24 placebo$.ti,ab,sh.
25 random$.ti,ab,sh.
26 Research design/
27 or/19-26
28 animal/ not (human/ and animal/)
29 18 or 27
30 29 not 28
31 11 and 30
32 (2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$).ed.
33 31 and 32
34 from 33 keep 1-9

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EBM Reviews - Cochrane Central Register of Controlled Trials 2nd Quarter 2007

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1 menorrhagia/
2 menorrhag$.tw.
3 (menstrua$ adj5 (bleed$ or blood)).tw.
4 (heavy adj5 menstrua$).tw.
5 (dysfunctional adj5 uter$).tw.
6 hypermenorrh$.tw.
7 or/1-6
8 Danazol/ or Danazol.tw.
9 (azol or cyclomen or danatrol or danazant or danocrine or danol or danoval).tw.
10 or/8-9
11 7 and 10
12 from 11 keep 1-30

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CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to April Week 4 2007

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1 menorrhagia/
2 menorrhag$.tw.
3 (menstrua$ adj5 (bleed$ or blood)).tw.
4 (heavy adj5 menstrua$).tw.
5 (dysfunctional adj5 uter$).tw.
6 hypermenorrh$.tw.

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7 or/1-6
 8 Danazol/ or Danazol.tw.
 9 (azol or cyclomen or danatrol or danazant or danocrine or danol or danoval).tw.
 10 or/8-9
 11 7 and 10
 12 exp clinical trials/
 13 Clinical trial.pt.
 14 (clinic\$ adj trial\$1).tw.
 15 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
 16 Randomi?ed control\$ trial\$.tw.
 17 Random assignment/
 18 Random\$ allocat\$.tw.
 19 Placebo\$.tw.
 20 Placebos/
 21 Quantitative studies/
 22 Allocat\$ random\$.tw.
 23 or/12-22
 24 11 and 23
 25 from 24 keep 1-6

EMBASE 1980 to 2007 Week 17

1 menorrhagia/
 2 menorrhag\$.tw.
 3 (menstrua\$ adj5 (bleed\$ or blood)).tw.
 4 (heavy adj5 menstrua\$).tw.
 5 (dysfunctional adj5 uter\$).tw.
 6 hypermenorrh\$.tw.
 7 or/1-6
 8 Danazol/ or Danazol.tw.
 9 (azol or cyclomen or danatrol or danazant or danocrine or danol or danoval).tw.
 10 or/8-9
 11 7 and 10
 12 Controlled study/ or randomized controlled trial/
 13 double blind procedure/
 14 single blind procedure/
 15 crossover procedure/
 16 drug comparison/
 17 placebo/
 18 random\$.ti,ab,hw,tn,mf.
 19 latin square.ti,ab,hw,tn,mf.
 20 crossover.ti,ab,hw,tn,mf.
 21 cross-over.ti,ab,hw,tn,mf.
 22 placebo\$.ti,ab,hw,tn,mf.
 23 ((doubl\$ or singl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).ti,ab,hw,tn,mf.
 24 (comparative adj5 trial\$).ti,ab,hw,tn,mf.
 25 (clinical adj5 trial\$).ti,ab,hw,tn,mf.
 26 or/12-25)
 27 nonhuman/
 28 animal/ not (human/ and animal/)
 29 or/27-28
 30 26 not 29
 31 11 and 30
 32 (2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$).em.
 33 31 and 32
 34 from 33 keep 1-35

WHAT'S NEW

Date	Event	Description
11 November 2008	Review declared as stable	The findings of this review are regarded as stable
7 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 2, 2002

Date	Event	Description
15 May 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Heather Beaumont: took the lead in writing the review, performed searches of databases for trials, involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials, was responsible for statistical analysis and interpretation of the data.

Cristina Augood: took the lead in writing the protocol, performed initial searches of databases for trials, involved in selecting trials for inclusion.

Kirsten Duckitt: wrote the background, performed initial searches of databases for trials, involved in selecting trials for inclusion, commented on drafts of the protocol and review.

Anne Lethaby: performed searches of databases for trials, involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials, commented on drafts of the protocol and review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, University of Auckland, New Zealand.
- Royal College of Obstetricians and Gynaecologists, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Danazol [*therapeutic use]; Estrogen Antagonists [*therapeutic use]; Menorrhagia [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans