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USE OF MIX-TREATMENT COMPARISON APPROACHES IN ASSESSING EFFICACY OF TREATMENT FOR HEAVY MENSTURAL BLEEDING

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Abstract:

A variety of pharmacological and surgical treatments have been developed for heavy menstrual bleeding (HMB), which can have negative physical, social, psychological, and economic consequences. We conducted a systematic literature review and mixed-treatment-comparison (MTC) meta-analysis of available data from randomized controlled trials (RCTs) to derive estimates of efficacy for 8 classes of treatments for HMB, to inform health-economic analysis and future studies.

A systematic review identified RCTs that reported data on menstrual blood loss (MBL) at baseline and one or more follow-up times. Eight treatment classes were considered: COCs, danazol, endometrial ablation, LNGIUS, placebo, progestogens given for less than 2 weeks out of 4 during the menstrual cycle, progestogens given for close to 3 weeks out of 4, and TXA. The primary measure of efficacy was the proportion of women who achieved MBL < 80 mL per cycle (month), as measured by the alkaline hematin method. A score less than 100 on an established pictorial blood-loss assessment chart (PBAC) were considered an acceptable substitute for MBL < 80 mL. Estimates of efficacy by treatment class and time were obtained from a Bayesian MTC model. The model also included includedeffects for treatment class, study, and the combination of treatment class and study and an adjustment for baseline mean MBL. Several methodological challenges complicated the analysis. Some trials reported various summary statistics for MBL or PBAC, requiring estimation (with less precision) of % MBL < 80 mL or % PBAC < 100. Also, reported follow-up times varied substantially.

The evidence network involved 34 RCTs, with follow-up times from 1 to 36 months. Efficacy at 3 months of follow-up (estimated as the posterior median) ranged from 87.5% for the levonorgestrel-releasing intrauterine system (LNG-IUS) to 14.2% for progestogens administered for less than 2 weeks out of 4 in the menstrual cycle. The 95% credible intervals for most estimates were quite wide, mainly because of the limited evidence for many combinations of treatment class and follow-up time and the uncertainty from estimating % MBL < 80 mL or % PBAC < 100 from summary statistics.

Keywords: *Mix-treatment Comparison; Treatment Efficacy; Menstrual Bleeding*

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INTRODUCTION:

Heavy menstrual bleeding (HMB) is actually a frequent but empirically complicated medical condition. Though HMB is described as menstrual flow exceeding 80 milliliters (mL) of blood decrease per menstrual cycle that shouldn't be revealed by natural pathology or professional medical infection, the prognosis is personal, certainly females vary in their thoughts of what exactly is appropriate blood loss and when to look for assistance. As part of surveys, between 13% and 52% of women describe having HMB, according to the {nation|location}, generation, and definition of HMB. Though, a lesser number of one in five women who met conditions for HMB in England experienced needed treatment from their general practitioner.

An additional study discovered that only one third of women referred to a gynecology clinic in Scotland for HMB actually had a mean menstrual blood loss (MBL) greater than 80 mL when this was formally measured, suggesting a more conservative prevalence of HMB between 11% and 13%. HMB can have negative physical, social, psychological, and economic consequences. MBL greater than 80 mL is likely to lead to anemia, which affected around one quarter of women hospitalized for HMB in one US study. HMB also impairs a woman's quality of life and is associated with a reduced likelihood of being employed. A variety of pharmacological and surgical treatments aimed to reduce MBL or eliminate menstruation altogether. Classes of treatments include combined oral contraceptives (COCs), tranexamic acid (TXA), oral or injectable progestogens, danazol, the levonorgestrel-releasing intrauterine system (LNGIUS), and endometrial ablation or resection.

An informed choice requires information on the clinical efficacy of relevant treatment options. In previous systematic reviews the evidence base on this topic has been weak, with few direct comparisons among treatment options; leading to uncertainty about the overall comparative effectiveness of the most commonly used treatments. We therefore conducted a systematic literature review and mixed-treatment-comparison (MTC) meta-analysis to inform the development of a micro simulation model that assessed the cost-effectiveness of pharmacological interventions and endometrial ablation for HMB. A type of network meta-analysis, MTCs combine information from direct and indirect comparisons of interventions, to allow estimation of the relative efficacy of interventions that have not been directly compared in head-to-head studies. Our focus, however, was on estimating absolute efficacy (for use in the micro simulation model), rather than on assessing relative efficacy. During the review and analysis we identified a number of methodological challenges that should inform future research.

MATERIAL AND METHODS:

Treatment Compared

We considered eight treatment classes: COCs, danazol, endometrial ablation, LNG-IUS, placebo, progestogens given for less than 2 weeks out of 4 during the menstrual cycle, progestogens given for close to 3 weeks out of 4, and TXA. We made no distinction between first- and second-generation endometrial ablation techniques.

Literature search

Figure 1 summarizes the literature search process. Most of the articles that provided data for the present analysis were identified as part of a systematic review of the literature on HMB, covering the period 1966–2009. That review included a replication and update of a literature review previously employed for the National Institute for Health and Clinical Excellence (NICE) HMB guideline.

The search used the Cochrane Library, MEDLINE, EMBASE, CINAHL, PsychINFO, and the National Health Service (NHS) Economic Evaluation Database and included manual searches of the bibliographies of all review articles, as well as ad hoc internet searches for key treatment-related terms. The titles and abstracts of the resulting items were reviewed against predefined inclusion and exclusion criteria. Items that had not been excluded were reviewed in full text, and data were extracted from items that passed this second level of review. Additional publications in the period 2009–2011 were identified through a manual search. Extracted data were reviewed for accuracy and completeness by an independent researcher. Articles were assessed for quality using the Centre for Evidence Based Medicine (CEBM), (University of Oxford) quality score and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) score.

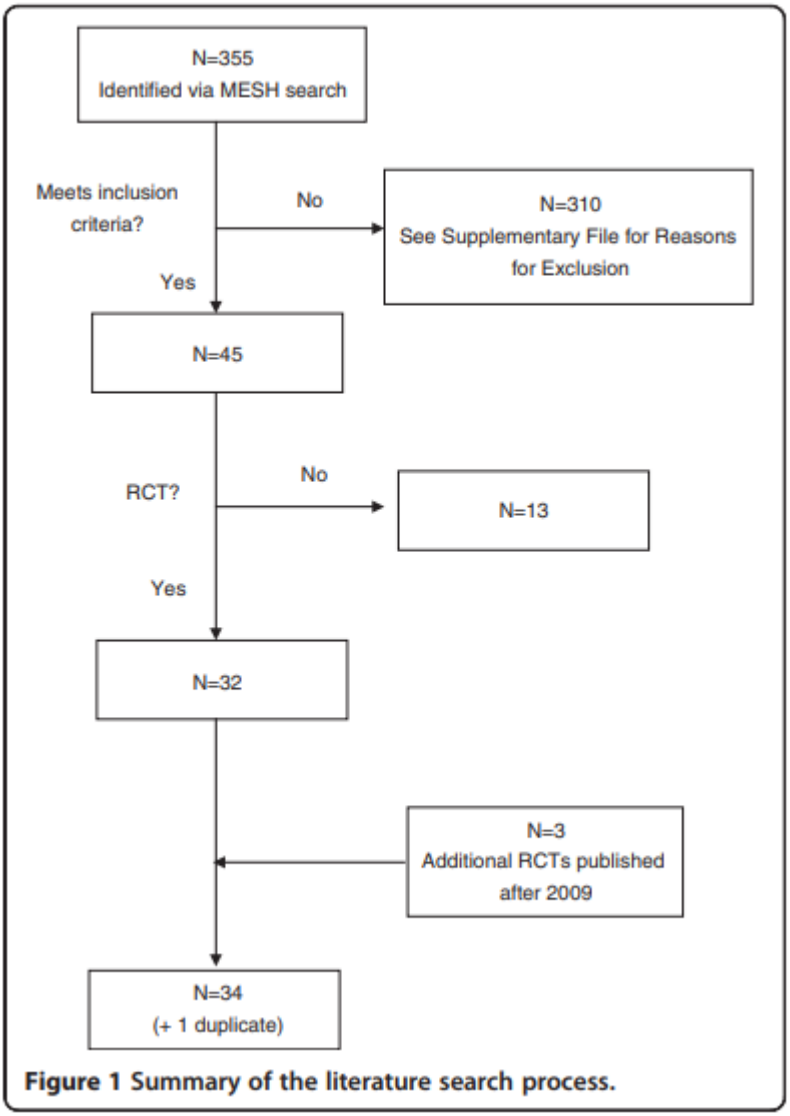

Figure 1 Summary of the literature search process.

Efficacy measures:

The primary measure of efficacy was the proportion of women who achieved MBL < 80 mL per cycle (month), as measured by the alkaline hematin method. This measure allows objective estimation of blood loss, provided the patient accurately collects all sanitary material and submits it for analysis. As a less burdensome substitute, several researchers have developed pictorial charts, on which the patient records the blood loss by its appearance on various types of sanitary material; an investigator then uses a scoring system to calculate a numerical score for the cycle. The most widely used is the pictorial blood-loss assessment chart (PBAC) developed by Higham et al., for which a score less than 100 is considered equivalent to MBL < 80 mL. The choice of MBL as the efficacy measure was determined mainly by the outcomes reported in the randomized controlled trials (RCTs). A patient-reported outcome would enhance generalizability and relevance of the results, but inconsistent use of different scales with unclear psychometric properties for the HMB population made such a measure infeasible.

We extracted data if authors used the alkaline hematin method to measure blood loss, or if subjects used the Higham PBAC chart to assess their blood loss. Studies in which MBL was objectively

measured could report the mean or median MBL with an accompanying measure of spread, or the proportion of women who achieved MBL < 80 mL per menstrual cycle at a particular follow-up time. The latter data were directly used as inputs for the analysis. We estimated the proportion of women with MBL < 80 mL from mean MBL data (with spread) and from median MBL data (with spread). These estimated proportions, along with estimates of their standard errors, were then used as inputs for the analysis. Data on the proportion of women with a PBAC score < 100 were also used directly as inputs. When studies reported a mean PBAC (with spread) or a median PBAC (with spread), we estimated the proportion of women with PBAC < 100 and used these estimates, along with estimates of their standard errors, as inputs. Additional file 2 discusses these calculations in more detail.

RESULTS:

Literature Search

A total of 355 articles met the inclusion and exclusion criteria for efficacy. The review of the full text excluded 310 articles for the reasons. The majority of the excluded articles did not report measures of efficacy suitable for the analysis (i.e., MBL or the PBAC score of Higham et al.). After all inclusion and exclusion criteria were applied, a total of 45 efficacy studies remained: 32 RCTs and 13 observational studies. The present analysis used only the RCTs. Assessment of the literature published after 2009 found 2 additional RCTs and a later article on one of the initial 32. Thus, efficacy data were available from a total of 34 RCTs; a table summarizing characteristics of the studies is available upon request.

Evidence network

Among the 34 RCTs, the most studied treatment classes were ablation (16 RCTs) and LNG-IUS (11 RCTs). Figure 2 shows the treatment classes and direct comparisons that comprised the evidence network. The total number of direct comparisons between treatment classes, 21, differs from the number of RCTs, because 9 studies compared two types of ablation, 1 study had three arms (progestogens administered for less than 2 weeks out of 4 during

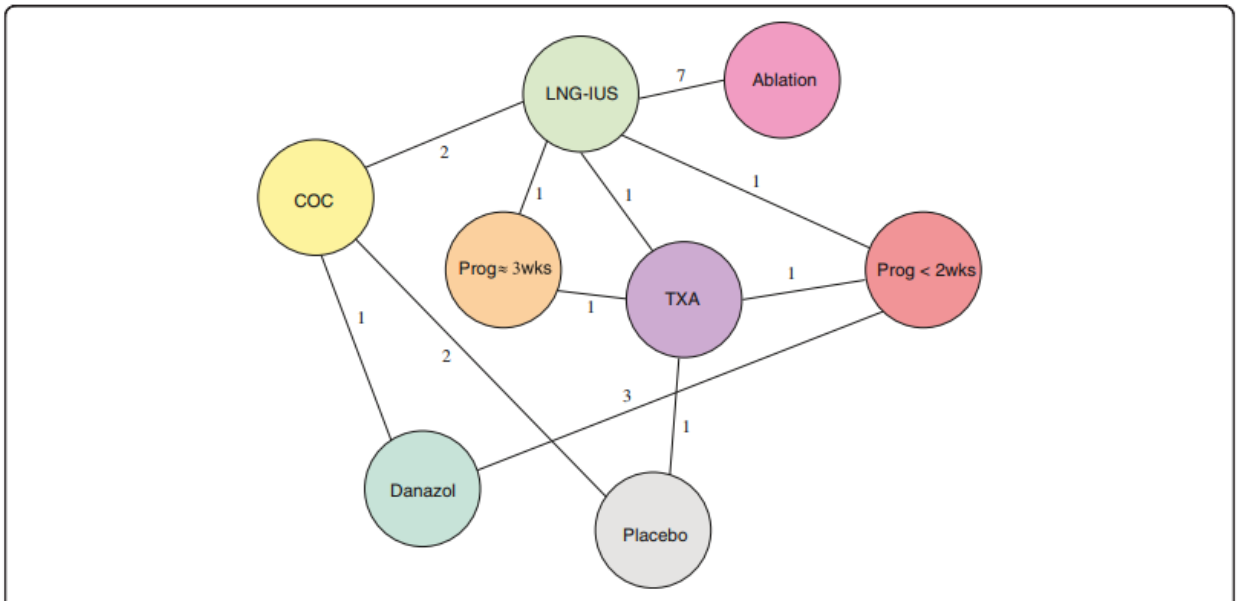

Figure 2 Evidence network of RCTs for MBL in HMB.

the menstrual cycle and two regimens of danazol), and 5 studies evaluated treatments not of interest for this study. The network is thinly connected: only two pairs of treatment classes have more than two direct comparisons, and seven have only one. Only at 3 months are all 8 treatment classes connected (Table 1). At other follow-up times, the number of treatment classes involved in any direct comparison ranges from 7 (at 1 month) to 2 (at 9, 24, and 36 months); at 1 month the network separates into three disjoint components. The trial of LNGIUS and TXA reported efficacy for the two arms at disjoint times (3, 6, and 12 months for LNG-IUS, and 2 months for TXA) and hence did not provide any direct comparison. The

total number of patients for a given direct comparison (based on the maximum number reported, usually at baseline) was often modest: 4 of the comparisons had fewer than 50 patients, and the largest number was 422.

Table 1 Comparisons in the evidence network: Number of RCTs that made the comparison, total number of patients in those RCTs, and number of direct comparisons by follow-up time

		Total N	Number of Comparisons							
			Follow-up Time (Months)							
Comparison	RCTs		1	2	3	6	9	12	24	36
Ablation & LNG-IUS	7	422			1	2		7	2	1
COC & Danazol	1	24		1						
COC & Placebo	2	355	2	2	2	2				
COC & LNG-IUS	2	91			1	1	1	2		
Danazol & Prog < 2 wks	3	72	1	1	3					
Placebo & TXA	1	166			1					
LNG-IUS & Prog < 2 wks	1	162			1	1				
LNG-IUS & Prog ~ 3 wks	1	38	1		1					
LNG-IUS & TXA	1	31								
Prog < 2 wks & TXA	1	46	1	1						
Prog ~ 3 wks & TXA	1	94			1					

Efficacy measures

The data on efficacy had a variety of forms: 11 studies reported the proportion of women achieving MBL < 80 mL; 5 studies reported mean and standard deviation of MBL, and 3 reported median and minimum and maximum of MBL; 11 studies reported the proportion of women with PBAC < 100, 8 studies reported mean and standard deviation of PBAC, 2 reported median and quartiles of PBAC, and 1 reported median and minimum and maximum of PBAC. Several studies reported more than one form, even different forms at different follow-up times for the same arm. The data extraction gave preference to the proportion of women with MBL < 80 mL over summary statistics for MBL when both were available, and similarly for PBAC. For four studies, we obtained data on the proportion of women with MBL < 80 mL or PBAC < 100 from a clinical study

report or a subsequent analysis. Only 15 studies reported a mean of MBL at baseline, ranging from 90.3 mL to 300 mL. The average (over study arms with non-missing data) was 169.64 mL.

Posterior summaries

In line with convention we report posterior medians with 95% credible intervals (CrI) (whose endpoints are the 2.5 and 97.5 percentage points of the posterior distribution). Table 2 presents these estimates of efficacy at 3 months (the interval at which patients in the economic model were evaluated). Because the statistical model adjusts for the baseline mean of MBL, those estimates are stated at a baseline MBL of 169.64 mL. Based on available data, estimates after 3 months of treatment indicate the following descending order of efficacy (posterior median): LNG-IUS and endometrial ablation with comparably high response rates (87.5% and 81.6% of women achieving MBL < 80 mL, respectively), followed by danazol (65.8%), progestogens given for close to 3 weeks out of 4 during the menstrual cycle (63.6%), COCs (63.4%), and TXA (48.2%). Progestogens administered for less than 2 weeks out of 4 (14.2%) were not better than placebo (17.7%). The widths of the 95% credible intervals range from 16 percentage points for LNG-IUS to 94 percentage points for ablation. Among the other six treatment classes, four widths range from 28 to 38 percentage points, one is 59, and the other is 75. Thus, most estimates had substantial uncertainty. Only LNG-IUS and COCs had credible intervals that did not overlap the interval for placebo.

Table 2 Efficacy estimates for the 8 treatment classes at 3 months

Treatment	% MBL < 80 mL (95% CrI)
LNG-IUS	87.5 (77.6–93.9)
Ablation	81.6 (5.6–99.7)
Danazol	65.8 (33.6–93.0)
Prog ≈ 3wks	63.6 (20.2–95.0)
COC	63.4 (44.3–78.7)
TXA	48.2 (28.8–65.4)
Placebo	17.7 (7.9–36.1)
Prog < 2wks	14.2 (3.7–41.7)

Posterior median with 95% CrI.

DISCUSSION:

The MTC framework was convenient for synthesizing available evidence and estimating % MBL < 80 mL at various follow-up times, but our focus was not on comparing treatment classes, nor on comparing treatments within classes were (the data generally not sufficient). The validity and reliability of the evidence for compounds within the same class (e.g., COCs) varies among studies, and pooled estimates for treatment classes may not account for some variation in efficacy within the class. The main aim was to estimate efficacy at a follow-up time of 3 months, with corresponding credible intervals, as inputs in a microsimulation economic model evaluating the relative cost and health impact of the eight treatment classes. The analysis produced posterior median estimates of % MBL < 80 mL that plausibly reflect the current evidence: a high level of efficacy for LNG-IUS and endometrial ablation [28] and somewhat lower efficacy for oral treatments. LNG-IUS and ablation, however, are designed for long-term (1 year or longer) reduction of menstrual

bleeding. For women who prefer oral treatments and reversible contraception, COCs are an appropriate option.

Our evidence synthesis used a Bayesian framework, rather than a frequents analysis, because Bayesian methods for indirect comparisons and MTCs are much more fully developed, offer greater flexibility in handling the special features of our data (e.g., availability of both direct and indirect evidence for some comparisons, uncertainty of % MBL < 80 mL and % PBAC < 100 estimated from summary statistics, accounting for missing data), and avoid problems associated with inverse variance weighting based on estimated variances, such as bias and confidence-interval coverage that departs substantially from the nominal value. However, the use of a treatment-class effect, rather than treatment-specific effects within a class, may not fully account for some variation in efficacy between interventions within the same class.

Lethaby et al. also evaluated a number of pharmacological therapies for HMB in a series of systematic reviews. They concluded that oral progestogens administered only during the luteal phase were less effective at reducing MBL than tranexamic acid, danazol, and LNG-IUS. Progestogens taken between day 5 and day 26 of the cycle, however, significantly reduced MBL from baseline, but were less effective than LNG-IUS. Danazol seemed to be more effective than placebo, progestogens, or COC, but confidence intervals were wide (based on pooled data from nine RCTs).

CONCLUSION:

Synthesis of the evidence in an MTC framework yielded plausible estimates of % MBL < 80 mL at 3 months for the eight treatment classes. LNG-IUS and endometrial ablation had the highest efficacy, but the 95% credible interval for ablation was very wide. The widths of the credible intervals reflect the various sources of uncertainty taken into account in the Bayesian model. Thus, more evidence is needed, particularly for the classes of oral treatments. Besides the sparse and fragmented nature of the evidence network, an important source of uncertainty arose from having to estimate % MBL < 80 mL or % PBAC < 100 from summary statistics. Consistent reporting of an outcome measure, reflecting a consensus of investigators studying HMB, could do much to reduce this uncertainty.

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