Norethisterone for hormone replacement therapy and dysfunctional uterine bleeding

Name of the organization preparing the application

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The aim of this review is to evaluate the efficacy of norethisterone usage in peroral dose of 5 mg for hormonal replacement therapy and dysfunctional uterine bleeding by searching all published papers and reports.

Norethisterone is currently listed on the WHO Model List of Essential Medicines as a medicine used for contraception, dysfunctional uterine bleeding and hormonal replacement therapy.

**Introduction**

Norethisterone (norethindrone) is a synthetic gestagen developed from testosterone. In the late 1930s it was discovered that the etinile substance on the testosterone molecule leads towards the development of orally active ethisterone preparation. Norethisterone, that kept the oral potentiality of its previous forms, was created by moving the 19-C atome from etistherone in 1951, but it almost completely changed the hormone's characteristics; a gestagenic preparation was made out of an androgenic substance. Since then, all gestagenic preparations developed from testosterone have been called derivates of 19-norethisterone, 19-nor denoting the lack of 19-C atome. Norethisterone and its derivates (norethinodrel, norethisterone acetate, ethinodiol diacetate and linestrol) have the same metabolic effect, considering the fact that after metabolization in gastrointestinal tract and liver, all derivates transform into the outcoming substance norethisterone. Besides its connection with progesterone receptors, norethisterone has the affinity of linking to both, estrogenic and androgenic receptors.

**Indications for use**

1) Treatment of menstrual disorders, including secondary amenorrhea and dysfunctional uterine bleeding (DUB) caused by hormonal imbalance in the absence of organic pathology.
2) Premenstrual tension
3) Dysmenorrhea
4) Treatment of endometriosis
5) Hormone replacement therapy (HRT)
   - continuous combined regimens,
   - sequential combined regimens.
   
   Progestins are used to oppose the effects of estrogen on the endometrium in menopausal women who take estrogens for HRT.
6) Contraception (alone or in combination with estrogens).


**Contraindications and Precautions**

1) Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a history of these conditions,
2) Undiagnosed vaginal bleeding,
3) Known sensitivity to the drug or any ingredients in the formulation,
4) Markedly impaired liver function or liver disease,
5) Carcinoma of breast- Norethisterone should not be used in patients with benign or malignant changes in tissues which respond to sex hormones.
6) Conditions that might be aggravated by fluid retention (asthma, seizure disorders, migraine, cardiac or renal dysfunction),
7) Mental depression or a history of these condition.


Adverse effects

1) menstrual irregularity, changes in menstrual flow, amenorrhea, breakthrough bleeding, spotting. (Irregular bleeding or spotting is common in the first year of continuous E+P HRT but following the first year of treatment, bleeding and spotting become more common in sequential E+P regimens. A large proportion of women taking continuous E+P HRT become amenorrheic after a year of therapy whilst withdrawal bleeding continues for women taking sequential regimens.)
2) fluid retention, edema, weight gain,
3) nausea,
4) breast tenderness,
5) headache,
6) mental depression.


Formulation and dosage regimens

Tablet: 5 mg

Oily solution: 200 mg/ml in 1 ml ampoule

At low dose (≤1 mg a day) it can be use in combination with oestrogens either as a contraceptive or in hormone replacement therapy. At higher dose (≥5 mg daily) it can be used for treatment of menorrhagia. Norethisterone is not available in a oral formulation greater than 5 mg. [1]

Summary of available efficacy data

Identification of clinical evidence

Medline (1950 to September Week1 2010), Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (3rd Quarter 2010) were searched to identify all published papers and reports evaluating the effectiveness of norethisterone in dose of 5 mg in hormone replacement therapy (HRT), and its effectiveness for treatment of dysfunctional uterine bleeding (DUB) (Figures 1-4).

Search Strategy for norethisterone and HRT

--------------------------------------------------------------------------------------------------------------------------
1  exp Hormone Replacement Therapy/
2  hormone replacement.mp.
3  estrogen replacement.mp.
Search Strategy for norethisterone and DUB

1  Norethindrone/
2  norethisterone.mp.
3  1 or 2
4  exp Uterine Hemorrhage/
5  (uter$ adj5 h?$emorrhage$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
6  (uter$ adj5 bleed$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
7  (irregular adj5 (period$ or menstrua$ or bleed$ or blood loss$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
The studies in languages other than English were excluded. Titles and abstracts of retrieved papers were reviewed. Studies were included for review if they were systematic reviews (SRs), randomized controlled trials (RCTs) or controlled clinical trials (CCTs). The citation lists of included studies were searched to identify any additional studies. Studies in which norethisterone was used as a part of combination of medicines for HRT were included for review, because norethisterone is indicated for use in combination with other medicines for the management of menopausal symptoms.

From the literature obtained, data relevant for evaluation of norethisterone effectiveness was extracted and tabulated (Tables 1-4).
Figure 1. Flow diagram for identification of systematic reviews evaluating the effectiveness of norethisterone (NET) for the management of hormone replacement therapy (HRT)

- **Identification**
  - Records identified through Medline (n = 17)
  - Additional records identified through CDSR (n = 15)

- **Screening**
  - Records after duplicates removed (n = 15)

- **Eligibility**
  - Records screened (n = 15)
  - Full-text articles assessed for eligibility (n = 4)
    - Records excluded (n = 11)
      - The titles and abstracts of these SR did not indicate that they are evaluating the effectiveness of NET for the management of HRT
    - Full-text articles excluded (n = 3)
      - The dose of NET in these SRs was different from our assignment (5 mg)

- **Included**
  - Studies included in tabular presentation of systematic reviews (n = 1)
Records identified through Medline (n = 463)

Records identified through CCRCT (n = 399)

Records after duplicates removed (n = 460)

Records screened (n = 460)

Records excluded (n = 454)
Other doses are reviewed in these articles

Full-text articles assessed for eligibility (n = 6)

Full-text articles excluded (n = 3)
In these trials there were no assessment of effectiveness of NET

Studies included in tabular presentation of clinical trials (n = 3)

Figure 2. Flow diagram for identification of clinical trials evaluating the effectiveness of norethisterone (NET) for the management of hormone replacement therapy (HRT)
Figure 3. Flow diagram for identification of systematic reviews evaluating the effectiveness of norethisterone (NET) for the management of dysfunctional uterine bleeding (DUB)

Records identified through Medline (n = 10)

Records identified through CDSR (n = 20)

Records after duplicates removed (n = 20)

Records screened (n = 20)

Records excluded (n = 11)
The titles and abstracts of these SRs did not indicate that they are evaluating the effectiveness of NET for the management of DUB

Full-text articles assessed for eligibility (n = 11)

Full-text articles excluded (n = 3)
Other treatment and indications are reviewed in these articles

Studies included in tabular presentation of systematic reviews (n = 8)
Figure 4. Flow diagram for identification of clinical trials evaluating the effectiveness of norethisterone (NET) for the management of dysfunctional uterine bleeding (DUB)

Records identified through Medline
(n = 190)

Records identified through CCRCT
(n = 103)

Records after duplicates removed
(n = 152)

Records screened
(n = 152)

Full-text articles assessed for eligibility
(n = 16)

Studies included in tabular presentation of clinical trials
(n = 10)

Records excluded
(n = 136)
Other indications are reviewed in these articles

Full-text articles excluded
(n = 6)
Other doses are reviewed in these articles
Summary of comparative effectiveness in different clinical settings

Use norethisteron as progestogen in hormone replacement therapy (HRT)

Menopause means the cessation of menstruation and typically occurs in women aged between 45 and 55 years with a mean age of about 51 years. Women are said to be postmenopausal when menstruation has ceased for 6 to 12 months and blood serum levels of follicle stimulating hormone (FSH) increase to at least 49 IU/L. The decline in circulating estrogen around the time of the menopause can induce symptoms that affect the well being and health of women, hot flushes, insomnia, declining bone mass, night sweats, mood disturbances and vaginal dryness have all been reported. As life expectancy and the proportion of older adults in the population increases, there has been an increased focus on the effects of ageing. Estrogen therapy has been utilised for the treatment of many of the menopausal symptoms, particularly hot flushes and vaginal dryness. HRT may consist of either unopposed estrogen or a combination of estrogen and progesteron. There is a number of different progestogens used in HRT, which can be classified according to their structure and/or bioactivity. The primary reason for adding a progestogen to HRT is to protect the endometrium against hyperplasia. Endometrial hyperplasia is regarded as a precursor of endometrial cancer but progression is dependent on the type of hyperplasia. The risk of hyperplasia and/or carcinoma appears to increase with higher doses and increased duration of unopposed estrogen treatment. Adding a progesteron to estrogen therapy significantly reduces the risk of hyperplasia [2], but can result in premenstrual symptoms which are problematic for some women. These symptoms and increased bleeding and spotting are often given as a reason not to continue HRT. An additional concern is that the addition of progesteron to estrogen also appears to increase the risk of cardiovascular disease and breast cancer.

As mentioned before, progestins are used in hormone replacement therapy to counteract estrogen-induced proliferation of the endometrium [2]. Aside from their local action, progestins act at different body sites including the central nervous system (CSN). In the CNS progestins may influence different functions among which the regulation of body temperature and mood. While the effect on body temperature may have metabolic implications, the effect on mood, particularly if negative, can be invalidating and induce non-acceptance or withdrawal from hormone replacement therapy [3,4,5].

In combined HT, progestogen can be taken either continuously (every day) or sequentially (a few days for each month or less frequently). It appears that continuous therapy may be more protective than sequential therapy in the long term prevention of endometrial hyperplasia [2].

HRT is an effective treatment for women with menopausal symptoms of hot flushes, night sweats and vaginal dryness and the duration of therapy should be decided for individual women based on an assessment of both benefits, in terms of menopausal symptom management and harms of therapy, such as venous thromboembolism. The duration of treatment with HRT should be reviewed by a woman with her doctor, because for most women hot flushes resolve within a year of onset of the menopause. About one third of women will continue to have vasomotor symptoms for up to 5 years and some women for even longer [2].
Table 1. Systematic reviews and meta-analysis evaluating the effectiveness of 5 mg norethisterone in hormone replacement therapy (HRT)

<table>
<thead>
<tr>
<th>No.</th>
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<th>Conclusions; Comment</th>
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<tbody>
<tr>
<td>01.</td>
<td>Zweifel (1997) [3]</td>
<td>Psychological Abstracts (from 1974 to 1995) and MEDLINE (from 1966 to 1995) were searched. 26 RCTs were included. There is just 2 RCTs (Magos, 1986[5]; Montgomery, 1987[6]) which used norethisterone, 5 mg 7 days/mo in combination with implant of estrogen 50 mg/day.</td>
<td>Assessment the effectiveness of HRT on menopausal depressed mood. The most commonly used measures were the Beck Depression Inventory (BDI), the Hamilton Rating Scale for Depression, and the Multiple Affect Adjective Checklist. HRT appeared to be effective in reducing depressed mood among menopausal women. The overall effect size (ES) for HRT was 0.68. This indicated that the average treatment patient had lower levels of depressed mood than 76% of the control patients. 1)estrogen significantly reduced depressed mood (ES=0.69); 2) progesteron (norethisterone) alone, and in combination with estrogen, was associated with smaller reductions in depressed mood (ES=0.39, ES=0.45, respectively); 3)androgen alone and in combination with estrogen was associated with greater reductions in depressed mood (ES=1.37; ES=0.90, respectively).</td>
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Table 2. Clinical trials evaluating the effectiveness of 5 mg norethisterone in hormone replacement therapy (HRT)

<table>
<thead>
<tr>
<th>No.</th>
<th>Article; Study Type; Study Design</th>
<th>Findings; Conclusion</th>
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<tr>
<td>1.</td>
<td>Cagnacci (2004) [4] RCT</td>
<td>Investigation the effects on body temperature, anxiety and depression of four different progestins all associated with the same estrogenic compound. All progestins except DYD increased (P &lt; 0.0001) BBT by 0.3–0.5 °C. Anxiety was decreased by DYD (−2.3 ± 1.1; P &lt; 0.01) and MPA (−1.5 ± 0.5; P &lt; 0.01), but not by NMG or NETA. Depression did not significantly increase during progestins and actually decreased during MPA (−3.0 ± 0.7; P &lt; 0.01). Only the effect of DYD on anxiety and that of MPA on depression were significant versus the control group (P &lt; 0.05).</td>
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<td>2.</td>
<td>Magos (1986) [5] RCT</td>
<td>Assessment the influence of NET on mood and behaviour. There were widespread adverse effects which were dose-related. Significant changes in five symptoms (pain-baseline vs NET p&lt;0.02, concentration –B vs NET p&lt;0.0001, behavioural change-B vs NET p&lt;0.02, water retention-B vs NET p&lt;0.0001 and negative affect-B vs NET p&lt;0.001) were found with 5 mg/day of the NET. The dose of NET should be the minimum to achieve the desired therapeutic effect.</td>
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<td>3.</td>
<td>Volpe (1986) [7] RCT</td>
<td>All the estrogen tested showed similar efficacy in the management of climacteric symptoms. As regards the available progesteron compounds, it would seem that CPA is safer than NET, since it does not antagonise the beneficial effects of estrogen on HDL levels. When NET was combined with either EV or CE there was a decrease in HDL cholesterol (p&lt;0.05 and 0.01 respectively) and a simultaneous increase triglycerides (p&lt;0.05), while NET+CE decreased serum cholesterol (p&lt;0.05).</td>
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Only three studies out of the 460 reviewed regarding the effectiveness of norethisterone in HRT met the inclusion criteria (Table 2). The 5 mg dose of norethisterone in HRT is rarely mentioned. After searching the references we concluded the following: hormone replacement therapy may be used to manage the menopausal symptoms, but it is currently recommended to be given at the lowest
effective dose and regularly reviewed by women and their doctor. In case of women with an intact uterus using HRT comprising estrogen and progestogen it is desirable to minimise the risk of endometrial hyperplasia which can develop into endometrial cancer.[2] The use of low dose estrogen plus progestogen (1 mg norethisterone acetate or 1.5 mg medroxyprogesteron acetate) taken daily (continuously) appears safe for the endometrium. For women within one year of menopause low dose estrogen combined sequentially with 10 days of progestogen (1 mg norethisterone acetate) per month appears safe for the endometrium [2].

Low dose HRT has less sideeffects, and women mostly continue with HRT. Only 2% of the patients give up from HRT after the first year usage.[2] The low-dose HRT has the same effect on vasomotor symptoms, urogenital atrophy, cardiovascular diseases, osteoporosis and CNS, as well as conventional treatment. NET has an individual effect on the bone, and therefore emphasizes preventive estrogen influence. That data is of great importance when considering low-dose HRT usage for women with osteoporosis [4].

The progesterone recommended for menopausal women receiving long-term estrogen replacement therapy is often associated with side-effects which limit the acceptability of combined treatment[5].

Peroral dose of 5 mg norethisterone in HRT causes the side-effects that prevail over the advantages of HRT in postmenopausal women. Therefore, it is recommended that norethisterone in 5 mg dose for HRT should not be used anymore.

**Norethisterone in the treatment of dysfunctional uterine bleeding (DUB)**

The diagnosis of DUB is made by the exclusion of organic disease as a cause of the abnormal menses; the condition accounts for about 80% of cases of menorrhagia. Of these, over 80% will have no abnormality of the hypothalamo-pituitary-ovarian axis, and it is likely that the disorder is the result of local endometrial factors. There appears to be not only a preponderance of vasodilatory prostaglandins in the endometrium of women with menorrhagia, but also an excessive increase in fibrinolytic activity within the uterine cavity. Once a diagnosis has been reached with the aid of history, examination, haematological and endocrine investigations, and dilatation and curettage when appropriate, medical treatment is the usual first line approach. Non-steroidal anti-inflammatory drugs such as mefenamic acid, or antifibrinolytic agents such as tranexamic or epsilon aminocaproic acids, will reduce blood loss by between 25 and 50% [8]. Nonsteroidal anti-inflammatory drugs reduce prostaglandin levels which are elevated in women with excessive menstrual bleeding and also may have a beneficial effect on dysmenorrhea. Medications which suppress ovarian function, such as danazol or gonadotrophin releasing hormone analogues, are highly effective in lessening, or inhibiting, menstrual loss, but at the expense of side-effects and convenience respectively. The combined contraceptive pill may reduce blood loss by 50% but is not appropriate for older women. Cyclical gestagens such as norethisterone have been widely employed, particularly for the treatment of anovulatory cycles, but their place in the management of ovulatory DUB is less clear[8].

The histological assessment of endometrial morphology constitutes a vital adjunct to hormonal therapy in cases of dysfunctional bleeding. In a considerable number of patients there is a need for progesterone treatment because of frequent anovulatory cycles. Prolonged stimulation by either endogenous or exogenous estrogens results in endometrial hyperplasia in some premenopausal and
postmenopausal women. It is still not known why only some women exhibit this abnormal response. The possible factors involved include disordered estrogen metabolism, reduced plasma levels of sex-hormone-binding globulin (SHBG) and increased sensitivity of the endometrium to estrogen stimulation [9].

The intrauterine coil device was originally developed as a contraceptive but the addition of uterine relaxing hormones, progestogens, to these devices resulted in a large reduction in menstrual blood loss. If medical treatment fails hysterectomy should be considered, though less invasive surgical methods of endometrial ablation are being developed. Finally, it should be remembered that in the absence of associated signs or symptoms of iron-deficiency anaemia, heavy menstrual bleeding is a subjective complaint and up to 50% of women describing menorrhagia will have a measured monthly blood loss within normal limits [8].
Table 3. Systematic reviews evaluating the effectiveness of 5 mg norethisterone for the management of dysfunctional uterine bleeding (DUB)

<table>
<thead>
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<tbody>
<tr>
<td>1.</td>
<td><strong>Coulter (1995) [10]</strong></td>
<td>Women with menorrhagia. Comparison effects of aminocaproic acid (3 g), danazol (200 mg), diclofenac (50 mg), ethamsylate (500 mg), flurbiprofen (100 mg), ibuprofen (600, 1200 and 1600 mg), meclofenamate sodium (100 mg), mefenamic acid (500 mg), naproxen (5, 250, 500, 750 and 1250 mg), <strong>norethisterone (5 mg)</strong>, oral contraceptive (low dose), tranexamic acid (1, 12 and 24 g), intrauterine devices (IUDs) and hormone-releasing IUDs. Outcomes were reduction in menstrual blood loss (MBL).</td>
<td>The interventions produced the following percentage reductions in menstrual blood loss: Hormone-releasing coil 58.6 (95% CI: 56.7, 60.6); danazol 49.7 (95% CI: 47.9, 51.6); tranexamic acid 46.7 (95% CI: 45.0, 46.7); mefenamic acid 29.0 (95% CI: 27.9, 30.2); diclofenac 26.9 (95% CI: 23.2, 30.6); naproxen 26.4 (95% CI: 24.6, 28.3); ibuprofen 16.2 (95% CI: 13.6, 18.7); ethamsylate 13.1 (95% CI: 10.9, 15.3) and norethisterone -3.6 (95% CI: -6.1, 1.1). Whereas the least effective drug, norethisterone, is the most frequently prescribed (to 38 % of patients). This comparison showed that hormone-releasing coils, danazol and tranexamic acid lead to significant reduction in menstrual blood loss.</td>
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<td>2.</td>
<td><strong>Lethaby (2008) [11]</strong></td>
<td>Comparisons of oral progestogen therapy versus placebo or other medical treatments in women of reproductive years with regular heavy periods. Progestogens were taken either during luteal phase (days 15 or 19 to 26) or for a longer course of 21 days. Norethisterone (NET) was the only type of oral progestogen that was assessed. NET taken for the longer course compared only with progesteron releasing IUS. Outcomes: menstrual blood loss (MBL).</td>
<td>NET administered from day 15 or 19 to day 26 of the cycle offer no advantage over other medical therapies such as danazol, tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs) and the progesterone releasing IUS in the treatment of menorrhagia. MBL: NET vs. NSAIDs effect size 22.97 [-0.62, 46.57], NET vs. danazol 55.63 [14.73, 96.54], NET vs. tranexamic acid 111.0 [43.54, 178.46], NET vs. IUS 51.0 [18.38, 83.62]. NET for 21 days results in significant reduction in blood loss although women found the treatment less acceptable than intrauterine levonorgestrel. NET for 21 days vs. IUS: -median MBL after 3 months of NET: 20 mls -median MBL after 3 months of LNG IUS. 6 mls, p=0.033</td>
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<tr>
<td></td>
<td><strong>Interventions:</strong></td>
<td><strong>Outcomes:</strong></td>
<td><strong>MBL:</strong></td>
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<td>3.</td>
<td>Mefenamic acid 500 mg 3 times daily on days 1 to 5 of menses, n=17. Control: Norethisterone 5mg 2 times daily on cycle days 19-26, n=15. Duration over 2 cycles. MBL (alkaline haematin method).</td>
<td>Number of days bleeding. Adverse events. Patient compliance.</td>
<td>NSAIDS vs NET odds ratio -22.97, 95% CI [-46.57, 0.62] Duration of bleeding: Odds ratio -0.41, 95% CI [-0.95, 0.13]. Total adverse events: Odds ratio 0.54, 95% CI[0.13, 2.26]. There is no significant difference in efficacy between NSAIDs and other medical treatments such as oral luteal progestogen.</td>
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<td>4.</td>
<td>Determination the effectiveness and acceptability of progestogens alone and estrogens and progestogens in combination in the management of DUB. The role of progestogens in anovulatory DUB was found in two trials. Assessment effectiveness of two types of progestogens (3x5 mg NET for 14 days from day 12 to 25 and 3x10 mg medroxyprogesterone acetate (MPA) for 14 days from day 12 to 25).</td>
<td></td>
<td>There is not enough evidence to show the effect of progestogens alone or in combination with estrogens for DUB. A significant reduction in MBL from a pretreatment mean of 131±40 mL to 80±31 mL during the first treatment cycle, and 64±14 mL in the second cycle. The duration of bleeding was also reduced following treatment, from a mean of 8.5±2.4 days before treatment to 6.2±1.7 days in the first treatment cycle, and 5.5±1.1 days in the second. No obvious difference was observed between the two progestogens.</td>
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<td>5.</td>
<td>Determination the effectiveness and acceptability of progesterone or progesterone-releasing intrauterine devices in achieving a reduction in heavy menstrual bleeding. The levonorgestrel-releasing intrauterine device (LNG IUS) has been compared to oral cyclical norethisterone administred on days 5 to 26 of the menstrual cycle. The outcome was reduction in MBL, satisfaction and acceptability.</td>
<td></td>
<td>The LNG-IUS is more effective than cyclical norethisterone. MBL median 6 ml vs median 20 ml. A greater proportion of women were amenorrhoeic after three months of treatment with LNG-IUS when compared with the NET (32% vs 0%). Rates of satisfaction with treatment did not differ between groups. A significantly greater proportion of women in the LNG – IUS group were willing to continue with treatment when compared with the NET (77% vs 22%).</td>
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<tr>
<td>6.</td>
<td>Determination the effectiveness of antifibrinolytics in achieving a reduction in heavy menstrual bleeding. Antifibrinolytics were compared to three other medical</td>
<td></td>
<td>In all groups of treatments, there was a significant reduction in menstrual blood loss (WMD -73.0, 95% CI-123.4 to -22.6; WMD -111.0, 95%CI -178.5 to -43.5; and</td>
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| 7. | **Beaumont (2009) [16]**  
Menstrual Disorders and Subfertility Group’s Specialised Register (April 2007), Cochrane Controlled Trials Register (Cochrane Library, Issue 2, 2007), MEDLINE (1966 to April 2007), EMBASE (1980 to April 2007), CINAHL (1982 to April 2007) were searched.  
Nine RCTs, with 353 women with were included. | Women with heavy menstrual bleeding.  
Comparison Danazol with other medical (non-surgical) therapy, included NET, for heavy menstrual bleeding in women of reproductive age with regular HMB.  
Outcome was menstrual blood loss (MBL). | Danazol appears to be more effective than placebo, progestogens NET 5 mg (OR - 35.60; 95% CI -102.20, 31.00), NSAIDS, and the oral contraceptives 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). 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 underpowered. |
|---|---|---|---|
| 8. | **Wellington (2003) [17]**  
Medical literature published in any language since 1980 to 2003 identified using MEDLINE and EMBASE. | Women with idiopathic menorrhagia (excluded organic ethyology).  
Comparasion tranexamic acid with other medical therapy, included NET.  
Outcome was MBL. | Tranexamic acid, 2-4.5 g/day for 4-7 days, was significantly more effective at reducing MBL than the oral NSAIDS mfenamic acid, 1.5 g/day (p<0.05), the oral haemostatic agent etamsylate, 2g/day for 5 days (p<0.001), and progesteron norethisteron 2x 5 mg/day administered orally for 7 days during the luteal phase (p<0.0001). Mean MBL increased by 20% in recipient of NET, compared with reduction of 45% in tranexamic acid recipients. Tranexamic acid was significantly less effective than levonorgestrel-releasing (20µg/day) IUD (p<0.01). |
Table 4. Clinical trials evaluating the effectiveness of 5 mg norethisterone for the management of dysfunctional uterine bleeding (DUB)

<table>
<thead>
<tr>
<th>No.</th>
<th>Article; Study Type; Study Design</th>
<th>Findings; Conclusion</th>
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</table>
| 1.  | **Franke (2006) [18]**  
Double blind RCT  
Perimenopausal women with DUB (N=31) for 6 months  
1. group received goserelin acetate (GA)+placebo  
2. group received goserelin acetate (GA)+CENT (combined E2+NETA) for 6 months  
Followed by 18 months of GA/CENT for all. | To assess the effects of adding combined estradiol/norethisterone acetate therapy (CENT) to goserelin acetate (GA) treatment of dysfunctional uterine bleeding (DUB) in perimenopausal women. Abdominal pain, number of bleeding days and endometrial thickness decreased in both groups, the between-group difference in decrease not being statistically significant. BMD decreased significantly in the GA/placebo group (-4.1%) compared with the GA/CENT group (-0.3%). Adding CENT to GA treatment for DUB in perimenopausal women initially prevented BMD loss and improved climacteric complaints, while having no negative impact on vaginal bleeding. Prolonged treatment did not result in a lasting prevention of bone loss. |
| 2.  | **Endrikat (2009) [19]**  
RCT  
Healthy women over 30 years of age suffering from idiopathic menorrhagia (n=39).  
1. group treated with levonorgestrel-releasing intrauterine system (LNG-IUS) N=20  
2. group treated with oral contraceptives (20 µg ethinyl estradiol+1 mg NETA)(n=19).  
The treated period was 12 months. | Assessing reduction of menstrual blood loss (MBL). In both groups, MBL decreased significantly from baseline to 12 months (P<0.001). MBL decreased significantly more in the LNG-IUS group (median from 228 to 13, mean percent change -83%) compared with 2. group (median from 290 to 72; mean percent change -68%) (P=0.002) after 12 months. In the LNG-IUS group, 80% of subjects had treatment success compared with 36.8% in 2. group (P<0.009). |
| 3.  | **Irvine (1998) [20]**  
Randomised comparative parallel group study  
44 women with heavy regular periods and a measured MBL≥ 80 ml.  
1. group had a LNG-IUD inserted within the first seven days of menses (n=22),  
2. group received NET, 3x5 mg daily, from day 5 to day 26 of the cycle for three cycles (n=22). | To compare the efficacy and acceptability of the LNG-IUD and NET for treatment of idiopathic menorrhagia. The main outcome measure was the change in objectively assessed menstrual blood loss after three months of treatment. When menstrual blood loss at three months was expressed as a percentage of the control, the levonorgestrel intrauterine system reduced menstrual blood loss by 94% (median reduction 103 ml; range 70 to 733 ml), and oral norethisterone by 87% (median reduction 95 ml; range 56 to 212 ml). After three cycles of treatment 76% of the women in the levonorgestrel intrauterine system group wished to continue with the treatment, compared with only 22% of the norethisterone group. Both the levonorgestrel intrauterine system and oral norethisterone in this regimen provided an effective treatment for menorrhagia in terms of reducing menstrual blood loss to within normal limits. The levonorgestrel intrauterine system was associated with higher rates of satisfaction and continuation with treatment, and thus offers an effective alternative to currently available medical |
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<td>and surgical treatments for menorrhagia.</td>
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| 4. | **Cameron (1990) [21]**  
RCT  
Women with menorrhagia (MBL≥80 ml per cycle).  
1. group received mefenamic acid, 500 mg three times daily during menses (n=17),  
2. group received norethisterone, 2x5 mg daily on days 19-26 of the cycle (n=15),  
For two additional cycles. | MBL was assessed.  
The median MBL was reduced from 123 ml (range 86-237) to 81 ml (22-193) (p<0.001) and from 109 ml (81-236) to 92 ml (43-189) (p<0.002) with mefenamic acid and NET, respectively.  
Apart from a decrease in the median number of days of bleeding, from 7 (5-8) to 5 (3-8) in those women treated with mefenamic acid, no other differences were seen between the groups.  
Conclusion is that mefenamic acid and NET were similiar effective in reducing the degree of MBL in women with proved menorrhagia, but that 52 and 67% of the women, respectively, remained menorrhagric after 2 months of treatment. |
| 5. | **Bonduelle (1991) [22]**  
RCT  
Women with dysfunctional uterine bleeding  
1. group received norethisterone, 5 mg three times a day from day 19 to 26 (n=14)  
2. group received danazol, 200 mg daily(n=10). | Comparation the efficacy NET vs. danazol for treatment of DUB.  
Bleeding intensity scores were significantly lower with danazol than with norethisterone for the third menses. This score was also significantly improved with danazol, but not with northisterone, by the 2nd and 3rd menses in comparison with baseline (P <0.02) as were the number of pads/tampons used (P <0.05). Some reduction in the symptoms of backache and abdominal pain accompanied both treatments although between treatment comparisons were not significant. |
| 6. | **Preston (1995) [23]**  
Double-blind RCT  
Women with ovulatory menorrhagia  
1. group received NET, 5 mg twice a day on days 19 to 26 (n=21),  
2. group received tranexamic acid(TA) (1 g four times daily on days 1 to 4)(n=25)  
For two cycles. | Comparasion the efficacy and safety of tranexamic acid and NET.  
Outcome: MBL was measured.  
TA reduced mean MBL by 45%, from 175 ml to 97 ml (95% CI for the difference in MBL 52 to 108, p = 0.0001), NET increased mean MBL by 20% from 173 ml to 208 ml (95% CI for the difference in MBL -64 to 2, p=0.26).  
14 women (56%) who received TA achieved a mean MBL of less than 80 ml per cycle during treatment, but only two(9.5%) who received NET achieved this mean MBL.  
There were no serius adverse events reported for either drug. |
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<td>Single-blind RCT</td>
<td>Assessment the effects of four medical treatment on MBL and endometrial prostaglandin (PG) concentration in women with menorrhagia. Endometrial biopses were obtained in the mid-luteal phase before and after treatment and assayed for PG content using radioimmunoassay. Treatment with NET had no effect on either MBL or the concentration of PGs in the endometrium. MBL was significantly reduced after treatment with mfenamic acid (p=0.05, n=6) and the progesteron coil (p&lt;0.05, n=6) and was reduced in 4 cases treated with danazol in whom endometrial biopses were available. Although there was no consistent change in endometrial PG concentrations in either the mfenamic acid or danazol groups, the lower MBL after insertion of the coil was associated with a reduced endometrial content of PGs (p=0.05).</td>
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<td>57 women with baseline mean MBL≥80 ml/cycle</td>
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<td></td>
<td>1.group received danazol, 200 mg/day (n=19) for three cycles,</td>
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<td>2.group received danazol, 200 mg/day for one cycle, 100 mg/day for one cycle, and 50 mg/day for one cycle (n=19),</td>
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<td>3. group received norethisterone, 5 mg three times daily on days 19 through 26 of the cycle for three consecutive cycles (n=19).</td>
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<td>Comperation the efficacy of the recommended dose of danazol, a reduced-dose danazol regimen, and norethisterone in the treatment of menorrhagia. The final MBL on treatment was significantly less for those patients who received both danazol regimens compared with those who received NET (p=0.017 for reducing dose danazol vs Net and p=0.043 for 200 mg of danazol vs NET). Significantly more recepients of 200 mg of danazol than of NET subjectively rated their treatment to be moderately or highly effective (p=0.033). Both danazol treatment regimens were associated with a higher incidence of adverse events than was NET therapy.</td>
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<td><strong>Saarikoski (1990) [9]</strong> RCT</td>
<td>The effects of NET and NMP on hystological, hormonal and lipid parameters were determined and the carry-over effect of each drug was also investigated. The sequential administration of NET significantly decrease the levels of E2(p&lt;0.001), SHBG (p&lt;0.001), FSH and LH (p&lt;0.01). The only change induced by NMP was a significant increase in the serum P (progestogene) level (p&lt;0.001). The hystological diagnosis, before treatment, in half of the cases was cystic glandular hyperplasia. This pattern disappeared in all cases after 6 cycles in the NET group. A proliferative endometrium was seen slightly more often in the NMP group. The long-term effects of NET and NMP were very week. Three months after cessation of therapy a regular secretory endometrium was found in only 25% of the patients as opposed to a hyperplastic or proliferative endometrium in 34%. With both progestogens only a slight decrease in total cholesterol was seen after 6 months of treatment (p&lt;0.05). The HDL-cholesterol and triglyceride levels decreased significantly in the NET group (p&lt;0.001 and &lt;0.02 ) respectively, but</td>
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<td>30 women with menorrhagia</td>
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<td>1.received danazol, 200 mg daily (n=6),</td>
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<td>2.group received mfenamic acid, 500 mg three times daily during menses (n=8),</td>
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<td>3.group received norethisterone, 5 mg twice daily from day 15-25 of the cycle (n=8),</td>
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<td>4. group was treated with progesteron-impregnated coil wich releasing 65µg progesterone daily (n=8).</td>
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<td>Assessment the effects of four medical treatment on MBL and endometrial prostaglandin (PG) concentration in women with menorrhagia. Endometrial biopses were obtained in the mid-luteal phase before and after treatment and assayed for PG content using radioimmunoassay. Treatment with NET had no effect on either MBL or the concentration of PGs in the endometrium. MBL was significantly reduced after treatment with mfenamic acid (p=0.05, n=6) and the progesteron coil (p&lt;0.05, n=6) and was reduced in 4 cases treated with danazol in whom endometrial biopses were available. Although there was no consistent change in endometrial PG concentrations in either the mfenamic acid or danazol groups, the lower MBL after insertion of the coil was associated with a reduced endometrial content of PGs (p=0.05).</td>
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<td>9</td>
<td>80 women with dysfunctional uterine bleeding. The endometrial (hyperplastic) morphology indicated a need for progesterone therapy.</td>
<td>The effects of NET and NMP on hystological, hormonal and lipid parameters were determined and the carry-over effect of each drug was also investigated. The sequential administration of NET significantly decrease the levels of E2(p&lt;0.001), SHBG (p&lt;0.001), FSH and LH (p&lt;0.01). The only change induced by NMP was a significant increase in the serum P (progestogene) level (p&lt;0.001). The hystological diagnosis, before treatment, in half of the cases was cystic glandular hyperplasia. This pattern disappeared in all cases after 6 cycles in the NET group. A proliferative endometrium was seen slightly more often in the NMP group. The long-term effects of NET and NMP were very week. Three months after cessation of therapy a regular secretory endometrium was found in only 25% of the patients as opposed to a hyperplastic or proliferative endometrium in 34%. With both progestogens only a slight decrease in total cholesterol was seen after 6 months of treatment (p&lt;0.05). The HDL-cholesterol and triglyceride levels decreased significantly in the NET group (p&lt;0.001 and &lt;0.02 ) respectively, but</td>
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| 10. | **Fraser (1990) [26]** | **RCT**
| | Anovulatory women with DUB (n=6) | 
| | 1. group received norethisterone (NET), 5 mg 3 times daily (n=3), | 
| | 2. group received medroxyprogesterone acetate (MPA), 10 mg 3 times daily (n=3). | 
| | Both groups received drugs for 14 days, from day 12 to day 25. | 
| | Ovulatory women with DUB (n=10) | 
| | 1. group received NET, 5 mg 3 times daily (n=5), | 
| | 2. group received MPA,10 mg 3 times daily(n=5). | 
| | Both groups received drugs for 21 days, from day 5 to day 25. | 
| | Outcomes (MBL and duration of menstrual bleeding) were measured immediately before treatment and during the first 2 cycles of treatment. | 

Anovulatory patients

MBL before treatment was 131 ml, and duration of MB was 8.5 days. During the first cycle of treatment MBL fell to 80 ml, duration 6.2 days; with a further fall to 64 ml, duration 5.5 days, in the second cycle (paired t test, t=4.638, p<0.005; t=4.025, p<0.011, respectively for first and second treatment cycles). There was no obvious difference between the 2 progestogens, and much larger numbers would be required for statistical comparison.

Ovulatory patients

MBL before treatment was 112 ml, and duration of MB was 6.1 days. During the first cycle of treatment MBL fell to 76 ml, duration 5.2 days. There was a further smaller fall to 71 ml, duration 5.0 days, during the second cycle. MBL during treatment was highly significantly reduced compared with control (paired t test; t=4.651; p<0.001). Duration of MB was slightly and significantly reduced (paired t=3.498; p=0.007). There was no obvious difference between the 2 progestogens.

Conclusion: These regimens are effective forms of management for most women with ovulatory or anovulatory DUB.

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**Norethisterone vs. levonorgestrel intrauterine system**

Both the LNG-IUS and oral norethisterone (5 mg three times daily, from day 5 to day 26) provided an effective treatment for menorrhagia in terms of reducing menstrual blood loss to within normal limits. The LNG-IUS was associated with higher rates of satisfaction and continuation with treatment, and thus offers an effective alternative to surgical treatments for menorrhagia (hysterectomy and endometrial ablation).[10,14,20]

**Norethisterone vs. danazol**

Danazol (both regimens, 100 mg daily and 200 mg daily) was significantly more effective than norethisterone in reducing the excessive menstrual blood loss of women with dysfunctional uterine bleeding. Significantly more recipients of 200 mg of danazol than of norethisterone subjectively rated their treatment to be moderately or highly effective. Both danazol treatment regimens were associated with a higher incidence of adverse events than was norethisterone therapy. [10,16, 22,24,25]

**Norethisterone vs. tranexamic acid**

Tranexamic acid (antifibrinolytic therapy) causes a greater reduction in menstrual blood loss when compared to norethisterone. This treatment is not associated with an increase in side effects compared with norethisterone. There has been a reluctance to prescribe tranexamic acid due to
possible side effects such as an increased risk of thromboembolic disease. There are no data available within RCTs which record the frequency of thromboembolic events. Change in the quality of life measures were significantly improved in the tranexamic acid group when compared to the norethisterone group. [10, 15, 23]

**Norethisterone vs. NSAIDs**

The mefenamic acid and norethisterone, two of the most common drug treatments for menorrhagia, are both effective in reducing blood loss in women with DUB. There was no evidence of a difference between the individual NSAIDs (naproxen and mefenamic acid) in reducing menstrual blood loss. The mefenamic acid (500 mg three times daily) and norethisterone were similarly effective in reducing the degree of menstrual blood loss. NSAIDs are less effective than either tranexamic acid, danazol or LNG-IUS. [10, 12, 19]

**Conclusion:**

Norethisterone is a hormone that suppresses endometrial growth and activity. NET may offer some help in reducing heavy menstrual bleeding but is not as effective as other therapies.

NET is taken by mouth either during days 15 or 16 to day 26 of the menstrual cycle (short course) or from day 5 to day 26 (long course). However, it is considered unacceptable for long-term use by many women due to the prevalence of side effects such as breast tenderness, bloating, headaches and they may also precipitate breakthrough bleeding.

Norethisterone can be used alone, or with oestrogen, to treatment anovulatory dysfunctional uterine bleeding. There is not enough evidence to show the effect of norethisterone in combination with estrogens for DUB. [13]

Many reviewed studies found that NET significantly reduced MBL, but was less effective than danazol, tranexamic acid, NSAID, and the progesterone-releasing intrauterine system (IUS). A decision analysis comparing the efficacy, side effects and consumer acceptability of these treatments ranked them in order shown above, with the LNG IUS coming top. Surgery may be indicated for women who have completed childbearing and for whom medical treatment is ineffective or intolerable.

Although it is not the first choice, peroral dose of 5 mg norethisterone is an effective form of management for most women with ovulatory or anovulatory dysfunctional uterine bleeding. Therefore norethisterone, in dose of 5 mg, can be recommended for treatment of dysfunctional uterine bleeding.

**Risk of bias assessment**

Risk of bias in the included clinical studies was assessed by using The Cochrane Collaboration’s risk of bias tool, which addresses the following domains: sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (Figs. 5-8). Information extracted from each report for the risk of bias tool is presented in the accompanying Excel spreadsheet, along with a judgement of low, high or unclear risk of bias, as described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions version 5.0.2

**Generation of allocation sequence**
Hormone replacement therapy
In two studies [4,7] patients were randomly assigned to study arms, without further explanation of the method of randomization. In one study there was no randomization procedure [5].

Dysfunctional uterine bleeding
Majority of studies (7 of 10) simply reported that subjects were randomly allocated to study arms, without providing any detail how the randomization sequence was generated, so the risk of bias in these cases was judged unclear. Two studies adequately reported that randomization was done “by computer-generated numbers” [20,23], and in one study there was no mention of randomization, so the risk of bias was judged to be high [26].

**Concealment of allocation sequence**
Hormone replacement therapy
Two studies reported no attempt to conceal the allocation sequence [4,7], and there was no randomization in the third study [5].

Dysfunctional uterine bleeding
Majority of studies (7 of 10) did not report any attempt to conceal the allocation sequence, so the risk of bias in these studies was judged unclear. Two studies adequately reported that the sequence was “placed in opaque, sealed, consecutively numbered envelopes” [20,23], and in one study there was no randomization and therefore no allocation sequence concealment [26].

**Blinding**
Hormone replacement therapy
In none of the included studies the blinding procedure was adequately described. Two studies were reportedly “double blinded” [4,5], and one of them stated that placebo tablet was identical to treatment [5]. In one study [7], pathologist who assessed endometrial biopsy was “unaware of the treatment given”, but the blinding for the patient-reported outcomes was not done, as groups had different therapeutic regimes and no attempt to mask the treatment was attempted.

Dysfunctional uterine bleeding
Adequate double-blinding, with the use of placebo tablets identical with the treatment, was reported in only two studies [18,23]. Three “open label” studies [19,20,22] and two studies that reported no attempt of blinding [21,26] were judged to have a high risk of bias in terms of blinding. Three studies had an unclear risk of bias – in two of them it was not clear who performed the assessment and whether these persons were blinded [9,25], and the third one was described as single-blind, but with no details on how the researchers/assessors were blinded [24]. In one study there were no researcher-assessed outcomes [22], and in another study there were no patient-reported outcomes [9].

**Incomplete outcome data**
Hormone replacement therapy
Two studies were judged to be under a high risk of bias regarding incomplete outcome data due to a high and poorly explained attrition [5,7]. In the third study [4], the risk of bias was low, as the attrition was relatively small and equally distributed among the study groups.

Dysfunctional uterine bleeding
Risk of bias regarding incomplete outcome data was judged high in four studies [9,19,22,25] due to a relatively high rate of attrition. In four studies this risk of bias was unclear – in two of them attrition was relatively high, but intention-to-treat analysis was performed [20,24], and in another two attrition was not clearly reported or explained [18,23]. In two studies the risk of bias regarding incomplete outcome data was low, as attrition was small and unlikely to have affected the results [21,26].

**Selective outcome reporting**
We did not attempt to find protocols for the included studies, but we compared the outcomes stated in the methods section with the ones reported in the results section.

Hormone replacement therapy
All outcomes stated in the methods section reported in the results section of all included studies.

Dysfunctional uterine bleeding
An adequate match between outcomes stated in the methods section and the ones reported in the results section was found in 9 of 10 studies, which were thus judged to be under a low risk of bias with regard to selective outcome reporting. The risk of bias was unclear in only one study which did report results for all outcomes mentioned in the methods section, but not fully [18].

**Other potential threats to validity**
Hormone replacement therapy
Other potential threats to validity were judged unclear in all three included studies, as there was no assessment of compliance, and no financial support or conflict of interest were declared.

Dysfunctional uterine bleeding
Attempt to assess the compliance to treatment regimen was reported in only one study [23], which also had a declared financial support (though from unclear source). This was the only study that was judged to have a low risk of bias in terms of other potential threats to validity. Three studies were judged to have an unclear risk of bias [9,22,25], as they did not attempt to assess the compliance and their financial support was either not declared, or non-industry related. The remaining six studies were judged to have a high risk of bias [18,19,20,21,24,26], as they did not attempt to assess the compliance, their financial support was either industry-related or undeclared, and they all have a small number of participants, which was likely to affect the precision of their estimates.
Figure 5. Risk of bias summary for hormone replacement therapy: review authors' judgements about each risk of bias item for each included study.

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Figure 6. Risk of bias graph for hormone replacement therapy: review authors' judgements about each risk of bias item for each included study.
Figure 7. Risk of bias summary for dysfunctional uterine bleeding outcome: review authors' judgements about each risk of bias item for each included study.

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Figure 8. Risk of bias graph for dysfunctional uterine bleeding outcome: review authors' judgements about each risk of bias item presented as percentages across all included studies.
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