ONLINE EXCLUSIVE

Q/Which medications work best for menorrhagia?

Allison Lale, MD, MPH; Elise Halajian, DO; Rick Guthmann, MD, MPH
Advocate Illinois Masonic Medical Center, Chicago

Joan Nashelsky, MLS
Family Physicians Inquiries Network, Iowa City

ASSISTANT EDITOR
Gary Kelsberg, MD
Valley Family Medicine Residency, University of Washington at Valley in Renton

EVIDENCE-BASED ANSWER

A/ **Four medications have been shown to reduce menstrual blood loss** (MBL) significantly in placebo-controlled randomized controlled trials (RCTs): the levonorgestrel-releasing intrauterine system (LNG-IUS), tranexamic acid, nonsteroidal anti-inflammatory drugs (NSAIDs), and danazol, a synthetic steroid (strength of recommendation: **A,** meta-analyses of RCTs).

A single trial showed that the LNG-IUS reduced MBL by about 100 mL, compared with placebo. In a meta-analysis of 4 placebo-controlled RCTs, tranexamic acid reduced MBL by about 53 mL, roughly a 40% to 50% decrease. The 8 NSAID trials (5 mefenamic acid, 2 naproxen, 1 ibuprofen) demonstrated effectiveness, but the effect size is difficult to quantify. The single danazol RCT used a subjective scoring system without reporting MBL.

No studies compared all effective medical therapies against one another. In head-to-head comparisons, women were more likely to experience improvement with the LNG-IUS than with tranexamic acid (number needed to treat [NNT] = 2 to 6). Both treatments are superior to NSAIDs. Danazol is also more efficacious than NSAIDs, but its use is limited by its adverse effects, including teratogenicity.

No placebo-controlled trials have studied oral contraceptive pills (OCPs) or oral progesterone to treat menorrhagia. However, multiple comparative RCTs have demonstrated that these commonly prescribed medications significantly decrease MBL. Trials have shown the reduction to be inferior to LNG-IUS and danazol and equivalent to NSAIDs.

Evidence summary

A 2015 Cochrane review of the LNG-IUS for menorrhagia included 1 placebo-controlled RCT; most of the remaining 21 RCTs compared the LNG-IUS to invasive procedures such as endometrial ablation or hysterectomy.[1] The placebo-controlled trial compared the LNG-IUS with placebo in 40 women on anticoagulation therapy and found a mean beneficial difference of 100 mL (95% confidence interval [CI], –116 to –83) using a subjective pictorial blood assessment chart.

Women are less likely to withdraw from LNG-IUS treatment

Four trials (379 patients) included in the Cochrane review compared LNG-IUS with combination or progesterone-only pills. All of the trials excluded women with palpable or large (> 5 cm) fibroids. In 3 trials (2 against OCPs and 1 against a 10-day course of oral progesterone), the LNG-IUS decreased MBL more than OCPs did. A fourth trial found LNG-IUS comparable to oral progesterone dosed 3 times a day from Day 5 to Day 26 of each menstrual cycle.

A recent large RCT (571 patients) that compared LNG-IUS with usual medical treatment (mefenamic acid [MFA], tranexamic acid, norethindrone, OCPs, progesterone-only pill, medroxyprogesterone acetate injection) found women significantly less likely to withdraw from LNG-IUS at 2 years (relative risk [RR] = 0.58; 95% CI, 0.49-0.70).[2]

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In head-to-head comparisons, women were more likely to improve with the LNG-IUS than tranexamic acid for reducing menstrual blood loss.

Estrogen and progestin contraceptives significantly reduce bleeding

In addition to the trials in the 2015 Cochrane review comparing OCPs with LNG-IUS, a 2009 Cochrane review included a single 2-month crossover trial of 45 patients.[3] This RCT compared OCPs with naproxen, MFA, and danazol to treat heavy menstrual bleeding (assessed using the alkaline haematin method).

Researchers didn't analyze the data using intention-to-treat. No group was found to be superior. The OCP group (6 women) had a 43% reduction in MBL over baseline (no *P* value reported).

Tranexamic acid outperforms oral progesterone and NSAIDs but not ...

A 2018 Cochrane meta-analysis of 13 RCTs (1312 patients) of antifibrinolytics for reproductive-age women with regular heavy periods and no known underlying pathology included 4 RCTs (565 patients) that used placebo as a comparator.[4] Therapy with tranexamic acid decreased blood loss by 53 mL per cycle (95% CI, 44-63 mL), a 40% to 50% improvement compared with placebo. Three of the RCTs (271 patients) reported the percent of women improving on tranexamic acid as 43% to 63%, compared with 11% for placebo, resulting in an NNT of 2 to 3.

One trial (46 patients) found tranexamic acid superior to luteal phase oral progesterone, and another study (48 patients) demonstrated superiority to NSAIDs, with a mean decrease in MBL of 86 mL compared with 43 mL ($P < .0027$).

On the other hand, tranexamic acid compared unfavorably with LNG-IUS (1 RCT, 42 patients), showing a lower likelihood of improvement (RR = 0.43; 95% CI, 0.24-0.77). Whereas 85% of women improved with LNG-IUS, only 20% to 65% of women improved with tranexamic acid (NNT = 2 to 6).

No statistical difference was found in gastrointestinal adverse effects, headache, vaginal dryness, or dysmenorrhea.[4] Only 1 thromboembolic event occurred in the 2 studies that reported this outcome, a known risk that prohibits its concomitant use with combination OCPs.

Different NSAIDs, equivalent efficacy

A 2013 Cochrane review of 18 RCTs included 8 (84 patients) that compared NSAIDs (5 MFA, 2 naproxen, 1 ibuprofen) with placebo.[5] In 6 trials, NSAIDs produced a significant reduction in MBL compared with placebo, although most were crossover trials that couldn't be compiled into the meta-analysis.

One trial (11 patients) showed a mean reduction of 124 mL (95% CI, 62-186 mL) in the MFA group. In another trial, women were less likely to report no improvement in the MFA group than in the placebo group (odds ratio [OR] = 0.08; 95% CI, 0.03-0.18). No NSAID had significantly higher efficacy than the others.

Danazol was superior to NSAIDs in a meta-analysis of 3 trials (79 patients) with a mean difference of 45 mL (95% CI, 19-71 mL), as was tranexamic acid in a single trial (48 patients) with a mean difference of 73 mL (95% CI, 22-124 mL).[5] Comparisons with OCPs, oral progesterone, and an older model of LNG-IUS showed no significant differences. The most common adverse effects were gastrointestinal.

Danazol linked to weight gain and other adverse effects

A 2010 Cochrane review evaluated 9 RCTs, including 1 (66 patients) comparing danazol 200 mg with placebo that showed a significant decrease in subjectively assessed MBL in the danazol group.[6] The study, which only 22 women finished, didn't address intention-to-treat and used an unidentified scoring system. Patients also reported a significant 6.7-kg weight gain (95% CI, 1-12.4) after 3 months of treatment.

In addition to the 2013 meta-analysis showing danazol to be superior to NSAIDs, several studies[6] compared danazol favorably with oral progesterone, although not all results reached significance. One study (37 patients) showed that women were more likely to rate the efficacy of danazol as moderate or high compared with progesterone (OR = 4.3; 95% CI, 1.1-17.0), but the mean difference in MBL (–36 mL; 95% CI, –102 to 31 mL) wasn't statistically significant.

Of note, both a meta-analysis of 4 of the

studies (117 patients) and another study comparing danazol with NSAIDs (20 patients) found significantly more adverse effects in the danazol group. Commonly reported adverse effects were acne, weight gain, headache, nausea, and tiredness.

Recommendations

A comparative effectiveness review by the Agency for Healthcare Research and Quality concluded that evidence showed efficacy for 4 primary care interventions for heavy cyclic bleeding: LNG-IUS, NSAIDs, tranexamic acid, and combination OCPs.[7]

The United Kingdom's National Institute for Health Care and Excellence (NICE) recommends pharmaceutical treatment when no structural or histologic abnormality is present or when fibroids are < 3 cm in diameter.[8] NICE advises considering pharmaceutical treatments in the following order: first, LNG-IUS if long-term use (at least 12 months) is anticipated; second, tranexamic acid or NSAIDs; and third, combination OCPs, norethisterone (15 mg) daily from Days 5 to 26 of the menstrual cycle, or injected long-acting progestogen.

Editor's takeaway

I was taught to use combination OCPs as first-line treatment for menorrhagia, but better evidence supports using any of these 4: LNG-IUS, tranexamic acid, danazol, or NSAIDs. In the absence of clear evidence demonstrating differences in efficacy, I would use them in the reverse order for cost-effectiveness reasons. JFP

References

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