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# A Benefit-Risk Review of Systemic Haemostatic Agents

## Part 2: In Excessive or Heavy Menstrual Bleeding

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## Abstract

The first part of this benefit-risk review examined the efficacy and adverse effect profiles of systemic haemostatic agents commonly used in major surgery. The second part of this review examines the efficacy and adverse effect profiles of systemic haemostatic agents commonly used in the treatment of excessive or heavy menstrual bleeding, and provides individual benefit-risk profiles that may assist clinicians in selecting appropriate pharmacological therapy in this setting. Historically, surgery has played a dominant role in treatment; however, pharmacological therapy is increasingly popular, especially in women who wish to retain their fertility. When selecting the appropriate treatment, patient preference should be considered, as well as the benefits and risks associated with each agent. Recommended pharmacological therapies that are effective and generally well tolerated include the levonorgestrel-releasing intrauterine system and the oral agents tranexamic acid, NSAIDs (e.g. mefenamic acid) and combined estrogen/progestogen oral contraceptives. In patients with an underlying bleeding disorder (e.g. von Willebrand disease), an additional option is intranasal desmopressin.

Part 1 of this benefit-risk review[1] examined the efficacy and adverse effect profiles of systemic haemostatic agents commonly used in major surgery. Here we consider the efficacy and adverse effect profiles of systemic haemostatic agents commonly used to manage excessive or heavy menstrual bleeding and provide individual benefit-risk profiles that may assist clinicians in selecting appropriate pharmacological therapy in this setting.

## 1. Agents Commonly Used in the Treatment of Excessive or Heavy Menstrual Bleeding

Excessive menstrual bleeding is one of the most common gynaecological problems seen in primary and secondary care and accounts for 5–20% of primary care consultations or outpatient referrals to specialist units.[2-4]

Hysterectomy or endometrial ablation are the surgical treatment options often preferred by women with excessive menstrual bleeding.[3] However, hormonal and nonhormonal medical therapies that reduce the amount of menstrual blood loss avoid the risks associated with surgery and have the added bonus of preserved fertility for women who have not completed their family.[2,3] Although no specific underlying cause is found in >50% of women with excessive menstrual bleeding,[4] the diagnosis of potential disorders of haemostasis, such as von Willebrand disease (10–20% of cases) or platelet disorders, such as Glanzmann's thromboasthenia, may also be of benefit in choosing the most efficacious treatment.[4,5] Recent treatment guidelines[6,7] have suggested that in the primary care setting, at least one non-surgical approach to management of excessive or heavy menstrual bleeding is tried for a minimum of 3 months before referral for secondary care.

Recommended medical treatments for excessive or heavy menstrual bleeding include the levonorgestrel intrauterine system (LNG-IUS), oral tranexamic acid, NSAIDs and combined estrogen/progestogen oral contraceptives (COCs).[2,3,7,8] In women with excessive or heavy menstrual bleeding and an underlying haemostatic disorder, tranexamic acid, COCs and the LNG-IUS are effective treatments; NSAIDs are contraindicated because of their inhibitory effect on platelet aggregation.[4] High-dose intranasal desmopressin also appears to be an effective option for these patients[4,9,10] and it is currently being evaluated in a clinical trial versus tranexamic acid or COCs.[11]

Although there is a relatively substantial and emerging body of evidence to support the clinical efficacy and safety of medical therapies for excessive menstrual bleeding, concerns over possible adverse effects (e.g. venous thromboembolism [VTE]) with some agents remain.[12]

### 1.1 Tranexamic Acid

When administered during menstruation, tranexamic acid is associated with reduced levels of tissue plasminogen activator (tPA) and plasmin activity in both peripheral blood and menstrual fluid (comprised of blood, serous fluid, endometrial debris) and the endometrium.[13,14] This is important, because fibrinolysis is increased in the endometrium and menstrual fluid of women with excessive or heavy menstrual bleeding.[13-15]

Oral tranexamic acid has been used for nearly four decades in the treatment of excessive or heavy menstrual bleeding.[16,17] In clinical studies in women with idiopathic heavy menstrual bleeding, tranexamic acid reduced menstrual loss from baseline by 45–60%, was more effective at reducing menstrual blood loss than diclofenac, mefenamic acid, etamsylate (ethamsylate) and 10 days of norethisterone and at half the usual daily dosage (i.e. 2 g/day orally, rather than 4 g/day) was equally as effective as oral medroxyprogesterone acetate.[18-23] There is an important correlation between the dosage of tranexamic acid (up to a maximum dosage of 6 g/day) with the objectively measured reduction in menstrual blood loss.[24] Recent National Institute for Health and Clinical Excellence (NICE) guidelines recommend tranexamic acid as an effective option to reduce menstrual bleeding, alongside NSAIDs and COCs.[7] In addition, oral tranexamic acid is recommended in managing severe menstrual bleeding in women with von Willebrand disease,[5] although a higher dose of the drug may be required.[25] Such a regimen is more convenient than other treatment options, such as factor VIII/von Willebrand factor concentrates, which are administered intravenously.[25]

The general tolerability and safety of tranexamic acid is discussed in detail in the first part of this review.[1] The incidence of VTE during the first 19 years (equating to 238 000 patient years) in which tranexamic acid was prescribed in Sweden for the treatment of excessive or heavy menstrual bleeding did not differ from that in women in the general population (0.0046% vs 0.0043–0.005%).[16] A review of the Swedish national registry of VTE events did not show an increased rate after oral tranexamic acid became available over-the-counter for the management of excessive or heavy menstrual bleeding.[26] On the basis of the 10 years' over-the-counter experience in Sweden, oral tranexamic acid is currently under consideration for reclassification from prescription-only medicine to pharmacy availability in the UK for this indication.[27]

### 1.2 Desmopressin

Numerous case reports, surveys and noncomparative studies have suggested that desmopressin is an effective treatment for excessive menstrual bleeding in women with an underlying haemostatic disorder (von Willebrand disease).[10] However, in two small randomized, placebo-controlled trials in patients with haemostatic disorders, intranasal desmopressin 300 μg for 2 days was not more effective than placebo in reducing overall menstrual blood flow.[28,29] Nevertheless, in one trial[29] mean blood loss was reduced during the two days of desmopressin therapy, and a significant decrease in total blood loss was evident when desmopressin was coadministered with tranexamic acid. Although desmopressin causes the release of large amounts of tPA, fibrinolytic activity and plasmin levels in menstrual fluid are unchanged after administration of the drug.[14] There is currently no consensus on the dose or duration of desmopressin required to control excessive menstrual bleeding in women with haemostatic disorders, and a decision to use the drug should be based on the patient's response to an initial trial of the drug.[4] The general tolerability and safety of desmopressin are discussed in the first part of this review.[1] Although rare, serious adverse events, such as hyponatremia, have been reported with intranasal desmopressin in women with excessive menstrual bleeding.[10]

### 1.3 NSAIDs

In women without an underlying bleeding disorder, NSAIDs are widely used for the treatment of excessive or heavy menstrual bleeding as they have been found to reduce menstrual blood loss by 25% to 35% or more in about three-quarters of women with this condition.[30] In addition, excessive or heavy menstrual bleeding may be associated with symptoms, such as dysmenorrhoea, and treatment with NSAIDs may also improve these symptoms substantially. The mechanism of action of NSAIDs has not been fully elucidated but prostaglandin levels, including that of the vasodilator prostaglandin $E_2$, are elevated in women with excessive or heavy menstrual bleeding and NSAIDs are prostaglandin synthesis inhibitors via their subjugation of the cyclo-oxygenase enzyme system.[31,32] There is also evidence that some NSAIDs (mefenamic acid, meclofenamic acid) dose-dependently inhibit the binding of vasodilator prostaglandin $E_2$ with its specific receptor.[31,33]

The agent most frequently studied has been mefenamic acid, but other NSAIDs such as naproxen, ibuprofen, flurbiprofen, indomethacin, diclofenac and meclofenamic acid have also been used.[30,32,34] With reduction in menstrual blood loss usually in the range of 20–35%, mefenamic acid is less effective than tranexamic acid[23,32] and danazol[32] and may be more effective than ethamsylate[23,32,35] and oral progestogens.[32,36,37]

The adverse effects of NSAIDs vary in frequency and severity and include gastrointestinal intolerance, bleeding and ulceration, headache, dizziness, rashes, bronchospasm, hypersensitivity reactions and, rarely, blood disorders such as haemolytic anaemia or thrombocytopenia.[30]

While the effectiveness of NSAIDs in controlling excessive or heavy menstrual bleeding is generally similar,[32] there are often differences in their tolerability among individual patients and this influences their selection.

### 1.4 Hormonal Agents

A number of hormonal preparations have also been found to be useful in controlling excessive or heavy menstrual bleeding, including cyclical oral progestogens (e.g. norethisterone, dydrogesterone

and medroxyprogesterone); LNG-IUS; COCs; danazol (although this is no longer recommended in the latest NICE guidance[7]); and gonadotrophin-releasing hormone (GnRH) agonists such goserelin.[7,30] These agents cause functional and histological changes to the endometrium, resulting in inhibition of endometrial growth and development.[6,30,38,39]

#### 1.4.1 Cyclical Oral Progestogens

Oral progestogens (e.g. norethisterone, medroxyprogesterone acetate, dydrogesterone) given to women with excessive or heavy menstrual bleeding have been shown to be beneficial in reducing blood loss. Treatment must be given for 21 days of each cycle, as shorter cycles are ineffective. However, they were not more effective than other treatments for excessive or heavy menstrual bleeding (i.e. tranexamic acid, danazol or NSAIDs), although the evidence base is of variable quality.[30,39] The frequency of adverse events was similar to that of mefenamic acid and tranexamic acid and less than danazol, and included break-through bleeding, premenstrual-like syndrome (i.e. bloating, fluid retention, breast tenderness), nausea, headache, skin reactions, hirsutism, alopecia.[30,39] Recent studies have shown that estrogen-progestogen combinations vary in their thrombogenicity, although the progestogens on their own have little, if any, direct influence on thrombotic tendency. Some studies have suggested that combinations of ethinyl estradiol with third generation progestogens (e.g. desogestrel, gestodene) may have a slightly higher risk of venous thrombosis than combinations with earlier generation progestogens.[40,41] However, this outcome is now being questioned, based on results of the EURAS (European Active Surveillance) study in >58 500 women that showed that a drospirenone-containing oral contraceptive had a risk of VTE similar to that associated with LNG-containing and other COCs.[42,43] Although oral progestogen-only agents are a third-line option in the recent NICE guidelines,[7] they may be a valuable option for women with underlying thrombophilia, such as a Factor V Leiden carrier or with a history of previous VTE.[44] Oral progestogens are also an effective treatment in women with anovulatory bleeding disturbances.[45]

#### 1.4.2 Levonorgestrel-Releasing Intrauterine System

The LNG-IUS reduces menstrual blood loss by up to 90%, with relatively few adverse effects.[6,30,46,47] The effectiveness of the LNG-IUS in reducing excessive or heavy menstrual bleeding has been linked to major reductions in hysterectomy rates in the UK[48,49] and the LNG-IUS is recommended as a first-line pharmacological treatment in the recently published NICE guidance for excessive or heavy menstrual bleeding in those women for whom an IUS may be suitable.[7] Long-term efficacy and tolerability data in this indication are still accumulating; however, 5-year results of a randomized study comparing the LNG-IUS with hysterectomy indicate similar satisfaction with treatment and improvements in health-related quality of life.[50] Preliminary evidence also suggests that the LNG-IUS may be of benefit in women with endometriosis, adenomyosis, fibroids or endometrial hyperplasia, disorders often linked with excessive menstrual bleeding.[46] This device also appears to be very effective in women with von Willebrand disease-related excessive or heavy menstrual bleeding; in one small study, 9 of 16 women with this disorder became amenorrhoeic.[51] Two small (44[52] and 51[53] patients) randomized comparisons between the LNG-IUS and medical treatments for excessive or heavy menstrual bleeding (most comparisons are versus surgical options) indicate that LNG-IUS is more effective than norethisterone[52] or mefenamic acid[53] at reducing menstrual blood loss.

The most common adverse effect of this preparation is intermenstrual bleeding/spotting in the first three cycles, which tends to subside thereafter.[30,46] Less common adverse effects include abdominal/pelvic pain, acne and oily skin, mood swings, headache, hair loss, reduced libido, hypertension and leg pain.[7,30,46] VTE associated with LNG-IUS was not evident in the clinical trials discussed in the Cochrane review.[47] This finding is to be expected, given that the levonorgestrel preparation is a progesterone derivative and as such does not demonstrate a thrombogenic tendency.[6,47] As with other intrauterine devices, perforation or penetration of the uterus or cervix may occur during insertion of the LNG-IUS (mainly in postpartum insertions); however, this is very uncommon (in <1 in 1000 insertions).[6,7,54]

#### 1.4.3 Combined Oral Contraceptives

Limited, mainly uncontrolled, data strongly suggest that COCs are effective in reducing menstrual blood loss by 40–50% in women with excessive or heavy menstrual bleeding.[30,38,55,56] The results of two major randomized controlled trials that are currently underway[57,58] are expected to clarify the extent to which COCs reduce menstrual bleeding. Minor adverse effects of COCs, which are often temporary, include headaches, nausea/vomiting, breast tenderness, spotting and breakthrough bleeding, fluid retention and skin reactions.[38] More serious adverse effects are rare, and include thrombosis, hypertension, liver function impairment and cholestatic jaundice.[30,59] The increased risk of thrombosis in COC users results from an increase in the procoagulant factors fibrinogen and factor VII, factor IX, Factor X and factor XII and a decrease in levels of the anticoagulant factors protein S and antithrombin that is reversed within 3 months of ceasing to use COCs.[41,60] Although the estrogen component is the major cause of the increased risk of VTE, some progestogen components modulate the risk associated with ethinyl oestradiol exposure; third-generation COCs may be associated with a slightly greater risk than second generation COCs.[40,41,61] Although the relative risk of VTE in women of reproductive age who use COCs is approximately 3-fold higher than that in nonusers,[40,42,43] the absolute risk of VTE with these agents is low (2–3 per 10 000 per year), is greatest in the first year of use and is related to the dosage of ethinyl estradiol.[62] Nevertheless, because of their widespread use, COCs are the most common cause of VTE in young women. Consequently, other treatment options may be recommended for women with excessive or heavy menstrual bleeding who do not require contraceptive protection, or in whom risk factors for VTE (e.g. Factor V Leiden, obesity, smoking) are present.[59,63] In the recently published NICE guidance,[7] COCs are recommended as an option for the management of excessive or heavy menstrual bleeding in women requiring contraceptive protection who are not suitable for or who do not wish to use an IUS.

#### 1.4.4 Danazol

Danazol, a synthetic steroid with multiple and diverse biological effects, is also more effective in reducing excessive or heavy menstrual bleeding than oral progestogens but adverse effects limit their long-term use.[30] This agent tends to induce cessation of menstrual bleeding (amenorrhoea). Danazol may cause muscle cramps, fatigue, headaches, fluid retention, oily skin, mood changes, alteration of lipoprotein profiles and hot flushes; masculinisation and androgenic effects, such as voice changes and hirsutism, are relatively common with longer-term treatment.[30] Cases of arterial thromboembolism or VTE have also been reported in patients receiving danazol[64-66] and it is not recommended in the NICE treatment guidelines for the management of excessive or heavy menstrual bleeding in otherwise healthy women.[7]

#### 1.4.5 Gonadotrophin-Releasing Hormone Agonists

GnRH analogues are also more effective in reducing excessive or heavy menstrual bleeding than oral progestogens but adverse effects limit their long-term use.[7,30] These agents also tend to induce cessation of menstrual bleeding. GnRH analogues may cause hypoestrogenic effects such as hot flushes, night sweats and vaginal dryness, and a temporary reduction in trabecular bone density.[7,30]

## 2. Other Agents

Etamsylate appears to have limited efficacy in excessive or heavy menstrual bleeding[23,35,37,67] and is not recommended in this indication.[7] Conjugated estrogens have been reported to reduce acute, excessive or heavy uterine bleeding in gynaecological patients;[68] however, as mentioned in the first part of this review,[1] the thrombotic profile, which is similar to that seen with COCs is of concern.[69,70]

## 3. Conclusion

Selection of an appropriate agent in women with excessive or heavy menstrual bleeding depends on whether they also require contraception. In the latter group of women, for those for whom an IUS is suitable, the LNG-IUS is an effective pharmacological therapy; for those desiring oral therapy, or for whom the LNG-IUS is unsuitable, COCs are a recommended treatment option. If contraceptive cover is not required, tranexamic acid is recommended, as are NSAIDs in women with normal haemostasis. For women with an underlying haemostatic disor-

**Table I.** Safety profiles of agents recommended in the management of excessive or heavy menstrual bleeding

| Agent | Adverse effect[a] | | | | |
|---|---|---|---|---|---|
| | thrombosis | nephrotoxicity | gastrointestinal tract | hypersensitivity reactions | other |
| Tranexamic acid | − | − | + | + | Retinopathy (rarely) |
| NSAIDs | − | − | +++ | ++ | Bronchospasm; blood disorders (rarely) |
| Levonorgestrel-releasing intrauterine system | − | − | − | − | Intermenstrual bleeding spotting (transient); amenorrhoea; uterine perforation (very rare) |
| Combined oral contraceptives | ++ | − | + | − | Hypertension; breakthrough bleeding (transient) |
| Cyclical progestogens | − | − | + | − | Premenstrual-like syndrome; breakthrough bleeding |
| Desmopressin | +[b] | − | − | − | Hyponatremia; vasomotor effects |

a Frequency of adverse effects is shown as − indicates none; + indicates low; ++ indicates medium; +++ indicates high.

b Arterial thrombosis only in at-risk patients.

der, the LNG-IUS and tranexamic acid are effective and desmopressin may be another useful option. The benefits of these agents must be weighed against their adverse effects (table I), which can contribute to poor satisfaction rates.

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