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Primary Care Management of Abnormal Uterine Bleeding

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

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Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Primary Care Management of Abnormal Uterine Bleeding

Structured Abstract

Objective: The <redacted> Evidence-based practice Center systematically reviewed evidence addressing primary care management of symptomatic abnormal uterine bleeding (AUB), both irregular and cyclic.

Data Sources: We searched MEDLINE®, CINAHL®, and Embase for randomized controlled trials (RCTs) published in English from January 1980 to November 2011 in women with symptomatic AUB. We also searched regulatory data and scientific publications for data about harms.

Review Methods: Using dual review with *a priori* criteria, we excluded 1877 publications because they did not address a key question, were not an eligible study design, or did not apply to the primary care treatment of AUB.

Results: Thirty-six RCTs (six good quality, eight fair quality, and 22 poor quality) evaluated 11 distinct interventions. These included seven studies of the levonorgestrel-releasing intrauterine system (LNG-IUS), 13 of nonsteroidal anti-inflammatory drugs (NSAIDs), six of tranexamic acid (TXA), and five of combined oral contraceptive pills (COCs). The majority of studies made direct comparisons to other drugs. Nine studies enrolled women with irregular uterine bleeding; the remainder focused on women with heavy cyclic bleeding. Among women with irregular menses, metformin, metformin with exenatide, and a tricyclic oral contraceptive improved menstrual regularity. Among women with heavy, cyclic menstrual bleeding all seven studies of LNG-IUS favored the intrauterine system in comparisons that included NSAIDs, COCs, progestogens and usual care. Reduction in menstrual blood loss ranged from 70 to 87 percent less than baseline. NSAIDs reduced bleeding in six of six studies when compared to placebo or progestogens. The degree of improvement was highly variable for individual women. TXA was more effective than progestogens and NSAIDs in three of four studies, and COCs provided benefit compared to placebo in two studies. Harms were rare and trials underpowered to assess harms for all interventions. For most interventions, surveillance studies of longer-term risks were not done in comparable populations.

Conclusions: Two interventions for irregular bleeding (metformin, COCs) and four for heavy cyclic bleeding (LNG-IUS, NSAIDs, TXA, COCs) have low or moderate strength of evidence for effectiveness. Several common interventions lack sufficient evidence. Across agents, data are sparse to evaluate long-term improvements and risk of harms.

Limitations include a predominance of small, short trials lacking standard terminology and diagnostic criteria for identifying and including women with AUB. Tools for collecting outcome data are crude (e.g., collection of sanitary products to measure blood loss) and may contribute to a high rate of attrition. Emphasis on biologic outcomes may neglect the importance of patient-reported outcomes that assess whether symptoms are considered resolved by women themselves.

Contents

Executive Summary ES-1
Introduction 1
Background 1
Condition 1
Terminology 1
Therapies 2
Primary Care Treatment Options 2
Levonorgestrel-Releasing Intrauterine System (LNG-IUS) 3
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) 3
Antifibrinolytics: Tranexamic Acid Therapy (TXA) 3
Combined Oral Contraceptives (COCs) 3
Progestogens 4
Behavioral and Lifestyle Interventions 4
Complementary and Alternative Medicine 4
Scope and Key Questions 5
Scope of the Review 5
Key Questions 6
Analytic Framework 6
Organization of This Report 7
Methods 9
Topic Refinement and Review Protocol 9
Literature Search Strategy 9
Search Strategy 9
Supplementary Information for KQ2 10
Inclusion and Exclusion Criteria 10
Study Selection 11
Data Extraction 12
Quality (Risk of Bias) Assessment of Individual Studies 12
Data Synthesis 12
Strength of the Body of Evidence 12
Applicability 13
Peer Review and Public Commentary 13
Results 15
Introduction 15
Results of Literature Searches 15
Description of Included Studies 17
Key Question 1A: Management of Irregular Uterine Bleeding 19
Description of Included Studies 19
Key Points 20
Detailed Synthesis 20
Key Question 1B: Management of Abnormal Cyclic Bleeding 26
Description of Included Studies 26
Levonorgestrel-Releasing Intrauterine System (Mirena ®) 26
Key Points 26
Detailed Synthesis 26
Description of Results 28
Nonsteroidal Anti-Inflammatory Drugs 32
Key Points 32
Detailed Analysis 33
Tranexamic Acid 43
Key Points 43

Detailed Synthesis 44
Combined Oral Contraceptives 48
Key Points 48
Detailed Synthesis 49
Use of Decision Aids in Treatment of Menorrhagia 52
Key Points 52
Detailed Synthesis 52
Key Question 2: Harms of Interventions for Management of Abnormal Bleeding 53
Description of Included Studies and Sources of Information 53
Key Points for Harms of Reviewed Treatments 54
Detailed Summary 55
Discussion 73
Key Findings 73
State of the Literature 73
Effectiveness of Interventions for Abnormal Bleeding 73
Applicability 76
Summary of Strength of Evidence and Findings 82
Implications for Clinical and Policy Decisionmaking 84
Limitations of This Comparative Effectiveness Review 84
Limitations of the Evidence Base 85
Ongoing Research 86
Future Research Needs 86
Conclusions 87
Abbreviations 89
References 90

Tables

Table A PICOTS ES-2
Table B Strength of Evidence for Improving Menstrual Regularity (KQ1A) ES-12
Table C Strength of Evidence for Improving Heavy Menstrual Bleeding (KQ1B) ES-13
Table 1 PICOTS 5
Table 2 Definitions of Eligible Patient Populations 11
Table 3 Medications From Studies Included in the CER 18
Table 4 Primary Outcomes of Medical Interventions for Irregular Uterine Bleeding 21
Table 5 Primary Outcomes of Medical Interventions for Irregular Uterine Bleeding in Women With PCOS 23
Table 6 Primary Outcomes of Behavioral Interventions for Irregular Uterine Bleeding in Women With PCOS 24
Table 7 Primary Outcomes of Acupuncture for Irregular Uterine Bleeding 25
Table 8 Primary Outcomes of LNG-IUS for Abnormal Cyclic Uterine Bleeding 27
Table 9 Percent Change in Blood Loss From Baseline in Studies of LNG-IUS 29
Table 10 Change in Blood Loss Volume From Baseline in Studies of LNG-IUS 30
Table 11 Primary Outcomes of NSAIDs for Abnormal Cyclic Uterine Bleeding 34
Table 12 Percent Change in Blood Loss From Baseline In Studies of NSAIDs 38
Table 13 Change in Blood Loss Volume From Baseline in Studies of NSAIDs 40
Table 14 Primary Outcomes of TXA for Abnormal Cyclic Uterine Bleeding 45
Table 15 Percent Change in Blood Loss From Baseline in Studies of TXA 46
Table 16 Change in Blood Loss Volume From Baseline in Studies of TXA 47
Table 17 Primary Outcomes of COCs for Abnormal Cyclic Uterine Bleeding 49
Table 18 Primary Outcomes of Decision Aids for Abnormal Cyclic Uterine Bleeding 53
Table 19 Percent of Participants Experiencing Side Effects Reported in Cabergoline Trials 64
Table 20 Strength of Evidence for Improving Menstrual Regularity (KQ1A) 83
Table 21 Strength of Evidence for Improving Heavy Menstrual Bleeding (KQ1B) 83

Figures

Figure 1 Analytic Framework 7

Figure 2 Flow Diagram of Literature Search and Screening (KQ1) 16
Figure 3 Flow Diagram of Literature Search and Screening (KQ2) 17

Appendixes

Appendix A Literature Search Strategies
Appendix B Abstract Review Form (KQ1)
Appendix C Abstract Review Form (KQ2)
Appendix D Full Text Review Form (KQ1)
Appendix E Full Text Review Form (KQ2)
Appendix F Cochrane Risk of Bias Tool
Appendix G Cochrane Risk of Bias Criteria
Appendix H Thresholds for Quality Assessment
Appendix I Evidence Table
Appendix J Risk of Bias and Quality Score for Individual Studies
Appendix K Reasons for Exclusion (KQ1)
Appendix L Reasons for Exclusion (KQ2)
Appendix M Labeled Indications for Drugs Included in Review
Appendix N Harms Extracted from Package Inserts of Drugs Included in Review
Appendix O Systematic Reviews
Appendix P Ongoing Studies

Executive Summary

Background

Abnormal uterine bleeding (AUB) is among the most common gynecologic complaints of reproductive age women in ambulatory care settings. It is estimated to affect 11 to 13 percent of reproductive age women at any given time. Prevalence increases with age, reaching 24 percent in those ages 36 to 40 years.[1, 2] Women generally present for care because the amount, timing, or other characteristics of the bleeding have changed from their individual norm. Population norms for menstrual bleeding, as established by 5th and 95th percentiles, are:[3-6]

- Frequency of menses within a 24 to 38 day window
- Regularity (i.e., cycle-to-cycle variation) within two to 20 days
- Duration of flow from four to eight days
- Blood loss volume from five to 80 ml

Symptoms outside this normal range, or different from normal for the individual, can become problematic and deserve evaluation because they can warn of underlying conditions. The effects of troublesome bleeding reduce quality of life and drive desire for information about causes and treatment options.[1, 7]

Nomenclature to classify AUB has evolved steadily over the past several decades.[8] Early classifications relied primarily on bleeding characteristics, using terms like menorrhagia (i.e., abnormally long or heavy menses) and metrorrhagia (i.e., bleeding at irregular intervals). These terms were often linked with timing and amount to infer whether or not regular and predictable ovulation was occurring. Over time, these differences in terminology and use of operational definitions resulted in inconsistent application of diagnostic terms.[3, 8-10]

Recent international consensus recommendations align terminology by creating two major groupings (i.e., discrete structural vs. nonstructural) for causes of bleeding. This comparative effectiveness review addresses the groups characterized by this recently adopted nomenclature as ovulatory dysfunction and endometrial.

In a recently published research article examining the practice patterns for medical treatment of AUB, authors reported that practicing obstetrician-gynecologists most frequently selected oral contraceptives for the treatment of both ovulatory and anovulatory heavy menstrual bleeding and lacked an overall awareness of current evidence on effectiveness of treatment options for AUB.[11]

There is not a clear consensus on the clinical evaluation of a patient presenting with abnormal bleeding. Recommendations suggest that initial evaluation should confirm the source and timing of bleeding, and exclude certain architectural etiologies (e.g., fibroids, polyps), cancer and precancerous changes in the cervix or uterus, and systemic disease. Current recommendations for management of irregular and abnormal cyclic uterine bleeding include levonorgestrel-releasing intrauterine system (LNG-IUS), nonsteroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics, combined oral contraceptives (COCs), and progestogens.[12-17] Surgical intervention is usually reserved for women with persistent bleeding that does not respond to medical therapy or for women who have finished childbearing and do not wish to indefinitely continue medical therapy.[2, 12]

Scope and Key Questions

The relevant population for this review includes nonpregnant women from menarche to menopause who have had AUB for three months or longer, and have undergone evaluation to rule out structural abnormalities, systemic illnesses, and medications as potential causes. This review evaluates the interventions and direct comparisons among treatments that are often used and promoted as first-line choices, with the goal of clearly describing their effectiveness and potential harms for use in primary care settings. We explicitly defined eligibility criteria using a PICOTS (population, intervention, comparator(s), outcome, timing, and setting) structure (Table A).

Table A. PICOTS

PICOTS Element	Description
Population:	Nonpregnant women from menarche to menopause who have had abnormal bleeding for three months or longer whose bleeding is not caused by structural abnormalities, systemic disease, cancer, or medication. Two specific subtypes of abnormal bleeding will be the focus: • *Irregular uterine bleeding:* problem bleeding of three months or greater duration, excluding regular cyclic/menstrual patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, and related systemic disease. • *Abnormal cyclic uterine bleeding*: problem bleeding of three months or greater duration, excluding irregular and unpredictable patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, and related systemic disease.

Interventions[1]:	• Medical therapies
	  o Nonsteroidal anti-inflammatory drugs
	  o Antifibrinolytics
	  o Oral hormone treatments (e.g., oral contraceptives, progestogens)
	  o Levonorgestrel-releasing intrauterine system
	  o Vaginal ring contraceptive device
	• Behavioral strategies (e.g., stress reduction, weight reduction, exercise)
	• Complementary and alternative medicine therapies (e.g., acupuncture, herbal medicine)

Comparator:	Direct comparison among interventions listed above or comparison to placebo.
Outcomes:	• Bleeding profile (e.g., amount, frequency, duration, pattern, symptom bother, hematocrit) • Quality of life including both bleeding specific and general quality of life measures • Pain related to bleeding • Sexual function as reported by sexual function measures, general measures of sexual activity, frequency and satisfaction • Patient satisfaction with outcomes and acceptability of treatment • Fertility • Time to conception • Additional interventions including concurrent and consecutive surgical and nonsurgical treatments • Harms[2] (e.g., thromboembolic events, emotional side effects, weight gain, short- and long-term harms)
Timing:	Interventions initiated after symptoms present most months for three months or longer.
Setting:	Research populations that are applicable to care of women receiving evaluation and treatment in primary care settings including general gynecology.

[1] Surgical interventions and procedures such as endometrial ablation are excluded.
[2] Includes treatment-related adverse events (e.g., drug side effects); does not include consequences related to the failure to adequately treat the symptom.

Key Questions (KQs)

Key Question 1A (KQ1A)

What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with irregular uterine bleeding?

Key Question 1B (KQ1B)

What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with abnormal cyclic uterine bleeding?

Key Question 2 (KQ2)

What are the harms, including adverse events, associated with medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) in women with irregular uterine bleeding or abnormal cyclic uterine bleeding?

Analytic Framework

We developed the analytic framework (Figure 1 of full report) based on clinical expertise and refined it with input from a Technical Expert Panel. The analytic framework illustrates the population, interventions, outcomes, and adverse effects that guided the literature search, study eligibility, screening, and synthesis. Input from the Key Informants was crucial in shaping the analytic framework.

Methods

Literature Search

For KQ1, we searched MEDLINE®, CINAHL®, and Embase. Search results were limited to papers published in English, and published in or after 1980. Search strategies used a combination of subject headings (i.e., controlled vocabulary) and keywords. (Appendix A of full report). We also searched the reference lists of included publications and recent systematic reviews related to management of AUB. For KQ2, we expanded our search of primary literature to include standard drug package inserts, and structured a separate literature search to identify publications that conducted surveillance for harms in large datasets. (Appendix A of full report)

Inclusion and Exclusion Criteria

We predefined inclusion and exclusion criteria related to the study population, intervention, comparators, outcomes, timing, and setting in order to assess the eligibility of the search results. Eligible studies had to explicitly define and describe the study population, interventions, and outcomes. We included randomized controlled trials (RCTs) of primary care interventions for women with irregular or abnormal cyclic uterine bleeding. We excluded studies of women with AUB caused by systemic disease, structural abnormalities, cancer, or medication side-effects. For KQ1A we included studies of women with polycystic ovarian syndrome (PCOS) if the

patient baseline and outcome data included information on cycle regularity. We excluded studies of women with infertility if the primary treatment goal was conception. Harms data to address KQ2 was captured from the included RCTs for KQ1, reports based on pharmacoepidemiological databases, large observational studies, large case-controlled studies, and postmarketing surveillance data.

Study Selection

We developed screening forms to assess eligibility for inclusion in the review for KQ1 and KQ2. We revised the forms following testing by the team. We conducted screening in two phases: abstract and full text screening. Publications were promoted to full text review when one reviewer indicated that the publication met all inclusion criteria or when the title and abstract did not provide adequate information to make a determination. Two reviewers independently reviewed each publication at the full text screening phase. Discordant classifications were resolved in team meetings including senior investigators.

Data Extraction

Two reviewers independently extracted relevant data from all included publications using a predefined evidence table shell. A senior investigator reviewed the evidence tables for accuracy and completeness. The final evidence tables are provided in Appendix I of the full report.

Quality (Risk of Bias) Assessment

We assessed quality of RCTs trials using the Cochrane Collaboration Risk of Bias Tool,[18] which evaluates domains including sequence generation, allocation concealment, blinding, outcome data reporting, and reporting bias. Two independent reviewers assessed risk of bias as low, high, or unclear for each domain. We used a pre-established threshold of criteria to rate the quality of each study based on the risk of bias assessment as good, fair, or poor. Discordant assessments were resolved in team meetings including senior investigators. A summary of all component items and overall risk of bias/quality score for each included study is provided in Appendix J of the full report.

Data Synthesis

We provide a systematic narrative synthesis of the available data from original research studies of acceptable quality for nonsurgical treatment of AUB. We present individual study data, grouped by KQ and then intervention. Within segments we have ordered interventions from those with the larger number of studies to fewer. Detailed study information is provided in evidence tables included in the appendix of the main report.

A meta-analysis was not feasible for this review. Few studies had comparable treatment doses, interval, or duration of followup. Among those that did, the ability to aggregate data is limited by differences in outcomes measures which included measures of blood loss from sanitary product collection, self-report using scoring systems, and self-reported using standardized pictorial systems. For regularity of bleeding no two measures of outcome were the same.

Strength of the Body of Evidence

For KQ1, we used explicit criteria to grade the overall strength of the evidence (e.g., low, moderate, high, and insufficient)on each intervention. We used established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes), the quality of evidence (i.e., from the quality ratings of individual articles), directness of the outcomes for informing the KQs, and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound principles of clinical or behavioral research and practice. For KQ2, we did not rate of strength of evidence because a fully inclusive assessment of harms could not be completed for each of the 11 interventions that have been widely studied in populations that lack direct applicability to this report.

Applicability

We assessed applicability of the results from the literature to the population of women with abnormal cyclic and irregular uterine bleeding. Using the PICOTS framework, we identified factors that may limit the applicability of individual research studies. We summarized the applicability of the body of evidence and described key elements from the PICOTS framework that characterize the applicability of the identified studies.

Results

For KQ1, we identified 1915 titles and abstracts for screening; 204 publications were identified as potentially eligible for inclusion and were promoted for full text review. We identified 38 publications from 36 unique studies that met criteria for inclusion. Nine studies included in the review addressed KQ1A; 29 publications representing 27 studies addressed KQ1B. We conducted a separate search and screening process for KQ2. We identified 2650 titles and abstracts for screening. Of these, 750 references were promoted for full text review. Using predefined criteria, we found 19 publications about harms that were eligible for inclusion. We obtained package inserts for each KQ1 included drug intervention.

Description of Included Studies (KQ1)

Thirty-six included studies evaluated NSAIDs (13 studies),[19-31] the LNG-IUS (seven studies),[19, 32-37] tranexamic acid (TXA) (six studies),[20, 25, 31, 38-40] COCs (six studies),[22, 32, 34, 41-43] metformin (three studies),[44-46] progestogens (one study),[47] cabergoline (one study),[48] lifestyle/behavioral changes (two studies),[49, 50] acupuncture (two studies),[49, 51] and patient decision aids (three studies)[52-54] using at least one comparator or placebo arm. The total number of interventions addressed is greater than the number of studies because of direct comparisons between one or more interventions within single studies. Study duration was typically six months or less. Four of the studies addressing KQ1B included a followup of one to two years.

KQ1A. Management of Irregular Uterine Bleeding

Nine RCTs addressed restoring menstrual regularity in those with irregular uterine bleeding. Three were conducted in the United States,[41, 46, 50] two in Italy,[45, 48] and one each in China,[51] Sweden,[49] Turkey,[47] and the United Kingdom.[44] The studies ranged in size from 13 to 201 participants and examined the efficacy of metformin (three studies),[44-46] progesterone (one

study),[47] triphasic birth control pills (one study),[41] cabergoline (one study),[48] diet and exercise (one study),[50] and acupuncture (two studies).[49, 51] The majority compared treatment to placebo or sham intervention; three included comparisons of effectiveness of two interventions. Two studies were classified as good quality,[41, 48] two studies as fair quality,[44, 51] and five studies as poor quality.[45-47, 49, 50]

Metformin and Exenatide

Metformin was an active treatment arm in three RCTs conducted among women with PCOS. Two RCTs compared metformin outcomes to a placebo group[44, 45] and one three-armed study compared metformin only, exenatide only, and both.[46] In each case, compared to baseline or placebo, metformin was effective for improving the regularity of bleeding over a number of months.[44, 45] Combination therapy improved cycle frequency better than metformin or exenatide alone in 60 women with PCOS.[46]

Progesterone

Vaginal and oral progesterone were studied in a single trial among women clinically classified as having dysfunctional uterine bleeding.[47] In this RCT, both routes of administration improved cycle regularity with 92 percent and 85 percent of participants, respectively, achieving cycle length of less than 35 days and no intermenstrual bleeding by the third cycle of use. Effects were statistically comparable, but the trial was not powered to show equivalence or noninferiority.

Combined Oral Contraceptives

A triphasic oral contraceptive was also studied in a single RCT among women with irregular uterine bleeding.[41] This trial included women with both short and long intervals between bleeding episodes and with both heavy and normal amounts of bleeding. The outcomes are provided by the authors in aggregate and not presented by initial bleeding characteristics. Overall, 68 percent of women taking the COC achieved excellent or good cycle control as assessed by the study investigators compared to 26 percent of those receiving a placebo.

Cabergoline

In a very preliminary investigation of cabergoline,[48] a drug indicated for the treatment of prolactinoma, treatment over six months was associated with return of regular menses in three of eight women compared to none of six receiving placebo. Women in the study had PCOS and normal prolactin levels.

Behavioral and Lifestyle Interventions

Among adolescents with PCOS, both a low-fat, calorie-restricted diet and a carbohydrate-restricted diet in conjunction with 30 minutes of aerobic activity three days a week resulted in more regular menses among those who lost weight.[50] This single small study did not present outcomes by the diet group to which participants were randomized. Presumably there was not a clear difference, meaning there is no evidence for which dietary approach to choose. A single trial of acupuncture in 84 women[49] also included an exercise control group at the same intensity as the diet and exercise trial. This group experienced a meaningful improvement in their menstrual frequency (42% increase from baseline as calculated by the study investigators) that

was comparable to acupuncture at 32 weeks. We did not find evidence comparing diet to exercise directly.

Complementary and Alternative Medicine

Two studies of acupuncture with different underlying hypotheses and different methods (conventional acupuncture and low-frequency electroacupuncture) found benefit for a specific style of acupuncture when compared to no intervention or alternate placement of acupuncture needles.[49, 51] By 32 weeks in the trial of electroacupuncture for PCOS,[49] women who received 14 acupuncture treatments over 16 weeks had a 121 percent improvement in cycle regularity while those who exercised only had a 42 percent improvement. Both were statistically comparable in this small trial. Both acupuncture and exercise were superior to no treatment. In the trial of two differing placements of needles every other day for three cycles,[51] women who received treatment for "mind tranquilizing and menstruation promotion" had greater improvements (no treatment failures among 21 women) compared to those receiving traditional placement (n=16) for "delayed menses" among whom 19 percent did not have improvements.

KQ1B. Management of Abnormal Cyclic Bleeding

We identified 29 publications representing 27 studies addressing primary care nonsurgical interventions for the management of abnormal cyclic uterine bleeding. The interventions evaluated in the studies included the LNG-IUS (seven studies),[19, 32-37] NSAIDs (13 studies),[19-31] TXA (six studies),[20, 25, 31, 38-40] or COCs (five studies).[22, 32, 34, 42, 43] We also identified three studies that evaluated decision aids for the management of AUB.[53-55] Included studies described nonsurgical interventions and compared these interventions to another intervention (15 studies),[19, 20, 22, 24, 25, 28, 29, 31-36, 39, 40, 55] placebo (eight studies),[21, 23, 26, 27, 30, 38, 42, 43] or usual care (four studies)[37, 52, 53, 54] Studies were conducted in 16 countries (United States, Canada, the United Kingdom, Australia, Finland, the Netherlands, Sweden, Czech Republic, Germany, Hungary, Poland, Ukraine, Turkey, India, Egypt, and Brazil). Of the 27 included studies, four studies were assessed as good quality,[26, 38, 42, 43] six as fair quality,[21, 29, 30, 33, 36, 40] and 17 as poor quality.[19, 20, 22-25, 27, 28, 31, 32, 34, 35, 37, 39, 52-54]

Levonorgestrel-Releasing Intrauterine System

LNG-IUS was an effective intervention for reduction of heavy menstrual bleeding in all seven of the identified studies.[19, 32-37] Five studies measuring menstrual blood loss (MBL) directly from collected sanitary materials documented 70 to 87 percent reductions in bleeding when comparing treated women with their baseline.[19, 32-34, 36] When measured, 80 percent or more of women who were enrolled because they met criteria for heavy menses achieved normal total blood loss. These improvements were significantly greater than changes in comparison groups treated with NSAIDs, COCs, progestogens, and usual care. Evidence suggests the LNG-IUS effectively reduces self-reported symptom severity and duration of bleeding. In a single study that evaluated whether women ultimately selected hysterectomy, hysterectomy was less likely in the LNG-IUS group compared to the usual care arm.[37]

Nonsteroidal Anti-Inflammatory Drugs

In 13 studies, NSAIDs including mefenamic acid, naproxen, meclofenamate, and flurbiprofen given at the onset of menses for up to five days reduce MBL when compared to

baseline.[19-31] NSAIDs are effective when compared to placebo.[26, 30, 56] Overall six of 13 studies provided statistical comparisons to baseline only. Evidence is equivocal, one trial each, showing NSAIDs are similar in effectiveness or superior to progestogens.[24, 28] When measured, specific NSAIDs have been shown to reduce blood loss by 20 to 59 percent.[19-22, 24-26, 29-31, 56] While NSAIDs can significantly reduce MBL, they did not consistently reduce bleeding to levels considered clinically normal (i.e., less than 80 ml) in all patients. There was considerable variability in response, with some patients experiencing an increase in blood loss during treatment. Studies evaluated treatment durations from one to six menstrual cycles. There were no differences in MBL between NSAIDs and oral progestogens, COCs, and Progestasert®, a progesterone-releasing intrauterine system that is no longer marketed. There were also no differences seen between individual types of NSAIDs, specifically mefenamic acid and naproxen. The most recent study found similar reductions in patient-reported assessments of bleeding severity when NSAIDs plus TXA was compared to TXA alone.[31]

Tranexamic Acid

All six RCTs including TXA treatment demonstrated effectiveness for improving heavy bleeding.[20, 25, 31, 38-40] TXA at a dose of 2.0 to 4.5 g per day for four to five days from the onset of bleeding led to a clinically significant reduction in MBL, ranging from a 40 to 60 percent decrease in studies lasting up to a year. Both biologic and self-reported symptoms of bleeding severity were improved. In comparison to progestogens, COCs, and NSAIDs, TXA provided greater reduction in MBL, however not all trials presented statistical analysis for head-to-head comparisons. No head-to-head comparisons of TXA versus LNG-IUS were identified.

Combined Oral Contraceptives

Five RCTs included groups treated with COCs.[22, 32, 34, 42, 43] The two primary studies which were comparisons to placebo found COCs effective for reducing menstrual bleeding and days of bleeding.[42, 43] Measured reduction in bleeding was from 43 to 68 percent with complete normalization of total volume of bleeding achieved in 30 to 44 percent of women. One crossover comparison to mefenamic acid in 24 participants found both to be effective but lacked power to determine if either treatment was superior.[22] In the two head-to-head comparisons between COCs and LNG-IUS,[32, 34] reductions in heavy menstrual bleeding were documented in both treatment groups. Women with a LNG-IUS had greater benefit.

Decision Aids

Three studies investigated decisions aids to assist women seeking treatment for heavy cyclic bleeding in making informed decisions about care.[52-54] Their findings suggest these tools do increase patient knowledge and enhance satisfaction with care. Overall decision aids did not result in choices that influence disease symptoms in directly measurable ways. One study found fewer women who received the decision aid ultimately choose surgical referral and hysterectomy.[53] However this treatment choice cannot necessarily be linked to improvement in bleeding symptoms.

KQ 2. Harms of Interventions for Management of Abnormal Bleeding

Capturing useful information about potential harms of treatment for reproductive-age women that is specifically applicable to interventions for abnormal bleeding is a challenge because many

agents have multiple indications and harms are often not well-studied in reproductive-age women. A wide range of interventions are used to treat abnormal bleeding. Eleven interventions relevant to the primary care setting were identified for this report. In this section we have restricted brief summaries to medications only (behavioral and lifestyle interventions, acupuncture, and decision support tools, each with little potential for serious harm, are discussed in the full report). We summarized harms and present findings in this order:

- Addressing the clinical trials included in this review.
- Compiling the key content of package inserts.
- Searching for surveillance studies that aimed to examine risk of harm in large populations of individuals (i.e., 1600 or more) for specific interventions.
- Providing information from existing contemporary reviews and guidance on harms for common medications with broad indications.

We have grouped the interventions together, presenting those for abnormal irregular bleeding first, followed by those for cyclic bleeding. In instances in which the agent was used for both conditions the information is presented only once.

Metformin and Exenatide

In the included trials metformin is associated with increased gastrointestinal (GI) symptoms including abdominal pain, nausea, and diarrhea.[44-46] This is compatible with the package insert.[57] Severe harms of metformin detected in larger studies, typically among older adults with type 2 diabetes, include lactic acidosis, serious hypoglycemia (most often in combination with other agents) and liver failure. Incidence of such serious harms is below 1 in 10,000 and may be as low as 1 per 100,000 person-years of exposure.[58]

Exenatide is typically used as a second agent when adequate glycemic control is not achieved with a single diabetes treatment. Its harm profile is uninformed by the literature in this review which included only one study with 40 women treated.[46] The package insert suggests hypoglycemia is the most serious side effect,[59] and large scale surveillance studies have not confirmed initial concerns that pancreatitis was more common among those treated.[60, 61] Reviews including data about harms identify metformin as a first-line agent of choice for diabetes management, and concur that both agents are associated with excess GI complaints. [62-64]

Progesterone

Route of progesterone administration was compared in one comparative effectiveness trial for women with irregular menses.[47] In the remaining studies, progestogens were included as the comparator arms (in each case hypothesizing and documenting the superiority of the agent under study) or within COCs.[24, 28, 33, 35, 36, 39, 40] The progesterone containing IUD is separately reviewed below.

Progestogens, like oral progesterone, depot medroxyprogesterone acetate (DMPA), and vaginal gel are associated with increased complaints of weight gain, fluid retention, abdominal pain, nausea, change of mood, and change in appetite. Many of these were documented in the included studies which were typically under-powered or made comparisons to other active agents, making comparisons of risk of side effects less informative. Among the most common complaints associated with progestogens is irregular bleeding. The package inserts also note potential dangers of exposure to high doses in pregnancy and rare outcomes such as porphyria

which has been linked to the specific agents, dydrogesterone and provera, the former at rates that resulted in dydrogesterones not being available in the United States.[65]

A surveillance study has linked DMPA to increased future rate of fractures (though analyses were not controlled for key confounders like smoking and BMI), [66] while another large study showed recovery of normal bone density within two to three years of ceasing use.[67] Some data suggest use of progestogens is associated with increased risk of deep venous thrombosis, though intriguing research restricted to those using particular drugs for the indication of heavy menses demonstrates that women with heavy menses have higher risk of deep vein thrombosis regardless of the intervention they use suggesting some degree of confounding by the indication for which the drug is given.[68] Reviews and meta-analyses confirm common side effects, including progestogens being a cause of irregular bleeding.[69]

Combined Oral Contraceptives

Primary care providers and many women are aware of the most serious risks of COCs and the more common side-effects including edema, nausea, breast tenderness, skin changes, and GI symptoms. The studies in this review reported harms profiles for common symptoms similar to package insert documents.[70-73] Certain risks like that for venous thromboembolism, myocardial infarction, cerebral hemorrhage, hypertension, gallbladder disease and benign liver tumors are also well documented. Patients and clinicians should be alert to contraindications which include cigarette smoking, advancing age (with 35 often used as a threshold), and predisposition to thrombotic events. Two recent systematic reviews have reiterated increased risk for deep venous thrombosis with a suggestion that risk is lowest in those COCs containing levonorgestrel or norgestimate as the progestogens.[74, 75]

Cabergoline

The sole study of cabergoline in this review was exploratory with 14 women with PCOS and 15 normal controls.[48] When used for treatment of prolactinoma, this drug is associated with nausea, headache, dizziness, lack of energy, and constipation. Cochrane reviews on three different conditions for which it has been explored find no difference in overall risk of harms compared to the placebo arms,[76, 77] however a review of use for Parkinson's patients revealed increased valvular heart disease on echocardiogram with few symptomatic individuals.[78, 79] The applicability of this data to young women with irregular menses is very limited.

Levonorgestrel-Releasing Intrauterine System

Participants in the included trial of use of the LNG-IUS for abnormal cyclic bleeding had few serious complications. Common side effects include changes in bleeding pattern including spotting and complete absence of menses. Abdominal pain/bloating, headache, depressed or altered mood, heavy bleeding, breast tenderness, and intrauterine device (IUD) expulsion are expected to occur in approximately five percent or more of women using this treatment, as reflected in package inserts.[80, 81] Surveillance studies provide good estimates from large registries of users. Difficult insertions occur in three to four percent of women, with painful insertion occurring in about one percent.[82, 83] Risk of uterine perforation is between 0.9 and 2.6 per thousand users and the majority are not recognized at the time of insertion.[82, 84-86] Nulliparous status and non-contraceptive indications do not appear to influence risk of perforation. Hair loss, that is known to be reversible in many but not all patients, occurs in about 1.8 per thousand users.[84] The LNG-IUS is not associated with increased risk of deep vein thrombosis in more than

8 million person-years of observation.[87, 88] Systematic reviews match package insert and surveillance data also noting that expulsion is not rare.[69, 89, 90]

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are generally dosed intermittently in young women with problem bleeding. This makes detection of harms challenging. Complaints commonly reported in trials included: abdominal pain, nausea, gastritis, and light headedness or dizziness. Less common events included rashes and itching. These agents include a boxed warning on the product labels about cardiovascular and GI risks.[91-93] Upper GI bleeding occurs in approximately one percent of patients treated for three to six months and at higher rates with longer use.[92, 94, 95] However, the majority of use assessed in this way is chronic, daily use. Product materials do note that short term use is not without risk but do not provide risk estimates. Other common side effects include edema, abdominal pain, constipation, nausea, vomiting, heart burn, headache, nervousness and conflicting central nervous system complaints like anxiety and tremor as well as malaise and somnolence. A pooled analysis of trials found mild neurologic and GI adverse events more common in those treated than among placebo users.[96] The available reviews note additional investigation is required to clarify potential cardiovascular risks.[97, 98]

Tranexamic Acid

Within studies in our review similar numbers of participants withdrew from TXA treatment arms as from placebo and comparison groups.[38, 39] Side effect profiles were similar across those treated and untreated with the agent who remained in trials. The Food and Drug Administration has examined concerns about changes in QT-interval changes on electrocardiograms, but overall the number of subjects included in trials was considered to be low for evaluating harms and drug safety.[99] The updated prescription label now includes headache, nasal and sinus symptoms, back pain, and abdominal pain as occurring in more than 10 percent of those taking the drug.[100] Joint pain, muscle cramps and spasms, migraine, anemia, and fatigue occur in more than five percent. Post-marketing reports have identified thrombosis, allergic reactions including anaphylaxis, and visual disturbances.[100] This led to contraindications similar to those for COCs recommending that women with any history of thrombotic disease, risk for thrombotic disease, who smoke, are over age 35, or who concomitantly use tissue plasminogen activator, avoid the drug. Several reviews have examined harms and concluded that GI effects are most common and no thrombotic events were identified in 10 study populations.[101-104] It is important to note that overall these trials are small and large-scale surveillance data over time will likely be required for definitive answers.

Discussion

Summary of Strength of Evidence and Findings

Overall the evidence to answer key questions about the management of AUB did not reach standards for high strength of evidence for any intervention. This was particularly true in the literature relevant to treatment of women with irregular uterine bleeding. COCs, as represented in a single good placebo controlled trial with a total of 201 participants, documented effectiveness.[41] The treatment effect was large and combined these factors provided moderate evidence of benefit. Use of metformin is supported by low strength of evidence predominately

related to small trials of somewhat limited quality. For the remainder of the interventions investigated for management of irregular uterine bleeding, there is insufficient evidence that follows from single or lower quality studies, or both. The strength of evidence tables that follow summarize the total number of studies and within those studies the number of women who received the specific intervention. The tables also provide the assessment of the risk of bias, consistency of findings across trials, directness of the evidence that treatment improves the symptom, and precision of the estimates provided by the literature.

Table B. Strength of evidence for improving menstrual regularity (KQ1A)

Intervention Quality: Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence	Notes
Progestogen Poor: 1(69)[47]	High	NA	Direct	Imprecise	Insufficient	Data not analyzed by arm; compared to baseline only
COC Good: 1(101)[41]	Low	NA	Direct	Precise	Moderate	Cycle control improved for 87% in ITT analysis
Metformin Poor: 2(31)[45, 46] Fair: 1(45)[44]	Medium	Consistent	Direct	Imprecise	Low	Cycle control improved, drop-out rates high in treated
Exenatide Poor: 1(20)[46]	High	NA	Direct	Imprecise	Insufficient	Single trial arm, superior to metformin alone when added
Cabergoline Good: 1(8)[48]	Low	NA	Direct	Imprecise	Insufficient	Small pilot
Diet Poor: 1(24)[50]	High	NA	Direct	Imprecise	Insufficient	Data not analyzed by arm, no ITT
Exercise Poor: 1(34)[49]	High	NA	Direct	Imprecise	Insufficient	No controlled comparisons
Acupuncture Poor: 1(33)[49] Fair: 1(23)[51]	High	Consistent	Direct	Imprecise	Insufficient	Small studies, preliminary evidence of benefit, no masking

Abbreviations: NA: not applicable; ITT: intention to treat.

For management of heavy cyclic bleeding the literature was more robust. COCs are supported by high strength of evidence for the purpose of decreasing MBL. The LNG-IUS, various NSAIDs, and TXA are also effective for reducing the amount of measured menstrual bleeding and are each supported by moderate strength of evidence. In head-to-head comparisons with statistically significant differences, the LNG-IUS has one trial showing superiority to NSAIDs[19], two showing superiority to COCs,[32, 34] and two showing superiority to progestogens.[33, 35, 36] COCs were equivalent in one trial compared to an NSAID.[22] TXA was also superior to NSAIDs,[20, 25] and when combined with an NSAID was superior to TXA alone.[31] Most of these interventions have been shown to have additional positive effects, typically including shorter duration of bleeding and improvement is symptoms when participants used standardized scoring systems to report on treatment response.

Table C. Strength of evidence for improving heavy menstrual bleeding (KQ1B)

Intervention Quality: Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence	Notes
LNG-IUS Poor: 5(173)[19, 32, 34, 35, 37] Fair: 2(104)[33, 36]	Medium	Consistent	Direct	Precise	Moderate	71% reduction in bleeding
NSAID Poor: 7(141)[20, 22-25, 27, 28] Fair: 3(129)[21, 29, 30, 56] Good: 1(32)[26]	Medium	Consistent	Direct	Imprecise	Moderate	20 to 59% reduction in bleeding
TXA Poor: 4(202)[20, 25, 31, 39] Fair: 1(25)[40] Good: 1(123)[38]	Medium	Consistent	Direct	Precise	Moderate	40 to 45% reduction in bleeding
COC Poor: 3(90)[22, 32, 34] Good: 2(269)[42, 43]	Low	Consistent	Direct	Precise	High	Reduced bleeding, improved iron levels
Progesterone Poor: 1(50)[39] Fair: 1(21)[40]	High	Consistent	Direct	Imprecise	Insufficient	Comparator in trials that favored the other intervention, little benefit

Applicability

Applicability describes the extent to which study populations, interventions, and outcomes in this literature apply to the group for which one plans to apply research evidence. Studies for this review were intended to provide information to inform primary care management of AUB, whether irregular or cyclic. To a large degree, through shaping of the methods for this review, we have engineered the report so that the included research is applicable to primary care of women with these complaints in the United States. Because we narrowed our focus to symptomatic women of reproductive age with chronic complaints of abnormal bleeding, this comes at the cost of fewer studies being addressed. However, it assures that studies included were explicitly designed to examine the effectiveness of the treatments for improving the outcomes of interest in the populations of interest. Applicability of the findings is therefore high.

For each intervention, it is important to note the following provisions. The results of this review apply for women:

- Who are reproductive age and state they have an irregular pattern of menstrual bleeding or heavy cyclic menstrual bleeding;
- Without abnormal findings on pelvic exam or on ultrasound report (fibroids, polyps);
- Without an IUD in place, and who are not pregnant or lactating;
- Who are healthy, and without renal impairment, hepatic impairment, intestinal disease, thyroid disease, abnormal cervical cytology, noncyclic bleeding, history or presence of significant medical problems (e.g., thromboembolic disease, coagulopathy, subarachnoid hemorrhage, endocrine disorders, or eye disease);
- For whom any additional clinically determined diagnostic and screening tests have been completed to rule out other causes of abnormal bleeding;

- Does not have any of the contraindications found in the Food and Drug Administration sources discussed in the main document and do not have risks of drug-drug interactions if they take multiple prescription medications.

This review was not designed to guide evaluation of women with abnormal bleeding, rather to address what treatments have evidence of effectiveness once the diagnosis is established and primary care management is to be initiated.

Overall applicability was high. However, often women who are in trials do not reflect the full range of those with abnormal bleeding seen in primary care. Study participants were more likely to be normal weight, nonsmokers, with few, if any concomitant conditions. The interventions (except in the case of specific comparators as noted) are available in the same doses and formulation in the United States. Outcomes such as measured blood loss, self-reported symptom severity and days of bleeding are of direct relevance to women with abnormal bleeding. Our findings are sparse for outcomes which can be considered essential for a condition like AUB that are defined by symptoms. Important outcomes include satisfaction with response to treatment, definitive assessments of whether or not the women considered their complaint resolved, and whether they wished to continue the same treatment or add additional treatments. Followup in general was brief, so the findings may not apply well to management of a chronic condition like abnormal bleeding. This makes findings about assessments of harms challenging since use of interventions over extended periods may have different risk profiles from short timeframes like one to six cycles.

Research Gaps

Recent improvements in unifying nomenclature and formalizing consensus definitions for the clinical groupings of bleeding abnormalities[105] will likely continue to have a positive influence on the ability to properly interpret the findings of individual studies, to identify groups of studies with comparable methods, and to aggregate results. An array of methodologic recommendations and specific research needs are detailed in the full report. Common themes included the need for larger, better controlled RCTs, with combinations of biological and patient-reported outcomes and that evaluate outcomes over longer periods of time, at least past one year. Populations need to become more representative of those seeking care (teens, heavier women, those with common comorbidities like diabetes) and need to more directly address common clinical interventions like COCs and progestogens that are represented in the literature by a surprisingly small number of older studies, given how ubiquitous their application is in clinical care. No studies examine trajectories through care, mapping sequential treatment options or costs of care based on the initial treatment strategy assigned. No studies examined combining effective treatments, especially in women who had improvements but did not reach satisfactory control of bleeding or cycle regularity. Overall trial designs should begin to shift towards effectiveness from efficacy, moving beyond the level of proof of concept that is required for drug and device approval to a deeper level that can better inform care, cost considerations and policy.

Conclusions

Women who have problematic irregular or heavy cyclic menstrual bleeding have a number of treatment options available that are supported by systematic review of the research literature. These include high strength of evidence that COCs can improve menstrual regularity for women

with irregular bleeding patterns. Metformin is supported by moderate strength of evidence for improving cycle regularity especially among women with PCOS. This provides both a contraceptive and a noncontraceptive option for irregular menses. Other interventions like progestogens are associated with statistically and clinically meaningful improvements from baseline patterns, however the overall evidence is insufficient from well-designed, larger studies with ability to directly compare treatment arms rather than only pre-post measures within groups.

Multiple interventions for heavy cyclic bleeding are supported by evidence that they reduce MBL. These include strong evidence that COCs are effective and moderate strength of evidence that the LNG-IUS, NSAIDs, and TXA reduce bleeding relative to baseline, decrease total volume of bleeding when comparisons are made across treatment groups, and when measured, decrease days of bleeding per cycle. In direct comparisons, LNG-IUS is superior to NSAIDs. TXA is superior to NSAIDs and TXA combined with an NSAID was superior to TXA alone. Results from COC and NSAID comparisons suggest comparable effectiveness. Not all women who are treated with any of these interventions that can be effective will improve. Across agents data are sparse to evaluate long-term improvements and risk of harms.

Limitations include a predominance of small, short trials lacking standard terminology and diagnostic criteria for identifying and including women with AUB. Tools for collecting outcome data are crude (collection of sanitary products) and may contribute to a high rate of attrition. Biologic outcomes, like measured blood loss and hemoglobin or hematocrit levels, may neglect the importance of patient-reported outcomes that assess whether symptoms are considered resolved by women themselves. Nevertheless, the variety of effective options suggests many women can achieve symptom relief and will have available to them choices that address both symptoms and contraceptive or fertility desires, as well as potentially improving other symptoms like menstrual cramping.

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Introduction

Background

Condition

Abnormal uterine bleeding (AUB) is among the most common gynecologic complaints of reproductive age women in ambulatory care settings—of similar frequency to the number seeking care for urinary tract infections and vaginitis. In the general population, AUB is estimated to affect 11 to13 percent of reproductive age women at any given time; this prevalence increases with age, reaching 24 percent in those ages 36 to 40 years.[1, 2] In addition to gynecologists, all primary care practitioners including pediatricians, family physicians, advanced practice nurses, and internists, will encounter the need to evaluate, treat, or refer women with bleeding-related symptoms.[3] Women generally present because the amount, timing, or other characteristics of the bleeding have changed from their individual norm.

Population norms for menstrual bleeding, as established by 5th and 95th percentiles, are:[4-7]

- Frequency of menses within a 24 to 38 day window
- Regularity (cycle-to-cycle variation) withint wo to 20 days
- Duration of flow from four to eight days
- Volume of blood loss from five to 80 ml

Symptoms outside this normal range, or different from normal for the individual, can become problematic and deserve evaluation because they can warn of underlying conditions. Common problems include worry about the cause, embarrassment if the bleeding includes flooding type bleeding with saturation of clothing, missed work and responsibilities, limitations of social activities and exercise, decreases in sexual activity, and frustration with costs of sanitary protection.[1, 8] Collectively, the effects of troublesome bleeding reduce quality of life and drive desire for information about causes and treatment options.[1, 8]

There is not a clear consensus on the clinical evaluation of a patient presenting with abnormal bleeding. Recommendations suggest that initial evaluation confirm the source and timing of bleeding, and exclude certain architectural etiologies, cancer, and systemic disease. The International Federation of Gynecology and Obstetrics (FIGO) classification recommends a structured history followed by uterine evaluation.[9] Diagnostic approaches are not within the scope of this review;[10, 11] however, the review will capture the operational definitions and address applicability in the analysis of the relevant literature.

AUB is a diagnosis of exclusion in which there is abnormal bleeding (i.e., quantity, frequency, duration, or regularity) from the uterus not caused by pelvic disease, uterine fibroids, ovarian cysts, endometrial polyps, coagulation disorders, malignancy, inflammation, medical illness, or pregnancy.

Terminology

Nomenclature to classify symptomatic problem bleeding has evolved steadily over the past several decades.[12] Early classifications primarily used characteristics of the bleeding to group women. Terms like menorrhagia (abnormally long or heavy menses) and metrorrhagia (bleeding at irregular intervals), were often linked with timing (short or long intervals) and amount (heavy

or light) to infer whether or not regular and predictable ovulation was occurring and further assign likely ovulatory or anovulatory status. These terms are generally applied without formal documentation of ovulatory status. Furthermore, previously applied terms like dysfunctional uterine bleeding also carried a variable element of recognition that the label was a diagnosis of exclusion.[12] The resulting challenge was that practitioners and researchers applied different exclusions before selecting interventions or enrolling patients. Over time, differences in terminology choice and in operational definitions resulted in wide inconsistencies in application of diagnostic terms.[4, 12-14]

Recent international consensus recommendations more consistently align terminology by creating two major groupings (i.e., discrete structural vs. nonstructural) for causes of bleeding. The FIGO classification includes nine categories of abnormal bleeding arranged according to the acronym PALM-COEIN:[9, 15] four have objective visual criteria detected by imaging, biopsy, or pathology (i.e., PALM: **p**olyps; **a**denomyosis; **l**eiomyomata; and **m**alignancy and hyperplasia) while another five are not directly related to structural abnormalities (i.e., COEIN: **c**oagulopathy; **o**vulatory dysfunction; **e**ndometrial; **i**atrogenic; and **n**ot yet classified).

This comparative effectiveness review addresses the groups characterized by this recently adopted nomenclature as ovulatory dysfunction and endometrial. The relevant population includes nonpregnant women from menarche to menopause who have had abnormal bleeding for three months or longer and have undergone evaluation to rule out structural abnormalities, systemic illnesses and medications as potential causes.

While some reviews further subdivide women experiencing AUB into age groups,[16] such as those near menarche and in the perimenopausal timeframe, we plan to retain an emphasis on categorization. Women across the reproductive lifespan can have abnormal bleeding that arises from ovulatory dysfunction or endometrial processes.[17] While the underlying causes may vary, for instance from lack of consistent regulation of the hypothalamic-pituitary-ovarian axis in teens near the onset of menses, and from lack of ovarian reserve in perimenopausal women, the treatment options overlap.[3] We will report when research was done with an age restricted population but will otherwise cover all the relevant literature regardless of reproductive age or reproductive history of participants.

In a recently published research article, Matteson and colleagues[18] examined the practice patterns and attitudes from a United States sample of obstetricians and gynecologists regarding the medical treatment of women with AUB. The authors reported that practicing obstetrician-gynecologists most frequently selected combined oral contraceptives for the treatment of both ovulatory and anovulatory heavy menstrual bleeding and that participants lacked an overall awareness of current evidence on effectiveness of common treatment options for AUB.[18]

Therapies

Primary Care Treatment Options

Pharmacologic therapies used for treatment of AUB in the ambulatory setting include estrogens, progestogens, combination (estrogen and progestogen) hormonal formulations, nonsteroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics, and progesterone-releasing intrauterine devices (IUDs). Medical interventions are generally considered first line treatment.[19, 20] Surgical intervention is usually reserved for women with persistent bleeding that does not

respond to medical therapy or for women who have finished childbearing and do not wish to indefinitely continue medical therapy.[2, 21]

Current recommendations from professional societies including the American College of Obstetricians and Gynecologists,[22-25] the American Academy of Family Physicians,[21] and the National Institute for Clinical Excellence[26] include the levonorgestrel-releasing intrauterine system (LNG-IUS), NSAIDs, antifibrinolytics, combined oral contraceptives (COCs), and progestogens and for management of irregular uterine bleeding and abnormal cyclic bleeding.

Levonorgestrel-Releasing Intrauterine System

Pooled data from five prospective randomized controlled trials (RCTs) reported that the LNG-IUS provided clinically and statistically significant sustained reductions in menstrual blood loss (MBL).[20, 25, 27, 28] Locally released progesterone from the IUD reduces growth of the uterine lining, minimizing the tissue available to be shed during menstruation. IUDs are used as contraception by approximately 5 percent of women in the United States.[29] Based on large-scale claims data, use of the LNG-IUS increased 19-fold between 2002 and 2008 to 7.7 women per thousand, becoming the most commonly used IUD in the United States.[30]

Nonsteroidal Anti-Inflammatory Drug

NSAIDs are commonly used to treat AUB because of the role of prostaglandins in the pathogenesis of heavy menstrual bleeding. Higher levels of prostaglandin E2 and F2a in the endometrium are associated with heavy menstrual bleeding.[31] Additional evidence points to an abnormal ratio of specific prostaglandins as a contributing factor to problems with hemostasis. NSAIDs act to reduce prostaglandin synthesis by inhibiting the enzyme cyclo-oxygenase and therefore reducing endometrial prostaglandin levels leading to increased vasoconstriction and reduced blood loss.[32] Based on a limited number of small studies, a 2007 Cochrane Review[33] found that NSAIDs were superior to placebo but less effective than tranexamic acid and LNG-IUS at reducing MBL.

Antifibrinolytics: Tranexamic Acid Therapy

TXA is an antifibrinolytic that slows the breakdown of fibrin in blood clots. By decreasing the degradation of physiologic blood clots, blood flow from uterine vessels sealed by the clot is decreased. Since it is not a hormonal agent and does not have contraceptive effects it may be useful for women who desire a pregnancy or for whom hormonal treatment in contraindicated. TXA appears to be well-tolerated and cost-effective, reducing blood loss considerably and improving health related quality of life for women with menorrhagia.[34]

Combined Oral Contraceptives

COCs are commonly used to manage abnormal bleeding associated with ovulation since they work in part by superimposing an organized cycle and discourage thick growth of the uterine lining. The American College of Obstetrics and Gynecologists 2010 Practice Bulletin for noncontraceptive uses of hormonal contraceptives recommends COCs as a reasonable choice to regulate and reduce menstrual bleeding, based on good and consistent scientific evidence.[24] However, according to a 2009 Cochrane systematic review,[35] there is insufficient evidence to establish the effectiveness of the oral contraceptive pill compared with other medical therapies,

placebo, or no therapy for the treatment of heavy menstrual bleeding.[35] In a clinical review for diagnosis and management of AUB,[36] authors assert that combined oral contraceptives are likely beneficial for treatment of anovulatory (i.e., acyclic) AUB but there is lack of good quality data to support their use in abnormal cyclic bleeding.[36] The combined oral contraceptive is also known to cause abnormal bleeding patterns. Additional data is needed on the number needed to treat and the number needed to harm for adverse effects.

Progestogens

During a normal cycle, the natural rise and fall of progesterone, which is produced by the ovary after ovulation, has multiple biological effects on the endometrium. These include "organization" that results in a coordinated withdrawal bleed, the menses, after progesterone levels fall. Administration of progesterone is intended therapeutically to mimic natural production of progesterone and then withdrawal, by providing the agent for a number of days, typically ten to 14 after which bleeding occurs. Other methods of administration of progesterone, such as by long acting injection or oral contraceptive pills that contain only a progestogen, exploit a different biologic property of progestogens. When continuously administered, progestogens encourage endometrial quiescence and prevent growth of the endometrium. Since less endometrium forms, there is less bleeding at the time of menses. The American College of Obstetrics and Gynecologists practice bulletins on management of anovulatory bleeding and noncontraceptive used of hormonal contraceptives note that progestogens are an appropriate first line choice for medical management of irregular bleeding that results from lack of regular, predictable ovulation.[22, 24]

Behavioral and Lifestyle Interventions

Diet and physical activity interventions have been proposed for irregular menstrual bleeding because irregular menses often indicate irregular or absent ovulation. Obesity and metabolic syndrome, including polycystic ovarian syndrome (PCOS), are associated with increased risk of anovulatory cycles. Trials that have achieved modest weight loss in infertile patients have restored regular ovulatory function in a majority of women with obesity-related subfertility.[37] Both aerobic and strength training as well as weight loss may improve blood sugar profiles and reduce relative or frank insulin resistance, which are intermediates to restoring regular menses in some women.

Complementary and Alternative Medicine

Initial literature scans suggested that there is an extremely limited body of literature on trials of complementary and alternative medicine for AUB. Complementary and alternative medicine based therapies are included as interventions of interest due to their increasing popularity among patients and growing interest to clinicians.[38]

Scope and Key Questions

Scope of the Review

The literature reflects various management options for women with AUB with conflicting recommendations/summaries. Interventions of interest for this review include medical, complementary and alternative medicine, and behavioral/lifestyle interventions. This review does not consider surgical interventions for AUB, as surgical management is adequately covered by other groups conducting systematic reviews.

This review is focused on the evidence available to inform selection of nonsurgical options to treat AUB with an emphasis on interventions that are accessible to and within the scope of usual practice for primary care practitioners in a clinical care setting. We address abnormal bleeding that is chronic in nature, meaning the symptom has persisted for the majority of the prior three months, and is of two primary and common types: (1) irregular in timing (i.e., acyclic); and (2) abnormal though cyclic. We explicitly defined eligibility criteria using a PICOTS (population, intervention, comparator(s), outcome, timing, and setting) structure (Table 1).

Table 1. PICOTS

PICOTS Element	Description
Population:	Nonpregnant women from menarche to menopause who have had abnormal bleeding for three months or longer whose bleeding is not caused by structural abnormalities, systemic disease, cancer, or medication. Two specific subtypes of abnormal bleeding will be the focus: • *Irregular uterine bleeding:* problem bleeding of three months or greater duration, excluding regular cyclic/menstrual patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, and related systemic disease. • *Abnormal cyclic uterine bleeding*: problem bleeding of three months or greater duration, excluding irregular and unpredictable patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, and related systemic disease.

Interventions[1]:	• Medical therapies
	  o Nonsteroidal anti-inflammatory drugs
	  o Antifibrinolytics
	  o Oral hormone treatments (e.g., oral contraceptives, progestogens)
	  o Levonorgestrel-releasing intrauterine system
	  o Vaginal ring contraceptive device
	• Behavioral strategies (e.g., stress reduction, weight reduction, exercise)
	• Complementary and alternative medicine therapies (e.g., acupuncture, herbal medicine)

Comparator:	Direct comparison among interventions listed above or comparison to placebo.
Outcomes:	• Bleeding profile (e.g., amount, frequency, duration, pattern, symptom bother, hematocrit) • Quality of life including both bleeding specific and general quality of life measures • Pain related to bleeding • Sexual function as reported by sexual function measures, general measures of sexual activity, frequency and satisfaction • Patient satisfaction with outcomes and acceptability of treatment • Fertility • Time to conception • Additional interventions including concurrent and consecutive surgical and nonsurgical treatments • Harms[1] (e.g., thromboembolic events, emotional side effects, weight gain, short- and long-

[1] Surgical interventions and procedures such as endometrial ablation are excluded.

	term harms)
Timing:	Interventions initiated after symptoms present most months for three months or longer.
Setting:	Research populations that are applicable to care of women receiving evaluation and treatment in primary care settings including general gynecology.

Key Questions

Key Question 1A (KQ1A)

What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with irregular uterine bleeding?

Key Question 1B (KQ1B)

What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with abnormal cyclic uterine bleeding?

Key Question 2 (KQ2)

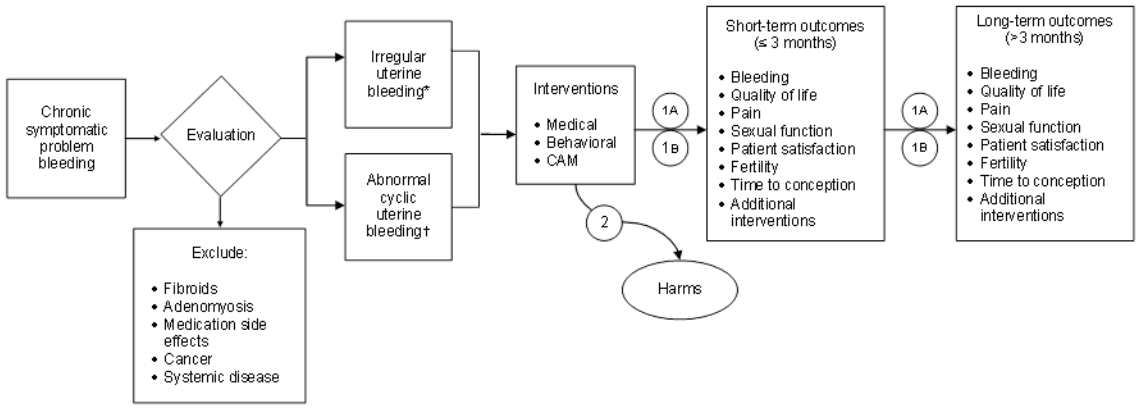
What are the harms, including adverse events, associated with medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) in women with irregular uterine bleeding or abnormal cyclic uterine bleeding?

Analytic Framework

We developed the analytic framework (Figure 1) based on clinical expertise and refined it with input from a Technical Expert Panel (TEP). The analytic framework illustrates the population, interventions, outcomes, and adverse effects that guided the literature search, study eligibility, screening, and synthesis. Input from the key informants was crucial in shaping the analytic framework.

[1] Includes treatment-related adverse events (e.g., drug side effects); does not include consequences related to the failure to adequately treat the symptom.

Figure 1. Analytic framework



Abbreviation: CAM: Complementary and alternative medicine

Organization of This Report

The Methods Chapter describes our processes including our search strategies, inclusion and exclusion criteria, approach to review of abstract and full publications, and methods for extraction of data into evidence tables, and compiling evidence. We also describe our approach to grading the quality of the literature and to describing the strength of the evidence.

The Results Chapter presents the findings of the literature search and review of the evidence by key question. When there are distinct populations in which the interventions have been studied such as enrollment based on differing criteria, we have discussed related data together. Within key questions we present summary information in the order: devices, medications, lifestyle and behavior interventions, and complementary and alternative medicine. Within a category such as medication, we have organized the results from greater number of studies to fewer, and presented the results of placebo controlled trials before direct comparisons.
The final section discusses the results and enlarges on the methodologic considerations relevant to each key question. We also outline the current state of the literature and needs for future research on management of AUB. We include a list of abbreviations and acronyms at the end of the report followed by appendixes to provide further detail on our methods and the studies assessed. The appendices are as follows:

- Appendix A Literature Search Strategies
- Appendix B Abstract Review Form (KQ1)
- Appendix C Abstract Review Form (KQ2)
- Appendix D Full Text Review Form (KQ1)
- Appendix E Full Text Review Form (KQ2)
- Appendix F Cochrane Risk of Bias Tool
- Appendix G Cochrane Risk of Bias Criteria
- Appendix H Thresholds for Quality Assessment
- Appendix I Evidence Table
- Appendix J Risk of Bias and Quality Score for Individual Studies

- Appendix K Reasons for Exclusion (KQ1)
- Appendix L Reasons for Exclusion (KQ2)
- Appendix M Labeled Indications for Drugs Included in Review
- Appendix N Harms Extracted from Package Inserts of Drugs Included in Review
- Appendix O Systematic Reviews
- Appendix P Ongoing Studies

Methods

The methods for this comparative effectiveness review (CER) follow those suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[39] The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[40]

Topic Refinement and Review Protocol

The topic for this report was nominated by a health care professional using the Effective Health Care website (http://effectivehealthcare.ahrq.gov/). Working from the nomination, we drafted the initial Key Questions and analytic framework and sought input from Key Informants representing family medicine, generalist and subspecialty obstetrics and gynecology, and midwifery. Key Informants uniformly stressed the importance of terminology and of establishing clear and distinct categories of women for whom the review is intended to apply and suggested framing the review from the vantage point of a primary care provider or specialist who is at the earliest stage of management of abnormal uterine bleeding (AUB), which is typically nonsurgical management. Key Questions were refined to reflect the feedback from Key Informants and address gaps in existing evidence reviews and knowledge base about management of AUB.

After review from AHRQ, the Key Questions and analytic framework were posted online for public comment. We received no comments during the public posting phase. We prepared final Key Questions and resubmitted them to AHRQ for review. We identified Technical Experts on the topic to provide assistance during the project. The Technical Expert Panel (TEP) included individuals with expertise in bleeding abnormalities, nomenclature and classification of AUB, and lead authors of ongoing reviews of surgical interventions. The TEP included five members serving as technical or clinical experts. To ensure robust, scientifically relevant work, we called on the TEP to review and provide comments as our work progressed. TEP members participated in conference calls and discussions through e-mail to:

- Refine the analytic framework and Key Questions;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria;
- Provide input on the information and domains included in evidence tables;

Literature Search Strategy

Search Strategy

Databases

We searched the following databases: MEDLINE® (PubMed interface), the Cumulative Index of Nursing and Allied Health Literature (CINAHL®), and Embase. All search results were limited to English language. Searches were further restricted from 1980 forward in order to ensure literature was relevant to current secular trends in practice as well as available treatment strategies. We carried out hand searches of the reference lists of recent systematic reviews

related to management of AUB and the reference lists of included publications. Searches were executed between September 2011 and March 2012.

Search Terms

Each search strategy used a combination of subject headings (i.e., controlled vocabulary) and keywords appropriate for each database (see Appendix A of the full report). The search strategies included terms related to AUB, along with drug and therapy terms relevant to the topic and focus of Key Question 1A (KQ1A) and Key Question 1B (KQ1B). For Key Question 2 (KQ2), we conducted a second, separate search in MEDLINE (PubMed interface), using controlled vocabulary and keywords focusing on adverse effects and harms associated with those drugs and treatments from our KQ1A and KQ1B included studies. We also employed a combination of subject headings and keywords to narrow retrieval to desired study types; for KQ1A and KQ1B, this included terms related to randomized controlled trials (RCTs), and for KQ2, terms geared toward also retrieving cohort and postmarketing surveillance studies.

Supplementary Information for KQ2

To further assess KQ2, we searched Internet resources to identify current research and regulatory information related to adverse effects and harms specific to those drugs and therapies from KQ1A and KQ1B included publications. These searches were executed between January and March 2012. The Scientific Resource Center invited manufacturers of drugs from our included studies to provide Scientific Information Packets.

For each included intervention, we conducted searches of the Food and Drug Administration (FDA) database of approved drugs (Drugs@FDA) and DailyMed to locate the most recent label information, determine the approval date, ascertain therapeutically equivalent drugs, and find other relevant information related to harms. For those drugs no longer marketed or unavailable in the United States, label information (including indications and usage, and harms) was also retrieved from the regulatory agencies of other countries where the drug is approved (e.g., HealthCanada's Drug Product Database), drug information databases (e.g., Micromedex® and LexiComp®), and manufacturer or pharmaceutical company websites. Additionally, we searched the FDA's safety information and adverse reporting website (MedWatch) to verify the most recent changes to label information were included in our harms data.

To supplement the harms data extracted from package inserts and relevant studies, we adapted our primary PubMed search strategy to identify systematic reviews and meta analyses examining the therapeutic agents identified in our analysis of the literature for KQ1, limiting to items published since 2005.

To ascertain current and ongoing research, we searched clinicaltrials.gov with topic keywords (e.g., “abnormal uterine bleeding”, “menorrhagia”, “heavy menstrual bleeding”), looked at both recruiting and completed studies, and again focused on those drugs and therapies from KQ1A and KQ1B included publications.

Inclusion and Exclusion Criteria

To be considered for inclusion, studies had to explicitly define and describe the study population, the interventions, and outcomes.

For this CER, the population of interest included women with symptomatic cyclic or irregular uterine bleeding (Table 2). We excluded studies of women with AUB caused by systemic disease (e.g., thyroid disease, coagulopathy), structural abnormalities (e.g., fibroids, polyps), cancer, or medication side effects. Studies that included patients with AUB of mixed or ill-defined etiologies were reviewed for evaluable data from patients meeting the description of the population of interest. For KQ1A we included studies of women with polycystic ovarian syndrome (PCOS) if the patient baseline and outcome data included information on cycle regularity. We excluded studies of women with infertility if the primary treatment goal was conception.

Table 2. Definitions of eligible patient populations

Patient group	Description
Irregular uterine bleeding	Problem bleeding of three months or greater duration, excluding regular cyclic/menstrual patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, and related systemic disease.
Abnormal cyclic uterine bleeding	Problem bleeding of three months or greater duration, excluding irregular and unpredictable patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, and related systemic disease.

To be considered for inclusion, clinical research studies had to evaluate a nonsurgical intervention. For KQ1 and KQ2 we included data from controlled clinical trials (e.g., RCTs) designed to evaluate an intervention or treatment strategy for individuals from the population of interest. For KQ2, we also included data from uncontrolled observational studies, namely high-quality, large cohort studies, postmarketing surveillance studies, and registries/databases, with a population of 1600 or more patients or records to capture information on adverse events or other harms.[41] We determined that a minimum sample size of 1600 was needed in order to reliably detect harms with an estimated prevalence of 1 percent. We did not specify a minimal population size for KQ1; several factors, including varying prevalence of cyclic and irregular patterns of AUB, the large number of interventions under consideration for this review, make it difficult to reliably establish a minimum sample size for evaluating treatment effectiveness.

To balance resources and focus on literature of most immediate relevance to primary care practice in the United States, we excluded papers that were not published in English.[42]

Study Selection

We developed individual abstract and full text screening forms for KQ1 and KQ2 (Appendixes B, C, D and E). We revised the forms following testing by the team. The forms were adapted for use in the Web-based systematic review product, DistillerSR (Evidence Partners, Ottawa, Canada).

We conducted screening in two phases: abstract and full text screening. Publications were promoted to full text review when one reviewer indicated that the publication met all inclusion criteria or when the title and abstract did not provide adequate information to make a determination. Two reviewers independently reviewed each publication at the full text screening phase. Discordant classifications were resolved in team meetings including senior investigators.

Data Extraction

We created uniform evidence tables to extract data and facilitate data synthesis. We collected those data related to population characteristics, type of abnormal bleeding, intervention characteristics, and outcomes including harms.

We evaluated the ability to capture data across publications about candidate effect modifiers and confounders of treatment response and uniformly extracted information about candidates including age, body mass index, parity, smoking status. When available we also collected current and prior contraception, perimenopausal status, fibroid status, and comorbidities including diabetes and PCOS. The final evidence tables are provided in Appendix I.

Quality (Risk of Bias) Assessment of Individual Studies

Two senior team members independently assessed quality of the included studies; disagreements were resolved through discussion or third party adjudication as needed. We recorded quality assessments in tables, summarizing each study. Data from studies that are considered to be fair or good quality are included in this analysis. Poor quality studies are identified but not included in the main synthesis. A summary of all component items and overall risk of bias/quality score for each included study is provided in Appendix J.

We used the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[39]and the Cochrane Risk of Bias Tool[43] (Appendix F), an existing tool with established validity and reliability, to assess methodological quality of included studies. This tool includes criteria for judging risk of bias for specific elements from five fundamental domains: sequence generation, allocation concealment, blinding, outcome data, and selective reporting (Appendix G) in RCTs. We gave a final quality grade of good, fair, or poor using the established criteria for the assessment tool, and specific thresholds for quality assessment (Appendix H).

We assessed quality for the included studies that addressed KQ1 only. For KQ2, we sought evidence from varied sources; it was not possible to systematically assess the quality of the evidence related to harm.

Data Synthesis

A meta-analysis was not feasible for this review. Few studies had comparable treatment doses, interval, length of treatment, or duration of followup. Among those that did, the ability to aggregate data was limited by differences in outcomes measures which included measures of blood loss from sanitary product collection, self-report using scoring systems, and self-report using standardize pictorial systems. For regularity of bleeding no two measures of outcome were the same. We provide an impartial narrative synthesis of the available data from original research studies of acceptable quality for nonsurgical treatment of AUB.[44] We group findings and summary tables by Key Question, intervention, and outcomes.

Strength of the Body of Evidence

We used explicit criteria for rating the overall strength of the evidence on each intervention into qualitative categories (e.g., low, moderate, high, and insufficient). We used established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes), the quality of evidence (i.e., from the quality ratings on individual articles), and the coherence or

consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge.

The strength of evidence evaluation is stipulated in *the Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[39, 45] The guide emphasizes the following four major domains: risk of bias (low, medium, high); consistency (inconsistency not present, inconsistency present, unknown or not applicable); directness (direct, indirect); and precision (precise, imprecise) of the evidence. Risk of bias was derived from the quality assessment of the individual studies that addressed the Key Question and specific outcome under consideration. For KQ1 each key outcome on each comparison of interest was given an overall evidence grade based on the ratings for the individual domains. For KQ2, we did not rate of strength of evidence because a fully inclusive assessment of harms could not be completed for each of the 11 interventions that have been widely studied in populations that lack direct applicability to this report.

The overall strength of evidence was graded as "high" (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); "moderate" (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate); "low" (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or "insufficient" (indicating that evidence is either unavailable or does not permit estimation of an effect).[45] When no studies were available for an outcome or comparison of interest, we graded the evidence as insufficient.

Two senior investigators independently graded the body of evidence and final assignment was reviewed with the project team. Alignment was achieved through group discussion with careful attention to application of consistent standards across each area item being graded.

Applicability

We assessed applicability of the results gathered from the literature to the population of women with abnormal cyclic and irregular uterine bleeding according to EPC methods guidance.[46] Assessments of applicability were done to account for any factors limiting the ability to apply interventions to other populations or other settings, such as inadequate description of the intervention or failure to report followup data.

Using the patient, intervention, comparator, outcome, timing, and setting (PICOTS) framework, we identified factors that may limit the applicability of individual research studies. We summarized the applicability of the body of evidence and described key elements from the PICOTS framework that characterize the applicability of a body of studies.

Peer Review and Public Commentary

Experts in reproductive endocrinology and primary care treatment of women were invited to provide external peer review. The draft report will be posted for 4 weeks to elicit public comment. We addressed all reviewer comments by revising the text as appropriate. Responses to peer and public review comments will be listed in the disposition of comments report. This report will be available on the AHRQ website three months after the posting of this final CER.

Results

Introduction

This chapter presents the results of the systematic review of the literature on primary care management of abnormal uterine bleeding (AUB). We present findings for Key Question 1 (KQ1) beginning with an overview of the content of the literature as a whole, followed by results and detailed analysis organized first by studies addressing irregular uterine bleeding (KQ1A) and then by studies addressing abnormal cyclic uterine bleeding (KQ1B). When there are distinct populations in which the interventions have been studied such as enrollment based on differing criteria, we have discussed related data together. Within Key Questions we present summary information in the order: devices, medications, lifestyle and behavioral interventions, and complementary and alternative medicine. Within a category such as medication, we have organized the results from greater number of studies to fewer, and presented the results of placebo controlled trials before direct comparisons. These analyses are followed by review of the studies and supplemental information addressing Key Question 2 (KQ2), which pertains to harms associated with the interventions identified for KQ1.

Studies also are described in summary tables, generally organized to present particular common outcomes, like change in volume of bleeding, in a single summary in the relevant section of text. Details on quality assessment and individual components of the quality scoring for individual studies can be found in Appendix J. Information about the overall strength of evidence supporting the effectiveness of specific interventions (or lack of utility) is summarized by related outcomes in the Discussion.

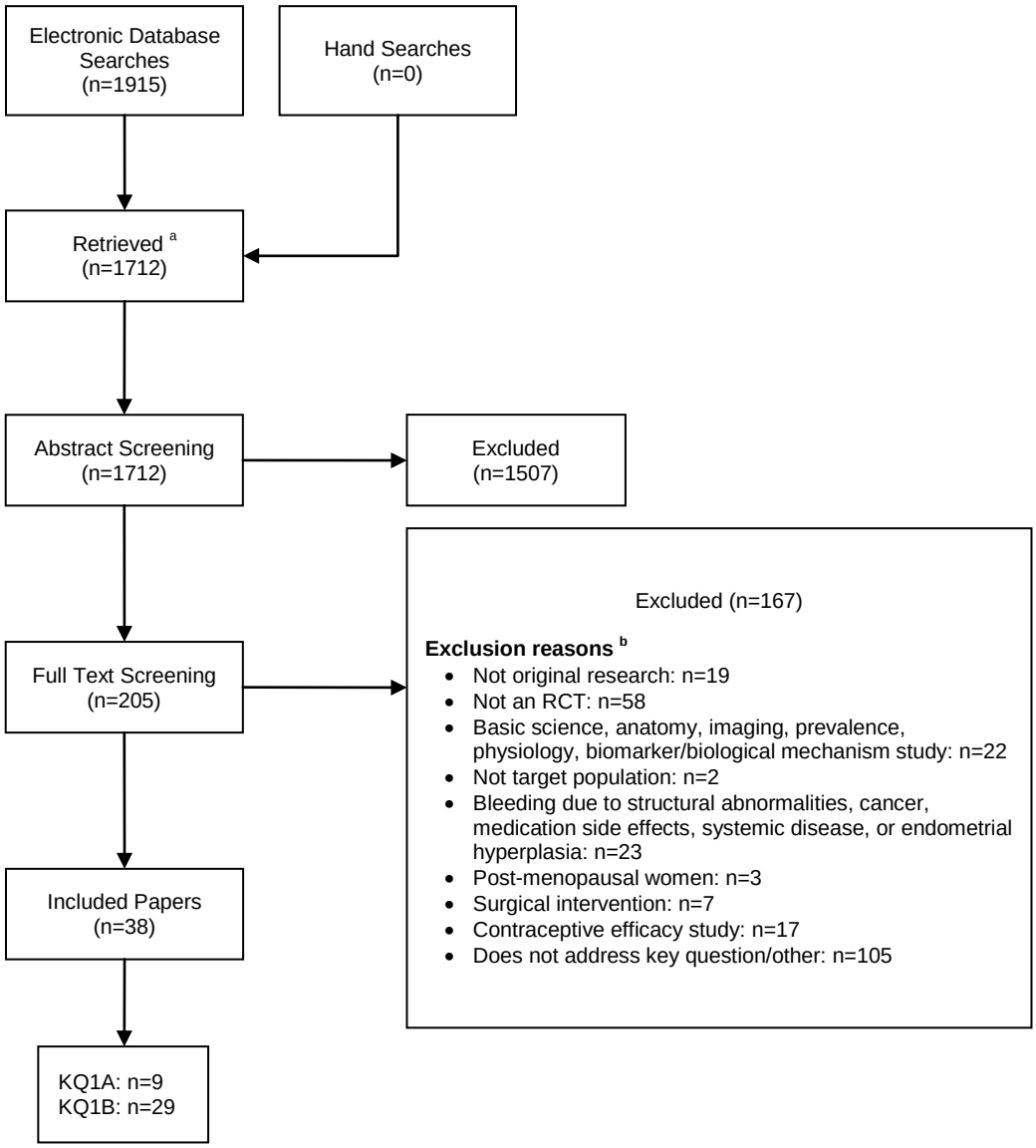
Results of Literature Searches

Searches identified 1915 titles and abstracts for screening. From this broad screening, we reviewed the publication abstracts and identified 204 publications as potentially eligible for inclusion. Following a review of the full text, we identified 36 studies described in38 publications that met the predetermined criteria for inclusion. Publications from nine studies addressed KQ1A. Twenty-nine publications from twenty-seven studies addressed KQ1B. Overall six of these studies were rated as good quality, eight as fair, and 22 as poor with regard to risk of bias in the findings. Details of the scoring of individual publications are included in Appendix J.

We conducted a separate search and screening process for KQ2. We identified 2650 titles and abstracts for screening. Of these, 750 references were promoted for full text review. Using predefined criteria, we found 19 publications that were eligible for inclusion. We received four of 17 requested industry packets and obtained package inserts for each KQ1 included drug intervention.

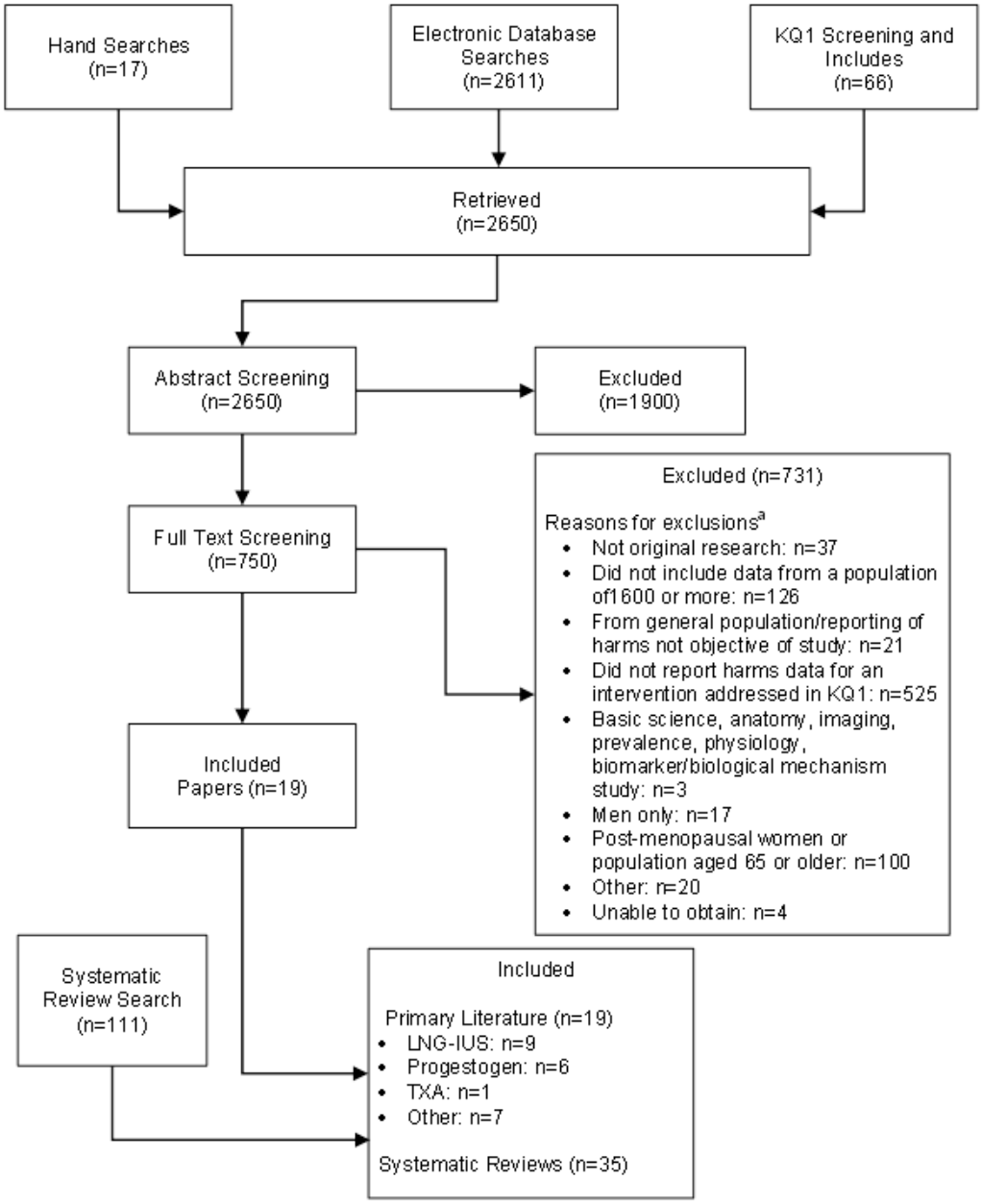
The complete list of excluded papers and exclusion reasons is provided in Appendix K for KQ1 and in Appendix L for KQ2.

Figure 2. Flow diagram of literature search and screening (KQ1)



Notes: [a] After duplicates removed; [b] Total does not equal number excluded as publications could be excluded for multiple reasons. **Abbreviations**: KQ: Key Question; RCT: randomized controlled trial

Figure 3. Flow diagram of literature search and screening (KQ2)



Notes: [a] After duplicates (n=44) removed; [b] Total does not equal number excluded as publications could be excluded for multiple reasons. [c] Systematic reviews excluded as not relevant to KQ2: n=76. **Abbreviations:** KQ1: Key Question 1; LNG-IUS: levonorgestrel-releasing intrauterine system; TXA: tranexamic acid

Description of Included Studies

Included studies evaluated 11 different interventions including: levonorgestrel-releasing intrauterine system (LNG-IUS), nonsteroidal anti-inflammatory drugs (NSAIDs), combined oral contraceptives (COCs), tranexamic acid (TXA), metformin, exenatide, progestogens, cabergoline, lifestyle/behavioral changes, acupuncture, and decision aids using at least one comparator or placebo arm. Table 3 includes a complete list of the medications from the included studies. Nineteen studies were head-to-head comparisons and 13 of the included studies established intervention efficacy by comparison to placebo. The majority of studies (27 studies reported in 29 publications) included in this review recruited women with complaints of abnormal cyclic uterine bleeding (KQ1B). Only nine of the included studies targeted women with irregular uterine bleeding (KQ1A). The duration of the studies included in this review were generally short. Studies addressing KQ1A had a duration of six months or less with most (7/9) lasting three to four months. For KQ1B, study duration ranged from two cycles to two years. The majority of the studies (20/27) evaluating an intervention for abnormal cyclic bleeding lasted six months or less. Two studies that compared the effectiveness of LNG-IUS with COC lasted for a year and two studies on the use of decision aids had a one- and two-year followup.

We did not identify publications that explicitly focused on reducing heavy menstrual blood loss (MBL) in the context of irregular menses, especially menses with extended intervals between episodes of bleeding. The publications included for KQ1A are focused exclusively on irregular bleeding patterns, most often oligomenorrhea (fewer cycles than normal across months). Studies that met the criteria for inclusion for KQ1A evaluated progestogens (one study),[47] COCs (one study),[48] metformin (three studies),[49-51] exenatide (one study),[51] cabergoline (one study),[52] diet (one study),[53] and exercise (one study),[54] and acupuncture (two studies).[54, 55] These total to more than nine since several were direct comparisons. Two were of good quality, two fair, and five poor.

For KQ1B, most of the included studies evaluated LNG-IUS (seven studies),[56-62] NSAIDs (13 studies),[60, 63-74] or TXA (six studies).[63, 68, 74-77] We identified five studies[56, 58, 65, 78, 79] that evaluated the use of COCs for the management of AUB. We found three studies[80-82] that evaluated decision aids for the management of AUB. Included studies evaluated the effect of these interventions on MBL, quality of life, menstrual cycle patterns, and other clinical and functional outcomes. Among the most common outcome metrics was change in MBL expressed as a percent. This was typically reported as a comparison of post-treatment blood loss to baseline.

For KQ2, we also reviewed and summarized harms reported in all included randomized controlled trials (RCTs) and in package inserts and indications for all products and prescription interventions and identified 19 publications reporting on harms of the included interventions.

Table 3. Medications from studies included in the CER

Medication	Brand name
Levonorgestrel-releasing intrauterine system	Mirena®
Antifibrinolytic agents	
Tranexamic acid, oral	Lysteda®
Combined oral contraceptives, oral	
Estradiol valerate and dienogest, oral	Natazia

Medication	Brand name
Ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg), oral	Nordette, Altavera, Levora, Marlissa, Portia 28
Ethinyl estradiol (0.20 mg) and norethindrone acetate (1.0 mg), oral	Loestrin® 21 1/20, Junel® 1/20, Microgestin® 1/20, Minestrin 1/20
Norgestimate ethinyl estradiol (triphasic), oral	Ortho Tri-Cyclen®, Tri-Sprintec®, Tri-Previfem, MonoNessa®, Ortho Tri-Cyclen® Low, Ortho-Cyclen®, Sprintec®, TriNessa®
Progestogens	
Dydrogesterone, oral	Gynorest International brand names: Dabroston, Dufaston, Duphaston®, Terolut
Medroxyprogesterone acetate, injectable suspension	Depo-Provera® CI, Depo-subQ Provera 104
Medroxyprogesterone acetate, oral	Provera®
Norethisterone/norethindrone, oral	Aygestin®
Progesterone, vaginal gel	Crinone
Nonsteroidal anti-inflammatory drugs	
Flurbiprofen, oral	Ansaid®
Meclofenamate	Meclomen®
Mefenamic acid, oral	Ponstel®
Naproxen sodium, oral	Naprosyn®, Anaprox® DS, Anaprox®, Naprosyn® Suspension, EC-Naprosyn®, Various OTC brands
Other	
Cabergoline, oral	Dostinex
Exenatide, injection	Byetta
Ethamsylate, etamsylate	International brand names: Altodor, Dicinone, Dicynene, Dicynone, Eselin®, Ethamsyl, Hemo 141, Hemoced, Impedil
Metformin hydrochloride, oral	Glucophage, Glucophage XR, Fortamet, Glumetza

KQ1A. Management of Irregular Uterine Bleeding

Description of Included Studies

As noted in the description of the overall literature yield for this review, we did not identify publications that explicitly focused on mitigating the heaviness of irregular uterine bleeding. Symptoms like gushing or soaking type bleeding commonly occur in the context of irregular menses, especially menses with extended intervals between episodes of bleeding. The publications available to be included for this key question focused on improving the regularity of bleeding and enrolled participants with bleeding categorized by the research teams as "dysfunctional uterine bleeding" or irregular bleeding with oligomenorrhea (fewer cycles than normal).

Studies were included whether or not participants reported menorrhagia (heavy bleeding) as long as the authors reported on the use of the intervention to improve cycle regularity. We did not review the literature on infertility or subfertility resulting from absent or infrequent ovulation, even when it included cycle regularity data. Interventions for fertility treatment in this group, like clomiphene, are distinct from those for symptom management used in primary care settings. Likewise research populations of infertile women likely lack comparability to the

broader population of women whose primary complaint is irregular cycles and may include women with subfertility who are seeking treatment for problem bleeding.

Overall nine studies addressed restoring menstrual regularity in those with irregular uterine bleeding. Three were conducted in the United States,[48, 51, 53] two in Italy,[50, 52] and one each in China,[55] Sweden,[54] Turkey,[47] and the United Kingdom.[49] The studies ranged in size from 13 to 201 participants and examined the efficacy of metformin (three studies),[49-51] acupuncture (two studies),[54, 55] diet and exercise (one study),[53] cabergoline (one study),[52] progesterone (one study),[47] and triphasic birth control pills (one study).[48] Two were classified as good quality, two as fair quality, and five as poor quality with respect to risk of bias in the assessment of effectiveness of the intervention of improving cycle regularity.

Key Points

- Metformin improves regularity of menstrual bleeding in women with polycystic ovarian syndrome (PCOS) when evaluated over months. When combined with exenatide, a newer injectable drug typically used for type 2 diabetes, the effect is greater than either metformin or exenatide alone over six months of followup in a single study of 60 women.
- In a very preliminary investigation of cabergoline, a drug typically used for elevated prolactin, three of eight women with PCOS and normal prolactin levels resumed regular cycles while none did in the six person placebo group.
- Both oral and vaginal progesterone administered on a cyclic schedule had comparable influence on normalizing timing of menses.
- Triphasic norgestimate-ethinyl estradiol birth control pills provided excellent or good control of bleeding abnormalities in 68 percent of those taking active pills compared to 26 percent of those receiving placebo.
- In adolescents both a low-fat, calorie-restricted diet or a carbohydrate-restricted diet along with 30 minutes of anaerobic exercise three days a week resulted in more regular menses if the individual lost weight.
- Acupuncture improved cycle regularity in two trials, one in which both acupuncture and exercise (30 minutes three days each week) resulted in improvements by 32 weeks compared to placebo. In this study acupuncture provided more rapid relief by 16 weeks than exercise. Another poorly-described study found more individuals “cured” using needle placement specific for mind tranquilizing and menstruation promotion compared to those for delayed menses.
- In summary a number of available interventions appropriate for use in primary care settings have preliminary evidence of effectiveness for increasing the regularity of menses. Only metformin consistently demonstrated benefit across studies and each of these studies enrolled women with oligomenorrhea and PCOS.
- Overall, literature is absent to inform choice of any of these modalities over another.

Detailed Synthesis

Medical Therapies

Six studies, two conducted in the United States, two in Italy and one each in the United Kingdom and Turkey, examined medical therapies to improve menstrual interval.[47-52] Four

included women who met detailed criteria for PCOS[49-52] (Table 4) and two included women classified as having dysfunctional uterine bleeding by clinical criteria that are not tightly operationalized (Table 4) but include extended intervals between cycles.[47, 48] We first present the findings for the RCTs that enrolled women with dysfunctional uterine bleeding and then the data from PCOS trials.

Table 4. Primary outcomes of medical interventions for irregular uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Cycle Control Outcomes
Davis et al., 2000[48] United States Good	**G1:** Triphasic norgestimate-ethinyl estradiol oral contraceptive (101) **G2:** Placebo (100)	• Data mixes women with oligomenorrhea, menorrhagia, menometrorrhagia, and polymenorrhea. • Investigators classified resolution of bleeding abnormalities from diaries as excellent or good in 41.2% and 26.8% of those receiving intervention and 10.5% and 15.8% of those on placebo (p<0.001). • Women's self-assessments were similar to the investigators' and indicated better outcomes in those receiving the oral contraceptive (p<0.001).
Karakus et al., 2009[47] Turkey Poor	**G1:** Vaginal micronized progesterone, 90 mg every other night for ten days (34) **G2:** Oral dydrogesterone (10 mg) daily for ten days (35)	• Both groups achieved comparable regularity of bleeding patterns in the three treated cycles observed: 92.6%, 88.9%, and 92.6% in the vaginal group, and 81.5%, 88.9%, and 85.2% in oral group (p>0.5). • Satisfaction with intervention was comparable between groups (p=0.5).

Progesterone Administration

Prior to menses without ovulation the sequence of biologic events that includes a rise in progesterone and then a precipitous drop does not occur. This is because the literal site of ovulation, the corpus luteum, is responsible for production of progesterone. In the absence of conception, the corpus luteum involutes and ceases production. This rise and fall in progesterone has multiple biological effects on the endometrium which include "organization" that results in a coordinated withdrawal bleed, the menses, after progesterone levels fall. Administration of progesterone is intended therapeutically to mimic natural production of progesterone and then withdrawal. A single RCT of progesterone sought to compare two methods of administration: orally for ten days starting on cycle day 15 or vaginally every other evening for ten days from cycle day 17 to 27. Both groups had improvements in cycle regularity compared to their baseline (p value not provided).[47] Regular bleeding patterns were observed in more than 89 percent of the three treated cycles in the vaginal administration group, and more than 82 percent of the oral group. Improvement in bleeding patterns was comparable for both groups (p>0.5). Satisfaction with the intervention was also comparable across groups.

Triphasic Oral Contraceptives

Oral contraceptives over-ride the hypothalamic-pituitary-ovarian axis coordination of ovarian sex steroid production. By providing exogenous estrogen and progesterone, oral contraceptives are intended to regulate cycle control pharmacologically. A single RCT[48] evaluated a triphasic norgestimate-ethinyl estradiol preparation compared to placebo among women classified as having dysfunctional uterine bleeding which included a variety of menstrual concerns including heavy periods, frequent periods, irregular and heavy periods, and rare episodes of bleeding.

Triphasic oral contraceptives have three distinct levels of progesterone (norgestimate in this study) and estrogen (ethinyl estradiol) over the course of the 21 days of active pills in a typical 28 day oral contraceptive pill pack, compared to monophasic pills which have the same hormone level provided across all 21 days of active pills. This particular RCT, with 201 participants, appears to have been conducted to expand the indication for a particular brand name to include cycle control for women with dysfunctional uterine bleeding. The trial was published in 2000 and was the only study identified that included women with problem bleeding from irregular and closely spaced or rare menses. The data is provided in aggregate for all participants regardless of their bleeding pattern or primary symptom.

This multicenter, industry-sponsored trial was conducted in the United States. The researchers randomized 201 women at a 1:1 ratio to receive either the study drug or placebo for three 28-day cycles. Data from 192 patients were included in the outcome analyses. The study drug regimen included 0.18 mg norgestimate and 0.035 mg ethinyl estradiol for days one to seven, 0.215 mg norgestimate and 0.035 mg ethinyl estradiol for days eight to 14, 0.25 mg norgestimate and 0.035 mg ethinyl estradiol for days 15 to 21, and inactive tablets for days 22 to 28. The primary efficacy outcomes included the investigator and the subject's overall assessment of improvement in AUB symptoms. Both the investigator assessments and subject assessments of symptom improvement indicated significant improvement in cycle control in the study drug group compared to the placebo group (both $p<0.001$). The investigator assessed some level of subject improvement (fair, good or excellent) in 81.4 percent of triphasic norgestimate ethinyl estradiol-treated patients as compared with 35.8 percent of placebo-treated patients; the proportions of subject-rated improvement were similar to investigator ratings. Among several quality of life measures assessed, improvement over baseline was only observed in physical functioning in the triphasic norgestimate ethinyl estradiol-treated patients compared with their placebo-treated counterparts.

Medical Therapies for Polycystic Ovary Syndrome

Three medical therapies were evaluated in trials that enrolled women with PCOS:

- Metformin, the most common choice for initial type 2 diabetes management. This drug reduces liver glucose production and increases uptake and use of glucose in other tissues throughout the body. Because relative insulin resistance is one of the manifestations of PCOS, metformin is believed to disrupt this part of the syndrome by improving insulin response.
- Exenatide, a newer agent for treatment of type 2 diabetes introduced in 2005, is administered by subcutaneous injection. This drug promotes increased insulin release in response to blood glucose and it dampens glucagon activity. Glucagon is the natural hormone which promotes glucose release from storage in the liver. It is often administered as a second agent to improve glycemic control in those with type 2 diabetes. As metformin, it may improve the relative insulin resistance seen in PCOS.
- Cabergoline, used in treatment of pituitary adenomas, which are benign hormone producing growths in the pituitary often producing elevated prolactin levels. Mechanism of effectiveness for restoring cycles in PCOS may include amplifying dopamine neurotransmitter actions in the central nervous system resulting in hypoprolactinemia and lower levels of hormone signals that increase androgen production by the ovary.[52]

Table 5. Primary outcomes of medical interventions for irregular uterine bleeding in women with PCOS

Author, Year Country Quality	Comparison Groups (n)	Key Cycle Control Outcomes
Paoletti et al., 1995[52] Italy Good	**G1:** Cabergoline, 0.5 mg each week (8) **G2:** Placebo (6)	• 3 of 8 women receiving cabergoline resumed regular cycles. • 5 of 8 had onset of menses within 32 to 37 days of treatment initiation. • Among women receiving placebo 3 had no menses and 3 had menstrual cycles that were widely separated in time. (No statistical comparisons are provided.)
Fleming et al., 2002[49] United Kingdom Fair	**G1:** Metformin, 850 mg twice a day (45) **G2:** Placebo (47)	• Mean time to first ovulation was shorter with metformin (23.6 days) than placebo (41.8 days)(p=0.02). • Total ovulation events where higher among women receiving metformin over 16 weeks (p=0.59). • Pregnancy rate not different among those who desired to conceive (4 of 23 in G1 and 1 of 19 in G2).
Moghetti et al., 2000[50] Italy Poor	**G1:** Metformin, 500 mg twice a day) (11)[a] **G2:** Placebo (12)[a]	• Study enrolled women with fewer than 6 menses per year and followed for 26 weeks. • "Menstrual frequency" improved with metformin compared to placebo (p=0.002).
Elkind-Hirsch et al., 2008[51] United States Poor	**G1:** Exenatide, 10 mcg twice a day (20) **G2:** Metformin, 500 mg twice a day (20) **G3:** Both (20)	• The combination of exenatide and metformin was superior to either medication alone for improving menstrual frequency. • Women taking both had 80% of menses predicted for a normal pattern, compared to 57% (G1) and 49% (G2).

Note: [a] Total n=23; exact group size not specified

One British[49] and one Italian[50] RCT evaluated metformin compared to placebo for improving menstrual cycle regularity among women with PCOS, defined by rare or absent menstrual cycles, and hyperandrogenic chronic anovulation. The larger trial in the United Kingdom enrolled 82 women and randomly assigned them to an 850 mg dose twice a day. As with typical administration the dose was initiated at a lower level and increased over a week to reduce risk of gastrointestinal distress. Over the course of 16 weeks those on metformin ovulated sooner, an average of 18.2 days earlier (p=0.02), than those receiving placebo. Those on metformin also had a higher total number of ovulatory events (p=0.059). The Italian study (n=23), used a metformin dose of 500 mg three times a day (also after a ramp up) and reported "menstrual frequency" improved (p=0.002), without additional definitions of the outcome.

A third trial, in the United States, compared three arms each with 20 participants: metformin (500 mg twice each day), exenatide (10 mcg twice a day) and both.[51] Participants were followed for six months. The primary outcome for this trial was the proportion of menses achieved over time compared to what would be a predicted normal pattern. For instance a woman predicted to have six menses over six and one half months would have a menstrual index of 50 percent if she in fact had only three menses over that time. Women taking metformin had 57 percent of expected menstrual bleeds and those on placebo had 49 percent. Those taking both metformin and exenatide had 80 percent of the predicted normal number of menses which was a significant advantage in effectiveness.

The RCT of cabergoline[52] was conducted in Italy and is unique among the PCOS studies in that the research team restricted the population of women with PCOS who were eligible for inclusion. In this preliminary study of 14 women, they compared time to onset of menses and

regularity to those on placebo. No statistical comparisons are reported, only the summary that five of the eight women receiving cabergoline had menses, with three of them resuming regular cycles over four months. All women taking placebo had either no cycles (n=3) or widely spaced cycles (n=3).

In summary, each of the studies of medical therapies reported findings that favor the medical intervention for establishing more predictable cycles in women with PCOS. No medication was effective for all participants though several exceeded 80 percent of those on active therapy achieving improvements in cycle regularity. The number and size of studies is small and overall the quality is fair to poor with one small pilot study of good quality design and implementation but limited by lack of statistical power.

Behavioral Interventions

Table 6. Primary outcomes of behavioral interventions for irregular uterine bleeding in women with PCOS

Author, Year Country Quality	Comparison Groups (n)	Key Cycle Control Outcomes
Ornstein et al., 2011[53] United States Poor	**G1:** Hypocaloric low-fat diet (12) **G2:** Carbohydrate restriction without caloric or fat targets (12)	• Both groups were asked to complete 30 minutes of aerobic exercise 3 times per week. • Both lost similar amounts of weight over 12 weeks. • Menstrual patterns are not reported by group. • Amount of weight loss correlated with menstrual regularity.

A single study in teens with PCOS in the United States (n=24), attempted to examine the influence of diet and exercise on restoration of normal menses.[53] The rationale for examining the effects of diet and exercise is based on similar effects to the diabetes medications studied. Exercise improves glucose utilization and insulin sensitivity. Likewise diet, with even modest weight loss, can also improve insulin response. The study advised girls in both intervention groups to spend 30 minutes in aerobic activity three times each week. One arm was instructed in how to keep a hypocaloric diet, consisting of less than 40 grams per day of fat. The other group was instructed in how to follow a low carbohydrate (i.e., no more than 20 grams per day) diet without specific calorie targets or fat restriction. Among the 16 who completed the study, both groups lost comparable amounts of weight over 12 weeks, an average of 6.5 percent of bodyweight. The authors did not report menstrual patterns by diet treatment group; they report only that degree of weight loss correlated with menstrual regularity ($r=-0.2$, $p=0.001$).[53]

Complementary and Alternative Medicine

Table 7. Primary outcomes of acupuncture for irregular uterine bleeding

Author, Year Country Population Quality	Comparison Groups (n)	Key Cycle Control Outcomes
Cai and Wu, 2009[55] China Dysfunctional uterine bleeding Fair	**G1:** Acupuncture at points for mind tranquilizing and menstruation promotion (21) **G2:** Routine acupuncture points for delayed menses (16)	• Based on self-reported scores, 67% of G1 were classified as cured compared to 19% of G2 over three cycles. • 25% of G1 classified as markedly relieved compared to 19% of G2. • There were no failures in G1 and 19% in G2 ($p<0.05$).
Jedel et al., 2011[54] Sweden PCOS Poor	**G1:** Low frequency electroacupuncture (33) **G2:** Brisk exercise at least 30 min., three days per week (34) **G3:** No active intervention (17)	• Electroacupuncture achieved greater improvement in regularity (+146% from baseline) compared to G2 (58% improvement) and G3 (17% worsening). All comparisons $p<0.05$ at 16 weeks. • By 32 weeks, electroacupuncture (+121% increase in cycle regularity) and exercise (+42%) were comparable and both superior to no intervention (−17%).

Two trials, one of fair quality[54] and another of poor quality,[55] report on use of acupuncture for menstrual regularity among women with oligomenorrhea from PCOS and dysfunctional uterine bleeding, respectively. The larger, higher quality study done in Sweden (n=84)[54] randomized participants to low frequency electroacupuncture for a total of 14 treatments, brisk exercise 30 minutes three times each week, or no active intervention. At 16 weeks electroacupuncture achieved greater improvement in menstrual regularity (146% from baseline) when compared to either exercise (58% improvement) or no active intervention (17% worsening) at 16 weeks. By 32 weeks, electroacupuncture (121% increase in cycle regularity) and exercise (42% increase in cycle regularity) were comparable and both superior to no intervention (17% decrease in cycle regularity).

The smaller study (n=37)[55] poorly describes inclusion criteria specifying only that women were clinically diagnosed with dysfunctional uterine bleeding, and poorly operationalizes outcomes, classifying participants as “cured” or not without providing a definition of what characteristics of the menstrual pattern or bleeding constituted a cure. The intervention of interest to the investigators was acupuncture for mind tranquilizing and menstruation promotion compared to a more conventional selection of needle sites used for delayed menses. Over “three cycles” more women were classified as cured using the mind-tranquilizing and menstruation promoting method (67% vs.19%); more women classified symptoms as markedly relieved, and there were no failures in the intervention compared to the usual approach arm (19%, $p<0.05$).

Overall these nine studies, that included women with irregular uterine bleeding, offer incomplete evidence that medications, possibly diet and exercise, and potentially acupuncture may offer some benefit for establishing more predictable menstrual bleeding patterns. They provide no direct evidence about the ability to reduce the heaviness of bleeding or the symptoms and bother associated with intermittent heavy bleeding because quantity of bleeding and patient-reported outcomes were not among the outcomes for these trials.

KQ1B. Management of Abnormal Cyclic Bleeding

Description of Included Studies

We identified 29 publications representing 27 studies addressing primary care interventions for the management of abnormal cyclic uterine bleeding. Most of the studies that qualified for inclusion evaluated the LNG-IUS (seven studies),[56-62] NSAIDs (13 studies),[60, 63-74] or TXA (six studies).[63, 68, 74-77] We identified five studies[56, 58, 65, 78, 79] that evaluated use of COCs for the management of AUB and three studies[80-82] that evaluated decision aids for the management of AUB. The total number of interventions addressed is greater than the number of studies because of direct comparisons between one or more interventions within single studies. Included studies described interventions appropriate for primary care and compared these interventions to another intervention (15 studies), placebo (eight studies), or usual care (four studies). The results are summarized below and details for each study are presented in the Evidence Table (Appendix I).

Levonorgestrel-Releasing Intrauterine System (Mirena®)

Key Points

- LNG-IUS causes a clinically significant reduction in MBL, ranging from 70 percent to 87 percent in studies lasting up to one year. However, there are no longer-term followup studies.
- In comparison to progestogens, combined hormonal pills, and nonsteroidal anti-inflammatory agents, LNG-IUS provided greater reduction in MBL. No head-to-head comparisons of LNG-IUS versus TXA were assessed. An indirect comparison of the percentage reduction and volume reduction in MBL suggests that LNG-IUS has a greater effect than TXA.

Detailed Synthesis

The LNG-IUS is an intrauterine, long-term, progestogen-only method of contraception licensed for five years of use. The system must be inserted and removed by a qualified practitioner, including primary care providers. The LNG-IUS has a T-shaped plastic frame with a rate-limiting membrane on the vertical stem that releases a daily dose of 20 micrograms of levonorgestrel into the endometrial space. The effects of the LNG-IUS are local and hormonal, including prevention of endometrial proliferation. The LNG-IUS is also licensed for the management of idiopathic menorrhagia or heavy menstrual bleeding.

Seven RCTs of LNG-IUS were included.[56-62] The number of study participants ranged from 39 to 165. The total number of women assigned to LNG-IUS was 275. The total number of women assigned to LNG-IUS for whom study endpoint outcome measures were reported (including intention to treat missing data protocols) was 255.

For one of the trials, the bleeding criterion for study entry was a mean MBL greater than 80 ml for at least two cycles.[57] For two of the trials, the bleeding criterion for study entry was a mean MBL greater than 80 ml for at least one cycle.[60, 61] For one trial, the inclusion criterion was self-defined heavy menstrual bleeding, although mean MBL was reported.[56] For one trial, a pictorial blood loss assessment chart score greater than 100 was utilized.[58] For one trial the inclusion criterion was intention to undergo hysterectomy for AUB, not due to a fibroid greater

than 3 cm.[62] In one trial, the authors did not adequately describe the inclusion criteria, although organic causes were excluded.[59] Among the four trials that used mean MBL, the baseline median MBL and baseline mean MBL values differed between trials.

The target intervention was the same for all seven trials: LNG-IUS; 52 mg levonorgestrel, initial release rate 20 mcg per 24 hours.

The comparator differed among the seven trials. Two trials utilized a combined oral contraceptive pill: continuous daily 30 mcg of ethinyl estradiol and 150 mcg levonorgestrel[56] and cyclic monthly 1 mg norethindrone acetate and 20 mcg ethinyl estradiol for days one to 21.[58] Three trials utilized progestogen by oral or intramuscular (IM) route: single shot of depot medroxyprogesterone acetate (DMPA) IM on first day of cycle versus medroxyprogesterone acetate (MPA) 5 mg tablet every day starting on first day of cycle,[59] oral MPA 10 mg one daily for ten days each cycle starting on cycle day 16,[57] and norethisterone 5 mg three times daily from day 5 to day 26 of the cycle for three cycles.[61] One trial compared oral mefenamic acid 500 mg three times daily for first four days of each cycle.[60] One trial assigned the patients in the control group to continue their pre-existing medical treatment for excessive uterine bleeding or symptoms of dysmenorrhea, or both.[62]

The primary outcome of most of the trials was change in blood loss. The alkaline hematin method for MBL was utilized in five trials.[56-58, 60, 61] One of these five reported both mean and median MBL.[57] Three studies only reported median MBL[58, 60, 61] and one study only reported mean MBL.[56] One trial utilized the pictorial blood loss assessment chart (a validated tool that helps participants more uniformly report bleeding as represented by the degree of saturation of sanitary pads and tampons) for the primary outcome measure.[59] Two trials utilized the pictorial blood loss assessment chart as a secondary outcome measure.[56, 60] One study utilized the proportion of women who cancelled their prior decision to undergo hysterectomy as the primary outcome measure.[62]

The timing of the summative outcome measure reporting varied among the trials. One trial reported after one menstrual cycle.[61] Three trials reported after three menstrual cycles.[57, 60, 61] Four trials reported after six menstrual cycles.[57, 59, 60, 62] Two trials reported after 12 months.[56, 58]

The setting varied: one trial was conducted in three countries: Brazil, Canada, and the United States,[57] two trials in the United Kingdom,[60, 61] the remainder in Egypt,[56] Canada,[58] Turkey,[59] and Finland.[62] Five were of poor quality, related to inadequate allocation concealment, lack of blinding of participants and assessors, and selective outcome reporting. Two were of fair quality.

Table 8. Primary outcomes of LNG-IUS for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Kaunitz et al., 2010[57] United States, Canada, Brazil Fair	**G1:** LNG-IUS (82) **G2:** MPA,10 mg daily for ten days of each cycle (83)	• Median reduction in MBL (measured by alkaline hematin) was −128.7 ml in G1 compared to −17.8 ml in G2 after 6 cycles (p<0.001). • Higher proportion of women with successful treatment (defined as MBL<80 ml and 50% or greater reduction in MBL from baseline) in G1 (84.8%) compared to G2 (22.2%)(p<0.001).
Irvine et al., 1998[61] United Kingdom Fair	**G1:** LNG-IUS (22) **G2:** Norethisterone, 5 mg three times daily day 5 to day 26 of cycle (22)	• MBL decreased significantly in both groups after 3 cycles (94% reduction for G1 and 87% reduction for G2). • More women in G1 (76%) wished to continue treatment after 3 month as compared to G2 (22%).

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Shabaan et al., 2011[56] Egypt Poor	**G1:** LNG-IUS (56) **G2:** Low dose COC, 30 mcg ethinyl estradiol and 150 mcg levonorgestrel (56)	• MBL assessed by alkaline hematin significantly (p<0.001) decreased in both groups from baseline. • Greater reduction in MBL measured by alkaline hematin at 12 months in G1 (87.4 ± 11.3%) compared to G2 (34.9 ± 76.9%) (p=0.01). • PBLAC scores decreased more in G1 (86.6 ± 17.0%) compared to G2 (2.5 ± 93.2%) (p<0.001). • Women in G1 had significant improvements in ferritin and hemoglobin at 12 months. No significant changes for women in G2. • Fewer bleeding days per year in G1 (34.5 ± 12.0) compared to G2 (65.1 ± 15.3) (p<0.001).
Endrikat et al., 2009[58] Canada Poor	**G1:** LNG-IUS (20) **G2:** COC, 1 mg norethindrone acetate and 20 mcg ethinyl estradiol (19)	• PBLAC score decreased significantly (p<0.001) in both groups at 12 months. • The MBL median score decreased more in G1 (from 228 to 13, −83% mean change) compared to G2 (from 290 to 72, mean change −68%) (p=0.002). • Proportion of women with successful treatment (defined as PBLAC score<100 at 12 months) higher in G1 (80%) compared to G2 (37%) (p<0.009). • Mean hemoglobin levels increased in both groups from baseline (p<0.001).
Kucuk and Ertan, 2008[59] Turkey Poor	**G1:** LNG-IUS (44) **G2:** DMPA, single shot (44) **G3:** MPA, 5 mg daily (44)	• More women in G1 (86%) with successful treatment compared to G2 (75%) or G3 (68%). • PBLAC scores, days of menstrual bleeding, and hemoglobin improved in all three groups from baseline. • Mean MBL scores at 6 months were lower in G1 (77) compared to G2 (146) and G3 (154) (p<0.01).
Reid and Virtanen-Kari, 2005[60] United Kingdom Poor	**G1:** LNG-IUS (25) **G2:** Mefenamic acid, 500 mg three times per day for first 4 days of cycle (26)	• MBL significantly reduced in both groups from baseline. • After 6 months median MBL was 5 ml in G1 compared to 100 ml in G2 (p<0.001).
Lahteenmaki et al., 1998[62] Finland Poor	**G1:** LNG-IUS (28) **G2:** Usual care control (28)	• Proportion of women cancelling hysterectomy was 64% in G1 versus 14.3% in G2 (p<0.001).

Abbreviations: LNG-IUS: levonorgestrel-releasing intrauterine system; COC: combined oral contraceptive; MBL: menstrual blood loss; PBLAC: pictorial blood loss assessment chart.

Description of Results

Blood Loss Outcomes

Four of the LNG-IUS trials[56, 57, 60, 61] used the alkaline hematin method to measure MBL. Two trials used the pictorial blood loss assessment chart for the blood loss outcome measure.[58] One trial reported the proportion of women who cancelled their prior decision to undergo hysterectomy as the primary outcome measure.[62]

Blood Loss Reduction Expressed as a Percent

A multicenter trial with 145 participants compared LNG-IUS with oral MPA and reported a 70.8 percent (SD ± 88.3%) reduction in MBL in the LNG-IUS group at the six month interval, compared to 21.5 percent (SD ± 35.8%) reduction in the MPA group (p<0.001).[57]

A trial conducted in Egypt with 112 participants compared LNG-IUS with continuous combined 30 mcg ethinyl estradiol and 150 mcg levonorgestrel (continuous COC) and reported a 87.4 percent (SD ± 11.7%) reduction in mean MBL in the LNG-IUS group at the 12 month interval, compared to 35 percent (SD ± 77%) reduction in the COC group (p=0.013).[56] The same study reported a 89.5 percent (SD ± 11.7%) reduction in the mean pictorial blood loss assessment chart score for the LNG-IUS group at the six month interval, compared to 41.6 percent (SD ± 53.6%) in the COC group.[56]

A Canadian trial with 39 participants compared LNG-IUS with 20 mcg ethinyl estradiol and 1 mg norethindrone acetate (cyclic COC) and reported a 83 percent reduction in the mean pictorial blood loss assessment chart score in the LNG-IUS group at the 12 month interval, compared to 68 percent reduction in the cyclic COC group (p=0.002).[58]

Table 9. Percent change in blood loss from baseline in studies of LNG-IUS

Author, Year	Comparator	LNG-IUS Group	Comparator Group	LNG-IUS vs. Comparator Group
Kaunitz et al., 2010[57]	Medroxyprogesterone	-70.8[b]	−21.5[b]	p<0.001
Shabaan et al., 2011[56]	Combined oral contraceptive, continuous	−87.4[b]	−35.0[b]	p=0.013
Shabaan et al., 2011[56]	Combined oral contraceptive, continuous	−89.5[c]	−41.6[c]	p=0.013
Endrikat et al., 2009[58]	Combined oral contraceptive, cyclic[a]	−83.0[c]	−68.0[c]	p=0.002

Note: [a] Norethindrone acetate/ethinyl estradiol; [b] Measured by alkaline hematin method; [c] Measured by pictorial blood loss assessment chart.

Blood Loss Reduction Expressed as a Volume

The multicenter trial with 145 participants reported a statistically significant reduction in median MBL after six menstrual cycles with LNG-IUS compared with those receiving MPA (128.8 ml reduction compared with 17.8 ml reduction, p<0.001).[57]

The United Kingdom trial with 44 participants and three months duration reported similar reductions in median MBL for the LNG-IUS group and the norethisterone group (104 ml vs. 94 ml, p=0.56).[61]

The trial conducted in Egypt with 112 participants that compared LNG-IUS with continuous COC reported a statistically significant reduction in mean MBL after 12 menstrual cycles with LNG-IUS compared with those receiving MPA (255.6 ml reduction compared with 156.1 ml reduction, p<0.001).[56] The same study reported a 275.1 reduction in the mean pictorial blood loss assessment chart score for the LNG-IUS group at the 12 month interval, compared to 50.8 reduction of the mean pictorial blood loss assessment chart score in the continuous COC group.[56]

A trial conducted in the United Kingdom with 51 participants that compared continuous LNG-IUS with mefenamic acid for first four days of each cycle, reported a statistically significant reduction in median MBL after six menstrual cycles with LNG-IUS compared with those receiving mefenamic acid (117 ml reduction compared with 21 ml reduction, p<0.001).[60]

The same study reported a statistically significant reduction in median pictorial blood loss assessment chart score: a 215 point reduction after six cycles with LNG-IUS compared with a 74 point reduction with mefenamic acid (p<0.001).[60]

A trial conducted in Turkey with 132 participants compared LNG-IUS with either a single intramuscular (IM) injection of DMPA or with daily oral MPA reported a statistically significant reduction in mean pictorial blood loss assessment chart score after six menstrual cycles with LNG-IUS compared to both groups that received a progestogen. The mean pictorial blood loss assessment chart score was reduced by 210 in the LNG-IUS group compared to a 138 point reduction with DMPA (p<0.01) and compared to a 76 point reduction with MPA (p<0.01). No significant difference was reported in the reductions in the pictorial blood loss assessment chart score between DMPA and MPA.[59]

Table 10. Change in blood loss volume from baseline in studies of LNG-IUS

Author, Year	Comparator	LNG-IUS Group	Comparator Group	LNG-IUS vs. Comparator Group
Kaunitz et al., 2010[57]	Medroxyprogesterone	−128.8 ml	−17.8 ml	p<0.001
Shabaan et al., 2011[56]	Combined oral contraceptive, continuous	−255.6 ml	−156.1 ml	p<0.001
Reid and Virtanen−Kari, 2005[60]	Mefenamic acid	−117.0 ml	−21.0 ml	p<0.001
Irvine et al., 1998[61]	Norethisterone	−104.0 ml	−94.0 ml	p=NS

Blood Loss Reduction Below the Standard Definition of Heavy Menstrual Bleeding

The multicenter trial with 145 participants that compared LNG-IUS with oral MPA reported a 84.8 percent (67/79) success rate in the LNG-IUS group at the six month interval, compared to 22.2 percent (18/81) in the MPA group (p<0.001).[57] For this study, treatment success was defined as MBL less than 80 ml at the end of study and 50 percent or greater reduction in MBL from baseline.[57]

The Canadian trial with 39 participants that compared LNG-IUS with cyclic COC reported a treatment success of 80 percent (16/20) in the LNG-IUS group at the 12 month interval, compared to 36.8 percent (7/19) in the cyclic COC group (p<0.009).[58] For this study, treatment success was defined as a pictorial blood loss assessment chart score less than 100 at 12 months.[58]

Total Bleeding Days and Total Spotting Days

The trial conducted in Egypt with 112 participants that compared LNG-IUS with continuous COC did not report baseline days of bleeding or spotting. The study did report that the endpoint number of bleeding days, adjusted for one year duration was 34.5 ± 12.0 for the LNG-IUS group and 65.1 ± 15.3 for the continuous COC group (p<0.001). The study also reported that the endpoint number of spotting days, adjusted for one year duration was not different between the two groups (p=0.273).[56]

The trial conducted in Turkey with 132 participants that compared LNG-IUS with either a single IM injection of DMPA or with daily oral MPA reported a statistically significant decrease

in mean bleeding days after six menstrual cycles with all three interventions. No significant difference was reported in the decrease in bleeding days between LNG-IUS and DMPA and MPA.[59]

Hemoglobin

The trial conducted in Turkey with 132 participants that compared LNG-IUS with either a single intramuscular injection of DMPA or with daily oral MPA reported a statistically significant increase in hemoglobin after six menstrual cycles with all three interventions. The mean hemoglobin score was increased by 0.8 g/dl in the LNG-IUS group compared to 0.5 g/dl with DMPA ($p<0.05$) and compared to 0.6 g/dL with MPA ($p<0.05$). No significant difference was reported in the increase in hemoglobin between DMPA and MPA.[59]

The trial conducted in Egypt with 112 participants that compared LNG-IUS with continuous COC reported a statistically significant increase in hemoglobin (1.2 g/dl) for the LNG-IUS group compared to the continuous COC group (decrease by 0.4 g/dl), $p<0.001$.[56] The United Kingdom trial with 44 participants and three months duration reported no significant differences in hemoglobin changes.[61] The Canadian trial with 39 participants that compared LNG-IUS with cyclic COC reported no significant differences in hemoglobin changes.[58]

Ferritin

The trial conducted in Egypt with 112 participants that compared LNG-IUS with continuous COC reported a statistically significant increase in ferritin (56.7 mcg/dl) for the LNG-IUS group compared to the continuous COC group (decrease by 34.3 mcg/dl, $p<0.001$).[56] The United Kingdom trial with 44 participants and three months duration reported no significant differences in ferritin changes.[61]

Treatment Failure

The trial conducted in Egypt with 112 participants that compared LNG-IUS with continuous COC defined treatment failure as initiation of an alternative medical treatment or need for surgery or expulsion of the LNG-IUS. The trial reported a statistically significant lower failure rate for the LNG-IUS group compared to the continuous COC group; hazard ratio 0.30 (95% CI, 0.14 to 0.73, $p=0.007$).[56]

Proportion of Women Who Cancelled Hysterectomy

An open randomized multicenter study conducted in Finland with 56 women aged 33 to 49 years who were scheduled to undergo hysterectomy for treatment of excessive uterine bleeding reported that after six months, 64.3 percent (95% CI, 44.1 to 81.4%) of the women in the LNG-IUS group compared to 14.3 percent (95% CI, 4.0 to 32.7%) in the control group (continued current medical treatment) had cancelled their decision to undergo hysterectomy ($p<0.001$).[62]

Head-to-Head Comparisons

LNG-IUS Versus Combined Oral Contraceptive

Both the trial that compared LNG-IUS to continuous daily 30 mcg of ethinyl estradiol and 150 mcg levonorgestrel[56] and the trial that compared LNG-IUS to cyclic monthly 1 mg norethindrone acetate and 20 mcg ethinyl estradiol for days one to 21[58] found that LNG-IUS was

superior to OCP for blood loss reduction expressed as a percent (83 to 90% reduction in mean pictorial blood loss assessment chart score for LNG-IUS, compared with 42 to 68% for OCP). One trial reported superiority of LNG-IUS for blood loss expressed as volume, total bleeding days, treatment failure, hemoglobin, and ferritin level.[56] One of the trials reported superiority of LNG-IUS for achieving blood loss below the definition of heavy menstrual bleeding.[58]

LNG-IUS Versus Progestogen by Oral or Intramuscular Route

The only outcome measure used by all three trials that compared progestogens to LNG-IUS was blood loss reduction by volume.[57, 59, 61] Two trials reported a significantly greater reduction with LNG-IUS, compared to oral MPA 10 mg one daily for ten days each cycle starting on cycle day 16[57] and compared to a single shot of DMPA on first day of cycle, and to MPA 5 mg tablet every day starting on first day of cycle.[59] The third trial reported no significant difference in the comparison between LNG-IUS and norethisterone 5 mg three times daily from day 5 to day 26 of the cycle for three cycles.[61] The trials used different progestogen formulations and used different measures of blood loss.[57, 59, 61] One of the trials reported significantly greater treatment success, reduction in blood loss as a percentage, and subjects achieving blood loss less than the definition of heavy menstrual bleeding, comparing LNG-IUS to oral MPA.[57]

LNG-IUS Versus Mefenamic Acid

A single trial reported significantly greater reduction in blood loss volume for LNG-IUS compared with mefenamic acid 500 mg three times daily for first four days of cycle (117 ml reduction compared with 21 ml reduction).[60]

Prevention of Hysterectomy

A single poor quality trial reported significantly more women (64.3%) had cancelled their decision to undergo hysterectomy in the LNG-IUS group (95% CI, 44.1 to 81.4%) compared with 14.3 percent in the control group, who continued current medical treatment (95% CI, 4.0 to 32.7%) ($p<0.001$).[62]

Nonsteroidal Anti-Inflammatory Drugs

Key Points

- The most commonly studied NSAID was mefenamic acid; other NSAIDs included naproxen, meclofenamate, and flurbiprofen.
- Overall, NSAIDs demonstrated significant reductions in MBL (20 to 59%) compared to baseline and were significantly more effective than placebo, but many women still have objective menorrhagia after treatment. Variability in treatment response with NSAIDs is considerable, including some individuals with increases in MBL with treatment.
- Comparing individual NSAIDs, there were no significant differences found in reductions of MBL between mefenamic acid and naproxen.
- In one RCT, LNG-IUS was significantly more effective at reducing MBL compared to mefenamic acid.
- In two trials, TXA had significantly greater reductions in MBL compared to either flurbiprofen or mefenamic acid.

- There were no significant differences between NSAIDs and either norethisterone, low dose COC, ethamsylate, or an older progesterone-releasing intrauterine device in five trials.
- Studies were mostly of short duration, with most from two to three cycles.
- No studies examined quality of life, sexual function, fertility, or time to conception as an outcome. Quality of life needs further attention since most women will be offered treatment based on complaints/perception rather than objective measurement.
- NSAIDs are also effective against menstrual-related abdominal pain and cramping.

Detailed Analysis

We identified 13 unique studies from 14 publications that examined the use of NSAIDs for abnormal cyclic uterine bleeding. Seven were parallel group RCTs[60, 63, 64, 66, 67, 71, 74] and six were randomized, crossover trials.[65, 68-70, 72, 73] Trials were conducted in seven different countries: Australia,[65, 73] Canada,[70] India,[66, 74] the Netherlands,[64] Sweden,[68] United Kingdom,[60, 63, 67, 71, 72] and the United States.[69] The number of participants in each trial ranged from 11 to 110 with crossover trials ranging from 14 to 69. One study was good quality, [69] three were fair quality,[64, 72, 73] and nine were poor quality.[60, 63, 65-68, 70, 71, 74]

Studies used different inclusion criteria for defining menorrhagia. Six trials used the objective alkaline hematin method with MBL more than 80 ml as criteria for inclusion.[60, 63, 64, 67, 68, 72] Two trials used the alkaline hematin method with MBL more than 50 to 60 ml,[69, 71] one study used a combination of subjective and objective criteria of MBL more than 80 ml,[70] and four trials used either subjective criteria or did not define heavy menstrual bleeding for inclusion into the trial.[65, 66, 73, 74] Some studies required women to have regular cycles.[60, 64, 65, 69, 70, 74] Most studies excluded populations who had underlying disease or IUD use. One study[73] included patients with IUD (n=6), fibroids (n=2), Von Willebrand disease (n=1) and reported changes in MBL separately for women with ovulatory menorrhagia from those with underlying disease. Another study also included patients with IUDs (n=7) in the eligible patient population.[69] Patients ranged in age from 14 to 51 years of age.

The target intervention differed among the 13 studies. For each NSAID, dose and duration did not vary greatly. The most commonly studied NSAID was mefenamic acid which was used in 11 trials.[60, 63-67, 70-74] The usual dose of mefenamic acid was 500 mg three times a day starting at the onset of menses for duration of five days or until cessation of menses. One study initiated mefenamic acid five days prior to onset of menses through cessation.[64] Another trial used slightly different regimen with 500 mg at onset of menses followed by 250 mg every six hours for three to five days.[70] One study included mefenamic acid at 250 mg three times a day from onset menses for five days in conjunction with TXA 500 mg three times a day for the same five day period.[74] One trial studied meclofenamate at a dose of 100 mg three times a day from onset of menses for duration of six days or until cessation of menses.[69] Naproxen was studied in two trials with initial loading doses of 500 to 550 mg then 250 to 275 mg every six hours for five days or until 24 hours after cessation of heavy bleeding.[65, 72] Flurbiprofen was studied in one trial at a dose of 100 mg twice a day from onset of menses for duration of five days.[68]

The comparator differed among the 13 studies. Mefenamic acid was compared to placebo in four studies, two RCTs[64, 66] and two crossover trials[70, 73] used placebo. One crossover trial compared meclofenamate to placebo.[69] Two crossover trials compared mefenamic acid to naproxen[65, 72] for two cycles. One of these crossover trials also used low dose COC with 30 mcg

ethinyl estradiol and 150 mcg levonorgestrel given daily for 21 days for two cycles.[65] Two RCTs used norethisterone 5 mg twice daily from day 19 to 26 of the cycle[67] or days 15 to 25 of the cycle[71] for two cycles. Two RCTs used progesterone-releasing intrauterine systems, including the LNG-IUS that releases 20 mcg of levonorgestrel per day for six cycles[60] and an older progesterone impregnated intrauterine coil that releases 65 mcg of progesterone daily for two cycles.[71] One RCT compared TXA 1 gram every six hours with ethamsylate 500 mg every six hours for the first five days of menses for three cycles.[63] One crossover trial compared flurbiprofen with 1.5 grams of TXA three times a day for the first three days of menses and 1 gram on days four to five for two cycles.[68] One RCT compared a combination of mefenamic acid and TXA at 500 mg three times a day from day one to five of menses to TXA alone for three cycles.[74] The primary outcome of these trials was change in MBL. Most studies (11/13) measured MBL objectively with the alkaline hematin method.[60, 63-65, 67-73] Seven studies reported mean MBL[63-65, 68-70, 73] and four studies reported median MBL.[60, 67, 71, 72] One trial used the pictorial blood loss assessment chart score[74] for the primary outcome measure of blood loss and a second trial used the pictorial blood loss assessment chart as a secondary outcome measure.[60] One trial reported the subjective relief of menorrhagia,[66] however the method of measurement was not provided.

Duration of treatment ranged from one[64] to six[60] menstrual cycles, with the majority consisting of two[65, 67-73] to three[63, 66, 74] cycles. Other secondary bleeding outcomes studied included duration of bleeding,[63, 66, 67, 69, 72, 73] number of pads/tampons used,[63, 66, 69, 72] and total menstrual fluid loss.[60] One trial examined patient satisfaction.[63] No studies examined quality of life, sexual function, fertility, or time to conception as an outcome.

Table 11. Primary outcomes of NSAIDs for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Vargyas et al., 1987[69] United States Good	**G1[a]:** Meclofenamate, 100 mg three times per day for two cycles followed by placebo for two cycles (15) **G2:** Placebo for two cycles, followed by meclofenamate for two cycles (17)	• Mean MBL during meclofenamate cycles (69.0 ± 6.3 ml) was significantly less than baseline (141.6 ± 15.9 ml) and during placebo cycles (135.6±11.3) (p<0.0001). • Mean number of bleeding days was shorter during meclofenamate cycles (4.8 ± 0.2) than during placebo cycles (5.4 ± 0.18) (p<0.0003). • Median hemoglobin, hematocrit, and serum ferritin levels did not change during the study.
Van Elijkeren et al., 1992[64] Netherlands Fair	**G1:** Mefenamic acid, 500 mg three times daily (6) **G2:** Placebo (5)	• Mean MBL decreased 40% in G1 from baseline mean 108 ml to 65 ml (p=0.01) compared to increase in G2 from 151 ml to 189 ml (p=0.46). • Patients were scheduled for hysterectomy.
Hall et al., 1987[72] United Kingdom Fair	**G1[a]:** Mefenamic acid 500 mg every 8 hours in phase 1 and naproxen in phase 2 (19) **G2:** Naproxen 550 mg loading dose followed by 275 mg every 6 hours in phase 1 followed by mefenamic acid in phase 2 (19)	• Treatment with mefenamic acid and naproxen reduced bleeding by average of 47 and 46% respectively.

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Fraser et al., 1981, 1984[73, 83] Australia Fair	**G1[a]:** Mefenamic acid, 500 mg three times daily for two cycles followed by placebo for two cycles (38) **G2:** Placebo for two cycles followed by mefenamic acid (31)	• Mefenamic acid significantly reduced mean MBL (28%) compared to placebo (p<0.001). • Reductions were greater (30%) among women with MBL >80 ml at baseline (p<0.001). • Only 30 out of 69 women had measured blood loss >80 ml during placebo cycles.
Najam et al., 2010[74] India Poor	**G1:** TXA 500 mg and mefenamic acid 250 mg three times daily (55) **G2:** TXA 500 mg three times daily (55)	• The mean PBLAC score in G1 declined from 246 to 100 at 6 months (p<0.01) and in G2 from 250 to 125 (p>0.05). • Hemoglobin levels significantly increased in both groups (from 8.6 to 12.3 in G1, p=0.016, and from 9.5 to 12.0 in G2 p=0.04).
Reid and Virtanen-Kari,2005[60] United Kingdom Poor	**G1:** LNG-IUS (25) **G2:** Mefenamic acid 500 mg three times daily for first four days of cycle (26)	• MBL significantly reduced in both groups from baseline but after 6 months median MBL was 5 ml in G1 compared to 100 ml in G2 (p<0.001).
Bonnar and Sheppard,1996[63] Ireland Poor	**G1:** Mefenamic acid 500 mg (25) **G2:** TXA 1 g (27) **G3:** Ethamsylate 500 mg (29)	• TXA reduced MBL by 54% (mean decreased from 164 ml to 75 ml) and mefenamic acid reduced MBL by 20% (from 186 ml to 148 ml). Ethamsylate did not reduce MBL. • Mean MBL for women in G1 remained > 80 ml after three treatment cycles (148 ml, range: 138 to 168 ml). • 77% in G2 and 74% in G1 wished to continue treatment • Improvement in dysmenorrheal was reported by 19% in G1, 13% in G2 and 4% in G3.
Fraser and McCarron, 1991[65] Australia Poor	**G1[a]:** Mefenamic acid 500 mg every 6 to 8 hours for two cycles; Naproxen 500 mg at onset followed by 250 mg every 6 to 8 hours for two cycles (15) **G2:** Mefenamic acid, 500 mg every 6 to 8 hours for two cycles; low dose COC (ethinyl estradiol 30 mcg and levonorgestrel 150 mcg) for two cycles (15)	• Mefenamic acid reduced MBL by 38% in G2 (p=0.002) and by 20% in G1 (p=0.198). • Women treated with low dose COC had 43% reduction in MBL (p<0.001). • Naproxen resulted in a 12% reduction in MBL (p=0.079).
Grover et al., 1990[66] India Poor	**G1:** Mefenamic acid, 500 mg, every 8 hours (40) **G2:** Placebo (40)	• 86% of women in G1 reported relief of menorrhagia compared to 20% in G2 (p<0.001). • Mean bleeding days in G1 reduced from 9.7 ± 3.1 to 4.1 ± 0.6.
Cameron et al., 1990[67] Scotland Poor	**G1:** Mefenamic acid, 500 mg three times daily (17) **G2:** Norethisterone, 5 mg twice daily (15)	• Median blood loss was significantly reduced in both groups from 123 ml to 81 ml in G1 (p<0.001) and from 109 ml to 92 in G2 (p<0.002). • Median percentage reduction in blood loss was 24% for G1 and 20% for G2 (p>0.1). • 52% of women in G1 and 67% in G2 still had menorrhagia after two months of treatment.

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Andersch et al., 1988[68] Sweden Poor	**G1[a]:** Flurbiprofen, 100 mg twice daily for two cycles followed by TXA for two cycles **G2:** TXA, 1.5 g three times daily on days one to three and 1 g twice daily on days four to five for two cycles followed by flurbiprofen for two cycles (15)	• Both treatments significantly reduced MBL (p<0.01). • Reduction in MBL was 53% with TXA compared to 24% for flurbiprofen (p<0.01). • Mean MBL reduced to 155 ± 33 ml with TXA and 223 ± 44 for flurbiprofen (baseline MBL was 295 ± 52). • Hemoglobin did not change with either treatment.
Tsang et al., 1987[70] Canada Poor	**G1[a]:** Mefenamic acid, 500 mg at onset followed by 250 mg every six hours for three to five days for two cycles followed by placebo **G2:** Placebo for two cycles followed by mefenamic acid for two cycles (14)	• 8/10 women experienced reduction in MBL while taking mefenamic acid compared to placebo (p<0.05).
Cameron et al., 1987[71] United Kingdom Poor	**G1:** Mefenamic acid, 500 mg three times daily (8) **G2:** Norethisterone, 5 mg twice daily (8) **G3:** Progesterone-impregnated coil releasing 65 mcg daily (8)	• Median MBL reduced in G1 (from 68 to 47 ml) (p=0.05) and in G3 (from 71 to 45 ml) (p<0.05). • Median MBL was unchanged in G2 (94 to 110).

Abbreviations: MBL: menstrual blood loss; COC: combined oral contraceptive; PBLAC: pictorial blood assessment chart; LNG-IUS: levonorgestrel-releasing intrauterine system. **Notes:** [a] Crossover study

Effects of NSAIDs on Outcomes of Interest

Although we aimed to collect data on measures of quality of life, sexual function, fertility and time to conception, none of the 13 clinical trials reported on these outcomes. One study reported on patient satisfaction based on their wish to continue treatment at the end of the study.[63]

Blood Loss Outcomes

All studies of NSAIDs examined bleeding outcomes. Eleven studies used the alkaline hematin method for an objective measure of MBL. Two trials used the pictorial blood loss assessment chart to assess blood loss.[60, 74] One study[66] used the perception of relief of menorrhagia for which methods were not provided.

Menstrual Blood Loss Reduction Expressed as a Percent

Three trials of fair to good quality reported statistically significant reductions in MBL compared to baseline, ranging from 28 to 49 percent among those who received one to two treatment cycles of NSAIDs, including mefenamic acid or meclofenamate.[64, 69, 73]

A good quality crossover trial conducted in the United States[69] randomized 32 women with MBL more than 60 ml to meclofenamate or placebo for two treatment cycles. Seven (21%) participants were using an IUD. Greater reductions in MBL were reported among those receiving meclofenamate (48.9% ± 3.7) compared to those receiving placebo (9.2% ± 5.3), p<0.0001.

A small, fair quality, RCT conducted in the Netherlands,[64] randomized women scheduled for a hysterectomy due to subjective menorrhagia to either mefenamic acid 500 mg (n=6) or placebo (n=5) three times daily starting five days before expected menses to cessation of bleeding for one treatment cycle. Eligible participants had regular cycles, no IUD, and MBL more than 80 ml. Those receiving mefenamic acid had greater reductions in mean MBL (40%) from baseline (p=0.01), compared with placebo where a nonsignificant increase (25%) in MBL was reported,

One crossover RCT of fair quality conducted in Australia and published in two papers[73, 83] randomized 85 women with menorrhagia to mefenamic acid or placebo for two cycles. Overall there was a 28.1 percent reduction in mean MBL among those who received mefenamic acid compared with those who received placebo (p<0.001). There was a 30.3 percent reduction (p<0.001) in blood loss among those with MBL more than 80 ml at baseline (n=30) but a 27.9 percent increase in blood loss among those with MBL more than 35 ml at baseline (n=14).

A randomized, double-blind crossover trial conducted in the United Kingdom[72] compared naproxen (550 mg at onset of menses then 275 mg every six to eight hours for five days) to mefenamic acid among 38 women with MBL more than 80 ml for two treatment cycles. Patients with pelvic inflammation, fibroids or other local disease were excluded. There were no significant differences in mean MBL reduction between the two groups receiving mefenamic acid (46%, 47%) and the two groups receiving naproxen (44%, 48%). Reductions in MBL compared to baseline were statistically significant (p<0.001) in both the groups receiving mefenamic acid and naproxen.

Seven poor quality trials also reported significantly reduced MBL compared to baseline levels. One poor quality RCT conducted in the United Kingdom[60] compared 51 participants randomized to either mefenamic acid or to LNG-IUS. This study reported a greater percent reduction in median MBL among those treated with LNG-IUS (95%) compared with those receiving mefenamic acid (23%) after six cycles of treatment. Both LNG-IUS and mefenamic acid had significant reductions compared to baseline (p<0.005).

One RCT[63] conducted in Ireland randomized women to either TXA (n=27), mefenamic acid (n=25), or ethamsylate (n=29) for three cycles. The study reported a 54 percent reduction in mean MBL from baseline for those receiving TXA (p<0.001), a 20 percent reduction for those receiving mefenamic acid (p<0.001), and a zero percent reduction for those receiving ethamsylate.

A small crossover trial[68] conducted in Sweden compared TXA to flurbiprofen for two treatment cycles. A greater reduction in mean MBL was reported among those receiving TXA (53%) compared to those receiving flurbiprofen (24%).

One RCT conducted in India[74] randomized 110 women with menorrhagia to a combination of TXA and mefenamic acid or TXA alone for three treatment cycles. The pictorial blood loss assessment chart score changed significantly from to baseline in those receiving mefenamic acid and TXA, (−59%, p<0.01) and in those receiving TXA alone (−50%, p>0.05).

One RCT conducted in the United Kingdom[67] examined the efficacy of mefenamic acid compared to norethisterone among 32 participants with MBL more than 80 ml for two cycles. Median percent change in blood loss volume was not significantly different between mefenamic acid (−24%, range: 5 to −83%) and norethisterone (−20%, range: 2 to −53%). Median MBL with treatment was 81 ml (range: 22 to 193 ml) for those receiving mefenamic acid and 92 ml (range: 43 to 189 ml) for those receiving norethisterone. One patient treated with mefenamic acid had an increase in blood loss.

One crossover trial[65] conducted in Australia examined the efficacy of mefenamic acid compared to low dose COC (30 mcg ethinyl estradiol and 150 mcg levonorgestrel given daily for 21 days) in one group and mefenamic acid compared to naproxen in another group, each for two cycles among women with a clinical history of menorrhagia. There was no significant difference in reduction of mean MBL between those receiving mefenamic acid (38%) and those receiving low dose COC (43%) or between those receiving mefenamic acid (20%) and those receiving naproxen (12%).

Table 12. Percent change in blood loss from baseline in studies of NSAIDs

Author, Year	NSAID	Comparator	NSAID Group	Comparator Group	NSAID vs. Comparator Group
Van Elijkeren et al., 1992[64]	Mefenamic acid	Placebo	−40.0	NR	NR
Fraser et al., 1981, 1984[73, 83]	Mefenamic acid	Placebo	NR	NR	p<0.001
Vargyas et al., 1987[69]	Meclofenamate	Placebo	−48.9	−9.2	p<0.0001
Hall et al., 1987[72]	Mefenamic acid	Naproxen	−47.0	−46.0	NS
Fraser and McCarron, 1991[65]	Mefenamic acid	Naproxen	−20.0	−12.0	NS
Cameron et al., 1990[67]	Mefenamic acid	Norethisterone	−24.0	−20.0	NS
Reid and Virtanen-Kari,2005[60]	Mefenamic acid	LNG-IUS	−23.0	−95.0	p<0.001
Fraser and McCarron, 1991[65]	Mefenamic acid	COC[a]	−38.0	−43.0	NS
Andersch et al., 1988[68]	Flurbiprofen	TXA	−24.0	−53.0	p<0.01
Bonnar and Sheppard,1996[63]	Mefenamic acid	TXA	−20.0	−54.0	NR
Bonnar and Sheppard,1996[63]	Mefenamic acid	Ethamsylate	−20.0	0	NR
Najam et al., 2010[74]	Mefenamic acid plus TXA	TXA	−59.0[b]	−50.0[b]	NR

Abbreviation: COC: combined oral contraceptive. **Note:** [a] 30 mcg ethinyl estradiol and 150 mcg levonorgestrel; [b] Measured by pictorial blood assessment chart.

Blood Loss Reduction Expressed as a Volume

In four trials of fair to good quality, treatment with meclofenamate, mefenamic acid or naproxen reduced MBL compared to baseline.[64, 69, 72, 73] Mean or median MBL after treatment ranged from 65 to 77 ml. Mefenamic acid and naproxen were comparable in effectiveness.[72]

A good quality crossover trial conducted in the United States[69] randomized 32 women to meclofenamate or placebo for two cycles. There was a significantly greater reduction in mean MBL from baseline with meclofenamate (72.6 ml) compared with placebo (6.0 ml).

A small fair quality RCT conducted in the Netherlands[64] that randomized women scheduled for a hysterectomy due to subjective menorrhagia to mefenamic acid (n=6) or placebo (n=5), there was a significant reduction in mean MBL from baseline in the treatment group (43 ml, p=0.01) compared with a 38 ml increase in MBL in the placebo group.

A fair quality crossover RCT conducted in Australia[73] reported greater reductions in mean MBL among those receiving mefenamic acid (18.8 ml) for two treatment cycles compared with those receiving placebo. Among the women with MBL more than 80 ml at baseline (n=30), there was a significant (p<0.001) reduction in mean MBL (33.6 ml) among those receiving mefenamic acid compared with those receiving placebo.

A fair quality crossover trial conducted in the United Kingdom[72] compared naproxen to mefenamic acid among 38 women with MBL more than 80 ml for two treatment cycles. Median reductions in blood volume from baseline for mefenamic acid ranged from 54 ml to 61 ml (p<0.001) and the reduction for naproxen ranged from 52 to 62 ml (p<0.001) over two treatment cycles. There were no significant differences in reductions in MBL between mefenamic acid and naproxen.

Seven poor quality studies reported similar findings; NSAIDS significantly reduced MBL compared to baseline. A poor quality RCT conducted in the United Kingdom with 51 women,[60] reported significantly (p<0.001) greater reductions in blood loss volume from baseline for those receiving LNG-IUS (117 ml, median 5 ml, range: 0 to 45 ml) compared to those receiving mefenamic acid (21 ml, median 100 ml, range: 46 to 168 ml). Greater reductions in mean pictorial blood loss assessment chart score were also reported with LNG-IUS (215 points) compared to mefenamic acid (74 points).

In an RCT conducted in Ireland,[63] 76 women were randomized to either TXA (n=27), mefenamic acid (n=25), or ethamsylate (n=29) for three cycles. Compared to baseline, those receiving TXA had an 89 ml reduction in MBL, those receiving mefenamic acid reported a 43 ml reduction, and those receiving ethamsylate reported an increase in MBL of 8 ml.[63] Those receiving TXA had a 46 ml greater reduction in MBL compared to those receiving mefenamic acid (p<0.05) and those receiving mefenamic acid had a 51 ml greater reduction in MBL compared to those receiving ethamsylate. Mean MBL after three cycles of treatment with mefenamic acid (148 ml, range: 138 to 168 ml) remained more than 80 ml.

A small crossover trial[68] conducted in Sweden that compared TXA with flurbiprofen for two treatment cycles, reported greater reductions in mean MBL from baseline for TXA (140 ml, p<0.01) compared with a reduction of 72 ml with flurbiprofen (p<0.01).

After three treatment cycles in an RCT conducted in India,[74] the pictorial blood loss assessment chart score was lowered by 146 points from baseline in the mefenamic acid and TXA group (p<0.01) and by 125 points from baseline in the TXA alone group (p>0.05).

In another small RCT conducted in the United Kingdom[71] median MBL was significantly reduced after two cycles of treatment with mefenamic acid (n=6), 38 ml reduction (median 47 ml, range: 39 to 210 ml) from baseline (85 ml, range: 68 to 169 ml), p=0.05, and was significantly reduced with a progesterone impregnated intrauterine coil (n=7), 19 ml reduction (median 45 ml, range: 31 to 77 ml) from baseline (median 64 ml, range: 56 to 164 ml, p<0.05). However, there was no significant reduction in median MBL after two cycles of norethisterone (21 ml, median 110 ml, range: 18 to 187 ml).

In one RCT[67] conducted in the United Kingdom, median MBL was reduced after two cycles of mefenamic acid from 123 ml (range: 86 to 237 ml) to 81 ml (range: 22 to 193 ml), a reduction

of 42 ml (p<0.001) and was significantly reduced with norethisterone from 109 ml (range: 81 to 236 ml) to 92 ml (range: 43 to 189 ml), a reduction of 17 ml (p<0.002), but there was no significant difference in reductions between mefenamic acid and norethisterone.

In a crossover trial[65] conducted in Australia, there were no differences in absolute reductions in MBL volume between mefenamic acid and low dose COC (30 mcg ethinyl estradiol and 150 mcg levonorgestrel given daily for 21 days) or between mefenamic acid compared with naproxen. Reductions in blood loss volume compared to baseline were reported for both those receiving mefenamic acid (38.1 ml, p=0.002) and those receiving COC (43.2 ml, p<0.001). In the other group, there were nonsignificant reductions in MBL from baseline for mefenamic acid (26 ml) and naproxen (15.5 ml).

In one small crossover trial conducted in Canada,[70] 8 of ten women with MBL of more than 80 ml experienced reductions in MBL with two cycles of mefenamic acid compared to placebo.

Table 13. Change in blood loss volume from baseline in studies of NSAIDs

Author, Year	NSAID	Comparator	NSAID Group	Comparator Group	NSAID vs. Comparator Group
Van Elijkeren et al., 1992[64]	Mefenamic acid	Placebo	-43.0 ml	+38.0 ml	NR
Fraser et al., 1981, 1984[73,]	Mefenamic acid	Placebo	NR	NR	p<0.001
Vargyas et al., 1987[69]	Meclofenamate	Placebo	-72.6 ml	-6.0 ml	p<0.0001
Hall et al., 1987[72]	Mefenamic acid	Naproxen	-57.5 ml	-57.0 ml	p=NS
Fraser and McCarron, 1991[65]	Mefenamic acid	Naproxen	-26.0 ml	-15.5 ml	p=NS
Cameron et al., 1990[67]	Mefenamic acid	Norethisterone	-42.0 ml	-17.0 ml	p=NS
Cameron et al., 1987[71]	Mefenamic acid	Norethisterone	-38.0 ml	-21.0 ml	NR
Cameron et al., 1987[71]	Mefenamic acid	Progesterone-releasing intrauterine coil	-38.0 ml	-19.0 ml	NR
Reid and Virtanen-Kari,2005[60]	Mefenamic acid	LNG-IUS	-21.0 ml	-117.0 ml	p<0.001
Fraser and McCarron, 1991[65]	Mefenamic acid	COC[a]	-38.1 ml	-43.2 ml	p=NS
Andersch et al., 1988[68]	Flurbiprofen	TXA	-72.0 ml	-140.0 ml	p<0.01
Bonnar and Sheppard,1996[63]	Mefenamic acid	TXA	-43.0 ml	-89.0 ml	p<0.05
Bonnar and Sheppard,1996[63]	Mefenamic acid	Ethamsylate	-43.0 ml	+8.0 ml	p<0.05

Abbreviations: COC: combined oral contraceptive; LNG-IUS: levonorgestrel-releasing intrauterine system; NS: nonsignificant.
Notes: [a] Ethinyl estradiol (30 mcg)/levonorgestrel (150 mcg).

Relief of Menorrhagia

Improvement in the subjective relief of menorrhagia with NSAIDs was reported in two trials. One RCT conducted in India[66] randomized 80 women with subjectively defined, cyclic, heavy bleeding to either mefenamic acid or placebo for three cycles. Relief of menorrhagia was significantly greater among those receiving mefenamic acid (86%) compared with those receiving placebo (20%). Another trial[63] reported a larger proportion of women who received either TXA (69%) or mefenamic acid (57%) though their blood loss was less compared to those receiving ethamsylate (44%) after three treatment cycles.

Duration of Bleeding and Total Menstrual Fluid Loss

Duration of bleeding (days) was measured as an outcome in six trials.[63, 66, 67, 69, 72, 73] Among two trials of fair to good quality, duration of menstrual blood flow was shorter among those receiving meclofenamate[69] and mefenamic acid[73] compared to placebo. Another fair quality study reported that both mefenamic acid and naproxen reduced the mean number of bleeding days.[72]

In two poor quality RCTs, bleeding duration was shorter with mefenamic acid,[66, 67] but there was no change with norethisterone.[67] In one three-arm trial[63] comparing the efficacy of mefenamic acid to TXA and ethamsylate, there was no difference in duration of menstrual bleeding between treatment arms. In one poor quality RCT, reductions were also seen in total menstrual fluid loss with greater reductions among those with LNG-IUS compared to mefenamic acid.[60]

Hemoglobin

In two trials,[68, 69] hemoglobin concentration did not increase during treatment with NSAIDs. In a good quality crossover trial conducted in the United States, the median hemoglobin, hematocrit, and ferritin levels were unchanged compared to baseline.[69] In a crossover trial conducted in Sweden[68], hemoglobin concentration during control cycles was no different from hemoglobin concentration during treatment. In the RCT in India,[74] mean hemoglobin increased significantly in the TXA group (12.0 gm/dl) and in the group receiving combined mefenamic acid and TXA (12.3 gm/dl).

Head-to-Head Comparisons

Mefenamic Acid Versus Naproxen

Two crossover trials compared mefenamic acid to naproxen.[65, 72] There were no differences in reduction of MBL between mefenamic acid and naproxen.

One fair quality crossover trial[72] conducted in the United Kingdom compared naproxen to mefenamic acid among 38 women with MBL more than 80 ml for two treatment cycles. Primary outcomes were mean MBL using the alkaline hematin method. Both mefenamic acid and naproxen reduced median MBL by 46 to 47 percent and 44 to 48 percent, respectively compared to baseline. The median reductions in MBL volume from baseline for mefenamic acid ranged from 54 ml to 61 ml ($p<0.001$); the reduction for naproxen ranged from 52 to 62 ml ($p<0.001$) over two treatment cycles. There were no differences in reductions in MBL between mefenamic acid and naproxen.

One poor quality crossover trial[65] conducted in Australia randomized 30 women with a clinical history of menorrhagia to either mefenamic acid or naproxen for two cycles. The same dose of mefenamic acid was compared to oral contraceptives in a second group (see section below). Primary outcome was MBL measured with the alkaline hematin method. Mefenamic acid reduced mean MBL by 20 percent compared to baseline though not statistically significant. Naproxen reduced mean MBL by 12 percent compared to baseline with no significant differences in reductions between mefenamic acid and naproxen. Despite these reductions, the majority of women receiving NSAIDs still had objective menorrhagia after treatment. There was considerable variability in response to both NSAIDs, with some women experiencing increases in MBL during treatment with NSAIDs.

Mefenamic Acid Versus Progesterone-Releasing Intrauterine Systems

Two poor quality RCTs conducted in the United Kingdom examined the efficacy of mefenamic acid compared to progesterone-releasing intrauterine systems. One studied the continuous LNG-IUS,[60] and the other studied an older progesterone impregnated intrauterine coil that releases 65 mcg of progesterone daily.[71] Both trials used objective measures of MBL with alkaline hematin for inclusion criteria, but with slightly different volumes (more than 80 ml[60] and more than 50 ml[71]) to assess MBL outcomes.

One RCT with 51 participants[60] reported a statistically significant greater reduction in median MBL from baseline in the women with LNG-IUS (117 ml) compared to the women receiving mefenamic acid (21 ml) after six cycles of treatment. Greater reductions in the mean pictorial blood loss assessment chart score were also reported with LNG-IUS (215 points) compared to mefenamic acid (74 points), $p<0.001$. Despite significant reductions with mefenamic acid, most patients still had objective MBL more than 80 ml.

One small RCT[71] reported reductions in median MBL after two cycle of treatment with both mefenamic acid (n=6), with a reduction of 21 ml (median 47 ml, range: 39 to 210 ml) from baseline (85 ml, range: 68 to 169 ml, $p=0.05$), and with the progesterone impregnated intrauterine coil (n=7) with a reduction of 19 ml (median 45 ml, range: 31 to 77 ml) from baseline (median 64 ml, range: 56 to 164 ml, $p<0.05$). No statistics for head-to-head comparisons were reported.

NSAIDs (Flurbiprofen, Mefenamic acid) Versus Tranexamic Acid

Two poor quality trials compared NSAIDs with TXA.[63, 68] One RCT[63] conducted in Ireland, randomized 76 women with MBL more than 80 ml to either TXA (n=27), mefenamic acid (n=25), or ethamsylate (n=29) for three cycles. One small randomized crossover trial[68] conducted in Sweden studied 15 women with MBL more than 80 ml comparing TXA to flurbiprofen. Both trials reported that women receiving TXA had significantly greater reductions in mean MBL compared to either mefenamic acid or flurbiprofen over three cycles.

A small crossover trial[68] reported a statistically significant reduction in mean MBL (53%) among populations receiving TXA (53%) compared to those receiving flurbiprofen (24%). Absolute reductions in blood loss volume from baseline were greater for TXA (140 ml) compared with flurbiprofen (72 ml).

One RCT[63] reported that the percent reduction in mean MBL from baseline over three treatment cycles was 54 percent for TXA ($p<0.001$), 20 percent for mefenamic acid ($p<0.001$),

and 0 percent for ethamsylate. The absolute change in blood loss volume compared to baseline was −89 ml with TXA, −43 ml with mefenamic acid, and +8 ml with ethamsylate.

Tranexamic Acid Plus Mefenamic Acid Versus Tranexamic Acid Alone

One poor quality RCT conducted in India[74] randomized 110 women with menorrhagia that was not objectively defined to a combination of TXA and mefenamic acid or to TXA alone. After three treatment cycles, the pictorial blood loss assessment chart score was significantly reduced in those receiving mefenamic acid plus TXA (59%, $p<0.01$) and in those receiving TXA alone (50%, p=ns). No statistics for head-to-head comparisons were reported.

Mefenamic Acid Versus Progestins (Norethisterone)

Two poor quality RCTs conducted in the United Kingdom examined the efficacy of mefenamic acid compared with norethisterone. [67, 71] Both trials examined the same dose and duration of mefenamic acid (500 mg three times per day on days one to five of menses) and the same dose of norethisterone (5 mg twice per day) but given during slightly different cycle days, (days 19 to 26[67] versus days 15 to 25[71]). Both trials used the alkaline method for MBL measurement for inclusion (50 to 80 ml) and outcome criteria.

One RCT[67] reported no difference in reductions of median MBL among those receiving two treatment cycles of mefenamic acid (n=17) compared to those receiving norethisterone (n=15). With either treatment, the majority of women still had MBL more than 80 ml. In the other small RCT,[71] no statistics for head-to-head comparisons were reported. Compared to baseline, median MBL was reduced after treatment with mefenamic acid (n=6) by 21 ml and by 19 ml (p=ns) among those receiving norethisterone (n=7). Median MBL with treatment was 47 ml (range: 39 to 210 ml) with mefenamic acid and 110 ml (range: 24 to 222 ml) with norethisterone.

Mefenamic Acid Versus Low Dose Combined Oral Contraceptive

One poor quality crossover trial[65] conducted in Australia examined the efficacy of mefenamic acid compared to low dose COC with 30 mcg ethinyl estradiol and 150 mcg levonorgestrel given daily for 21 days among 30 women with a clinical history of menorrhagia. There were no differences between mefenamic acid and COC in reductions in mean MBL (38% vs. 43%) or absolute reductions in MBL volume (38 ml vs. 43 ml).

Tranexamic Acid

Key Points

- TXA at a dose of 2.0 to 4.5 g per day for four to five days from the onset of bleeding causes a clinically significant reduction in MBL, ranging from 40 percent to 60 percent in studies lasting up to one year. However, there are no long-term follow-up studies.
- In comparison to progestogens, combined hormonal pills, and nonsteroidal anti-inflammatory agents, TXA appeared to provide greater reduction in MBL. No head-to-head comparisons of TXA versus LNG-IUS were assessed.
- The number of reports of side-effects and adverse effects was generally not significantly different between TXA and the comparison.

- Although no thromboembolic events were reported in any of the five studies, there are concerns about the possible increased risk of thromboembolic events in particular women, and the Food and Drug Administration (FDA) has issued precautions and contra-indications.

Detailed Synthesis

TXA is a competitive inhibitor of plasminogen activation, thereby acting as an antifibrinolytic agent. TXA does not appear to affect platelet numbers or aggregation but acts to reduce the breakdown of fibrin in a preformed clot. Because menstrual bleeding involves liquefaction of clotted blood from the spiral endometrial arterioles, a reduction in this process is the putative mechanism of reduced menstrual bleeding.

Six RCTs of TXA were identified.[63, 68, 74-77] One study compared TXA alone to TXA plus mefenamic acid, and is discussed in the NSAIDs section above.[74] For the five other studies of TXA, study population ranged from 15[68] to 196.[75] The total number of women assigned to TXA was 240. The total number of women assigned to TXA for whom study endpoint outcome measures were collected, (including intention to treat missing data protocols), was 205.

For four of the trials, the bleeding criterion for study entry was a mean MBL greater than 80 ml for at least two cycles.[63, 68, 75, 77] For a fifth trial, a pictorial blood loss assessment chart score greater than 100 was utilized.[76] Mean MBL at baseline was similar for three of the trials (range: 153 to 186 ml).[63, 75, 77] The baseline mean MBL (295 ml) was higher in one trial.[68]

The intervention dosage differed among the five trials. The TXA administration protocols for each menstrual cycle were: 2 g per day for five days,[76] 3.9 g per day for up to five days,[75] 4 g per day for four days,[77] 4 g per day for five days,[63] 4.5 g per day for three days and then 2 g per day for two days.[68]

The comparator differed across all five trials and included: placebo for five days,[75] oral medroxyprogesterone for 20 days,[76] oral norethisterone for seven days,[77] mefenamic acid for five days,[63] ethamsylate for five days,[63] and flurbiprofen for five days.[68]

The primary outcome of the trials was change in blood loss. The alkaline hematin method for MBL was used to measure bleeding in four trials.[63, 68, 75, 77] Three of these four reported mean MBL,[68, 75, 77] and three reported median MBL.[63, 75, 77] One study only reported median MBL,[63] and another only mean MBL.[68] One trial used the pictorial blood loss assessment chart, which is a validated chart that helps participants more uniformly report bleeding as represented by the degree of saturation of sanitary pads and tampons, for the outcome measure.

The timing of the summative outcome measure reporting varied among the trials. Two trials reported after two menstrual cycles.[68, 77] Four trials reported after three menstrual cycles.[63, 68, 76] One trial reported after six menstrual cycles.[75]

The setting varied: one trial was conducted in United States,[75] three in Europe,[63, 68, 77] and one in India.[76] Overall one was good quality, one fair quality and one poor. Details of quality scoring for individual publications are included in Appendix J.

Table 14. Primary outcomes of TXA for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Lukes et al., 2010[75] United States	**G1:** TXA 1.3 g three times daily up to five days per	• Mean reduction in MBL measured by alkaline hematin after 6 cycles was greater in G1 compared to G2 (p<0.001).

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Good	cycle (123) **G2:** Placebo (73)	• Proportion of women with at least 50 ml reduction in MBL was 56% in G1 and 19% in G2 (p<0.0001). • Women in G1 reported improvements in quality of life (measured by the Menorrhagia Impact Score) compared to G2 (p<0.01).
Preston et al., 1995[77] United Kingdom Fair	**G1:** TXA 1 g four times daily for four days (25) **G2:** Norethisterone 5 mg twice a day on days 19 to 26 (21)	• Mean reduction in MBL from baseline was 45% for G1 (p<0.0001); mean MBL increased in G2 (p=NS). • Fourteen (56%) women in G1 and two (9.5%) women in G2 achieved MBL<80 ml.
Kriplani et al., 2006[76] India Poor	**G1:** TXA 500 mg four times daily for five days (50) **G2:** MPA 10 mg twice daily days five to 25 (50)	• Both groups had significant (p<0.005) reductions in PBLAC scores after 3 months and mean reduction in blood loss was 60.3% in G1 and 57.7% in G2. • Hemoglobin levels rose in both groups (p<0.05 for both). • Three women in G1 (6.1%) and 13 (28.9%) in G2 did not respond to treatment (p=0.003).
Bonnar and Shepard, 1996[63] Ireland Poor	**G1:** TXA 1 g (26) **G2:** Ethamsylate 500 mg (27) **G3:** Mefenamic acid 500 mg (23)	• Women in G1 had blood loss reduction of 54% compared to 20% for women in G3. • No reduction in blood loss for G2.
Andersch et al., 1988[68] Sweden Poor	**G1:** [a] TXA for two cycles followed by flurbiprofen for two cycles **G2:** [a] Flurbiprofen for two cycles followed by TXA for two cycles (15)	• MBL was significantly reduced during treatment with flurbiprofen and TXA. • MBL was significantly (p<0.01) lower during treatment with TXA compared to flurbiprofen.

Note: [a] Crossover study. **Abbreviations:** MBL: menstrual blood loss; PBLAC: pictorial blood assessment chart.

Description of Results

Menstrual Blood Loss

The alkaline hematin method for MBL was used as an outcome measure in the two TXA trials of fair quality[75, 77] and two trials of poor quality.[63, 68] One poor quality trial utilized the pictorial blood loss assessment chart for the blood loss outcome measure, with menorrhagia defined as a score of 100 or greater.[76]

Menstrual Blood Loss Reduction Expressed as a Percent

The placebo-controlled trial reported a statistically significant reduction in mean MBL occurred among women in the modified intent-to-treat population receiving TXA for six menstrual cycles compared with those receiving placebo: 40.4 percent reduction compared with 8.2 percent reduction (p<0.001). The attributable reduction for TXA was 32.2 percent (p<0.001).[75]

The trial that compared TXA with norethisterone reported a statistically significant reduction in mean MBL occurred among women receiving TXA for two treatment cycles compared to those receiving norethisterone: 45 percent reduction (95% CI, 23% increase to 93% reduction; p<0.0001 versus baseline) compared with 20 percent increase (95% CI, 114% increase to 62% reduction; p=0.26 versus baseline).[77]

A trial that compared TXA with ethamsylate and with mefenamic acid reported that over three treatment cycles the mean reduction in MBL from baseline for the group receiving TXA was 54 percent (p<0.001). For the mefenamic acid group the mean reduction in MBL from baseline was 20 percent (p 0.001). For the ethamsylate group no effect was reported.[63]

A small crossover trial (n=15) that compared TXA with flurbiprofen reported that over two treatment cycles the mean reduction in MBL from baseline for TXA was 53 percent (p<0.01), compared to 24 percent for flurbiprofen (p<0.01).[68]

The trial that used the pictorial blood loss assessment chart score as the blood loss measure compared TXA with oral MPA and reported that over three treatment cycles the mean reduction in the pictorial blood loss assessment chart score from baseline for TXA was 60.3 percent, compared to 57.7 percent for MPA (p<0.005 for both interventions).[76]

Table 15. Percent change in blood loss from baseline in studies of TXA

Author, Year	Comparator	TXA Group (%)	Comparator Group (%)	TXA vs. Comparator Group
Lukes et al., 2010[75]	Placebo	-40.4	-8.2	p<0.001
Preston et al., 1995[77]	Norethisterone	-45.0	+20.0	p<0.0001
Bonnar and Shepard, 1996[63]	Mefenamic acid	-54.0	-20.0	NR
Bonnar and Shepard, 1996[63]	Ethamsylate	-54.0	0	NR
Andersch et al., 1988[68]	Flurbiprofen	-53.0	-24.0	p<0.01
Kriplani et al., 2006[76]	Medroxyprogesterone	-60.3	-57.7	p=NS

Abbreviations: NS: nonsignificant; NR: not reported.

Menstrual Blood Loss Reduction Expressed as a Volume

The placebo-controlled trial reported a statistically significant reduction in mean MBL occurred among women in the modified intent-to-treat population receiving TXA for six menstrual cycles compared with those receiving placebo: 69.6 ml reduction compared with 12.6 ml reduction (p<0.001). The attributable reduction for TXA was 57 ml (p<0.001). The calculated least-squares mean reduction in MBL in the modified intent-to-treat population receiving TXA was greater compared with those receiving placebo: 66.3 ml reduction compared with 17.8 ml; attributable reduction of 48.5 ml (p<0.001).[75] The trial had a predetermined threshold of 36 ml or greater representing a blood loss reduction considered meaningful to women.[75] The effect size for TXA (standardized observed effect), based upon the modified intention to treat analysis and the standard deviation was 0.67; the effect size, based upon the least squares mean change analysis and the standard deviation was 0.49.[75] The effect size for TXA compared to placebo is large.

A trial that compared TXA with norethisterone reported a statistically significant reduction in mean MBL occurred among women receiving TXA for two treatment cycles compared to those receiving norethisterone: 79 ml reduction (95% CI, 62 to 108 ml reduction) compared with 34 ml increase (95% CI, −2 to 64 ml increase).[77]

A trial that compared TXA with ethamsylate and with mefenamic acid reported that the pretreatment MBL in the group given TXA ranged from 143 to 178 ml, and over three treatment cycles the mean MBL was 72 to 77 ml, a mean reduction in MBL of 89 ml (range: 24 to 214 ml, no statistical analysis provided). For the ethamsylate group, the pretreatment MBL ranged from 157 to 185 ml, and over three treatment cycles the mean MBL was 161 to 185 ml, a mean increase of 8 ml (range: 280 to 103 ml, p=NR). For the mefenamic acid group, the pretreatment MBL ranged from 159 to 199 ml, and over three treatment cycles the mean MBL was 138 to 168 ml, a mean reduction in MBL of 43 ml (range 82 to 179 ml, no statistical analysis provided).[63] Head-to-head comparisons of the results of treatment on absolute changes in blood loss showed that TXA reduced the mean loss by 97 ml more than with ethamsylate (95% CI, 54 to 140 ml, p<0.001) and by 56 ml more than with mefenamic acid (95% CI, 2 to 90 ml, p<0.05).[63]

A small crossover trial that compared TXA with flurbiprofen reported that over two treatment cycles the mean reduction in MBL from baseline for TXA was 140 ml (SD ± 33 ml, p<0.01), compared to 72 ml for flurbiprofen (SD ± 44, p<0.01).[68]

The trial that used the pictorial blood loss assessment chart as the blood loss measure compared TXA with oral MPA and reported that over three treatment cycles the mean reduction in the pictorial blood loss assessment chart from baseline for TXA was from 356.96 baseline to 141.64, compared to a reduction from 370.24 baseline to 156.67 for MPA; both reductions were reported to be statistically significant (p<0.005).[76]

Table 16. Change in blood loss volume from baseline in studies of TXA

Author, Year	Comparator	TXA Group	Comparator Group	TXA vs. Comparator Group
Lukes et al., 2010[75]	Placebo	−69.6 ml	−12.6 ml	p<0.001
Preston et al., 1995[77]	Norethisterone	−79.0 ml	+34.0 ml	NR
Bonnar and Shepard, 1996[63]	Mefenamic acid	−89.0 ml	−43.0 ml	NR
Bonnar and Shepard, 1996[63]	Ethamsylate	−89.0 ml	+8.0 ml	NR
Andersch et al., 1988[68]	Flurbiprofen	−140.0 ml	−72.0 ml	NR

Abbreviations: NR: not reported.

Menstrual Blood Loss Reduction Below the Standard Definition of Heavy Menstrual Bleeding

The placebo-controlled trial reported a statistically significant difference for achieving a MBL below 80 ml (standard definition of heavy menstrual bleeding) in the modified intent-to-treat population between women receiving TXA for six menstrual cycles compared with those receiving placebo: 43 percent versus 17 percent (p<0.001).[75]

Quality of Life

The placebo-controlled trial reported a statistically significant difference in social or leisure activities, and in physical activity, favoring TXA (p<0.001).[75]

Head-to-Head Comparisons

Tranexamic Acid Versus Placebo

The placebo-controlled trial reported a statistically significant reduction in mean MBL in the subjects in the modified intent-to-treat population receiving TXA for six menstrual cycles compared with those receiving placebo: 40.4 percent reduction compared with 8.2 percent reduction ($p<0.001$); 69.6 ml reduction compared with 12.6 ml reduction ($p<0.001$).[75] The trial reported a statistically significant difference for achieving a MBL below 80 ml (standard definition of heavy menstrual bleeding) in the modified intent-to-treat population between women receiving TXA for six menstrual cycles compared with those receiving placebo: 43 percent versus 17 percent ($p<0.001$).[75]

Tranexamic Acid Versus Norethisterone

The trial that compared TXA with norethisterone reported a statistically significant reduction in mean MBL for women receiving TXA for two treatment cycles compared to no reduction for women receiving norethisterone.[77] Expressed as percentage reduction: 45 percent reduction (95% CI, 23% increase to 93% reduction; $p<0.0001$ versus baseline) compared with 20 percent increase (95% CI, 114% increase to 62% reduction; $p=0.26$ versus baseline); expressed as a measure of volume: 79 ml reduction (95% CI, 62 to 108 ml reduction) compared with 34 ml increase (95% CI, −2 to 64 ml increase).[77]

Tranexamic Acid Versus Mefenamic Acid, Ethamsylate, Flurbiprofen, and Medroxyprogesterone Acetate

The trial that compared TXA with ethamsylate and with mefenamic acid did not report statistics for head-to-head comparisons.[63] The trial that compared TXA with flurbiprofen did not report statistics for head-to-head comparisons.[68] The trial that compared TXA with oral MPA did not report statistics for head-to-head comparisons.[76]

Combined oral contraceptives

Key Points

- In two medium-sized RCTs, treatment of affected women with estradiol valerate and dienogest led to improvement in a range of AUB symptoms, including both overall complete response and effects on relevant laboratory values (e.g., hemoglobin, ferritin).
- In one small RCT and one small randomized crossover study of combination therapy with ethinyl estradiol and levonorgestrel and one small RCT assessing therapy with ethinyl estradiol and norethindrone acetate, COC treatment was associated with significant reductions in MBL loss as compared with baseline.

Table 17. Primary outcomes of COCs for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Fraser et al., 2011[78] United States, Canada Good	**G1:** estradiol valerate and dienogest (149) **G2:** placebo (82)	• Full resolution of qualifying abnormal menstrual symptoms during the first 90 days of treatment observed in 29.5% of G1, as compared with 1.2% of G2 (p<0.0001). • Significant reductions in volume of MBL (p<0.0001), days of bleeding (p=0.0186), and number of sanitary protection items used (p<0.0001) observed in G1 vs. G2. • G1 participants had significant improvements vs. baseline in hemoglobin, hematocrit, and ferritin values; no similar change in G2.
Jensen et al., 2011[79] Australia, Europe Good	**G1:** estradiol valerate and dienogest (120) **G2:** placebo (70)	• Full resolution of qualifying abnormal menstrual symptoms during the first 90 days of treatment observed in 43.8% of G1 vs. 4.2% of G2 (p<0.001). • Mean reduction in MBL was 353 ml in G1 vs. 130 ml in G2 (p<0.001). • G1 participants had significant improvements vs. baseline in hemoglobin, hematocrit, and ferritin values; no similar change in G2.
Shabaan et al., 2011[56] Egypt Poor	**G1:** LNG-IUS (56) **G2:** ethinyl estradiol and levonorgestrel (56)	• COC associated with significant reduction in MBL at 12 months vs. baseline, from 274.3±142.6 ml to 118.2±75.0 ml (p<0.001). • Reduction in MBL at 12 months was significantly greater in the LNG-IUS group vs. the COC group. • Significant improvements in patient assessment of overall health noted in both treatment groups.
Endrikat et al., 2009[58] Canada Poor	**G1:** LNG-IUS (20) **G2:** ethinyl estradiol and norethindrone acetate (19)	• Both arms experienced a significant decreased in MBL at 12 months as compared with baseline, with a decrease from a median MBL of 290 ml at baseline to a median of 72 ml at 12 months observed in the COC group (mean decrease 68%, p<0.001).
Fraser et al., 1991[65] Australia Poor	**G1[a]:** mefenamic acid (12) **G2[a]:** ethinyl estradiol and levonorgestrel (12)	• Significant reduction in MBL observed during the COC treatment cycles as compared with baseline (mean 43% reduction, p<0.001). • At least 20% reduction in MBL as compared with the preceding baseline cycles was observed in 10 of 12 patients during mefenamic acid treatment and 9 of 12 during COC treatment.

Abbreviations: LNG-IUS: levonorgestrel-releasing intrauterine system; MBL: menstrual blood loss; COC: combined oral contraceptive. **Note:** [a] Crossover study

Detailed Synthesis

We identified five RCTs that explored the effects of therapy with COCs on the incidence and severity of abnormal cyclic uterine bleeding, including two studies examining estradiol valerate and dienogest,[78, 79] two examining ethinyl estradiol plus levonorgestrel,[56, 65] and one examining the combination of norethindrone acetate and ethinyl estradiol.[58] All five studies were industry-sponsored.[56, 58, 65, 78, 79] Three were multicenter RCTs, involving Australia and Europe,[78] the United States and Canada,[79] and Canada,[58] and two were academic single center studies, one conducted in Egypt[56] and one conducted in Australia.[65] Two of the studies included seven 28-day cycles of therapy with the primary response rate determined after 90 days of therapy,[78, 79] while one examined outcomes after six months[65]and two assessed outcomes after 12 months[56, 58] . Two

studies employed a placebo comparison group,[78, 79] two compared COCs to LNG-IUS,[56, 58] and one included a randomized crossover comparison of a COC to mefenamic acid.[65]

All studies assessed measures related to changes in MBL, including use of the alkaline hematin method[56, 65, 78, 79] and the pictorial blood loss assessment chart.[56, 58] Other outcomes included number of sanitary items used, a composite outcome of menstrual bleeding-related factors,[78, 79] and related hematologic parameters (i.e., hematocrit, hemoglobin, and/or serum ferritin).[56, 58, 78, 79] One study also assessed potential impact on health-related quality of life[56] and one described effects on a menorrhagia symptom severity score.[58]

Among the five studies of COC therapy, two were good quality[78, 79] and three were poor quality.[56, 58, 65] None of the studies assessed any potential effect modifiers.

Estradiol Valerate and Dienogest

Two multicenter RCTs with the same industry sponsor assessed the utility of estradiol valerate and dienogest in treatment of women with AUB, defined as prolonged, frequent, and/or heavy bleeding. The first RCT[78] was conducted in Australia and Europe and comprised 231 women, randomized at a 2:1 ratio after a 90-day run-in period to receive estradiol valerate and dienogest for seven 28-day cycles. The study drug regimen included estradiol valerate 3 mg on days one to two, estradiol valerate 2 mg and dienogest 2 mg on days three to seven, estradiol valerate 2 mg and dienogest 3 mg on days eight to 24, estradiol valerate 2 mg on days 25 to 26, and placebo on days 27 to 28. Complete response, defined as full resolution of qualifying abnormal menstrual symptoms during the first 90 days of treatment as compared with the 90-day run-in phase, was observed in 29.5 percent of the estradiol valerate and dienogest group, as compared with 1.2 percent of the placebo-treated patients ($p<0.0001$). Treatment with estradiol valerate and dienogest was also associated with significant reductions in volume of MBL ($p<0.0001$), days of bleeding ($p=0.0186$), and number of sanitary protection items used ($p<0.0001$) as compared with the placebo group. The estradiol valerate and dienogest-treated patients also experienced significant improvements versus baseline in hemoglobin, hematocrit, and ferritin values; similar improvements were not observed in the placebo-treated group.

The second RCT[79] was conducted at centers in the United States and Canada, employing the same dose and randomization schema and including 190 women with AUB. Complete response, defined as full resolution of qualifying abnormal menstrual symptoms during the first 90 days of treatment as compared with the 90-day run-in phase, was observed in a significantly greater proportion of the estradiol valerate and dienogest group (35/80, 43.8%) as compared with the placebo group (2/48, 4.2%, $p<0.001$). The mean reduction in MBL was also greater in the estradiol valerate and dienogest (−353 ml or −64.2% vs. loss during run-in phase) when compared with the placebo group (−130 ml or −18.7% vs. observed run-in loss, $p<0.001$). Individuals in the estradiol valerate and dienogest group also experienced significant improvements in hemoglobin, hematocrit, and ferritin values as compared with the run-in phase, while similar improvements were not observed in the placebo group.

Ethinyl Estradiol and Levonorgestrel

Two randomized controlled trials assessed the utility of an ethinyl estradiol (30 mcg) and levonorgestrel (150 mcg) combination in women with menorrhagia.[56, 65] One of these trials was a single center RCT involving 112 women with idiopathic menorrhagia randomized to LNG-IUS (n=56) or ethinyl estradiol plus levonorgestrel (n=56) for 12 months.[56] Efficacy data from the

LNG-IUS arm of the study is discussed further in the levonorgestrel-releasing Intrauterine System section of this report. In this trial, the COC regimen was associated with significant reduction in MBL as assessed by the alkaline hematin method at 12 months as compared with baseline, from 274.3 ± 142.6 ml to 118.2 ± 75.0 ml ($p<0.001$); however, the overall reduction in MBL was significantly greater in the LNG-IUS group as compared with the COC group. Significant improvements in patient assessment of overall health and reduction in physically ill days were noted in both treatment groups.

The other trial assessing the use of ethinyl estradiol and levonorgestrel was a crossover study in women with menorrhagia, with one arm comparing outcomes of 12 women treated sequentially with mefenamic acid (500 mg every 12 hours from first sign of menses until 24 hours after usual duration of heavy bleeding) and COCs for two cycles each in random order, with a two cycle washout period between treatment cycles.[65] Additional efficacy details for mefenamic acid and for another treatment arm in this study involving naproxen are further discussed in the NSAIDs section of this report. A significant reduction in MBL as measured by the alkaline hematin method was observed during the COC treatment cycles as compared with baseline (mean 43% reduction, $p<0.001$); the reduction in the mefenamic acid treatment period was not significantly different than the COC treatment period. A response of at least 20 percent reduction in MBL as compared with the preceding baseline cycles was observed in 10 of 12 patients during mefenamic acid treatment and 9 of 12 during COC treatment. One patient responded to COCs but not to mefenamic acid, and two patients exhibited a response to mefenamic acid but not to the COC regimen.

Ethinyl Estradiol and Norethindrone Acetate

One multicenter randomized controlled trial compared the combination of ethinyl estradiol (20 mcg) and norethindrone acetate (1 mg) to use of an LNG-IUS over 12 months in 39 women with idiopathic menorrhagia.[58] Efficacy data from the LNG-IUS arm of the study is also discussed further in the levonorgestrel-releasing intrauterine system section of this report. The LNG-IUS arm included 17 women and the COC arm included 12. Both arms experienced a significant decreased in MBL at 12 months as compared with baseline values ($p<0.001$ for both groups), with a decrease from a median MBL of 290 ml at baseline to a median of 72 ml at 12 months observed in the COC group (mean decrease 68%). The decrease in MBL, however, was significantly greater in the LNG-IUS group versus the COC group ($p=0.002$). Treatment success, defined as MBL less than 100 at 12 months, was observed in a significantly greater proportion of the LNG-IUS participants as compared with the COC group, 80 percent versus 36.8 percent respectively ($p<0.009$). Menorrhagia symptom severity scores were also significantly lower in the LNG-IUS group at six months as compared with the COC group ($p=0.045$). No significant changes in hemoglobin concentration were observed in either group during the study.

Use of Decision Aids in Treatment of Menorrhagia

Key Points

- Three RCTs evaluated decision aids to assist patients with menorrhagia. All were of poor quality due to lack of blinding of participants and care providers.

- Improvements in general health status, the primary outcome for two studies, were not associated with decision aids. One study reported lower use of hysterectomy among women who had an interview prior to their consultation while another study did not show differences in hysterectomy rates after one year. Two studies did not report differences in treatment outcomes after six months or one year.

Detailed Synthesis

Decision aids are interventions to inform patients of their treatment options when more than one option exists. A recent Cochrane review of RCTs of decision aid[84] found that decision aids are beneficial in increasing patient knowledge of treatment options, help to clarify benefits and harms associated with therapeutic choices, and increase patient participation in decision selection. They have been shown to reduce elective surgery and have no apparent adverse effects on patient outcomes or satisfaction.[84]

We identified three RCTs with four publications[80-82, 85] about medical decision aids in women with menorrhagia. All of the studies used a written decision aid booklet; one study evaluated a computerized decision aid in conjunction with the pamphlet and one study also mailed participants a videotape and conducted an interview prior to clinical appointment. Diagnosis of menorrhagia was determined from medical records and not quantified in any of the studies. Length of followup ranged from six months to 2 years. Two studies were conducted in the United Kingdom[81, 82] and one was conducted in Finland.[80] These studies were all of poor quality.

The largest study (n=894), conducted in England, randomized women to receive booklet and videotape with interview, materials without interview, or standard practice groups.[81] General health status improved significantly and menorrhagia severity decreased in all three groups. Treatment rates were similar in all groups after two years. Women in the interview group had a lower rate of hysterectomy and reported greater satisfaction with treatment results. A medium sized Finnish study evaluated the effectiveness of a mailed information booklet on treatment outcomes and general health status after one year.[80, 85] More women who received the decision aid were less likely to receive newer treatment methods including minor surgery or LNG-IUS (16% vs. 26%, p=0.03). Most of the measured health outcome scores improved after one year for both groups with no significant difference in patient satisfaction, knowledge, anxiety or sexual satisfaction.

A small English study[82] conducted from 2003 to 2005 evaluated a computerized decision aid in conjunction with a patient leaflet. Women in the intervention group had significantly less decisional conflict at two weeks and higher knowledge scores at six months. There were no significant group differences in anxiety or treatments received after six months.

Although decision aids do help to increase patient knowledge, here are some methodological limitations in these studies, including low participation rates, large number of drop outs, and lack of blinding. The diagnosis of menorrhagia was not quantified and no effect modifiers were examined in any of these studies.. Information on harms was not reported in any of the decision aid studies.

Table 18. Primary outcomes of decision aids for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Outcomes	Results
Protheroe et al., 2007[82] United Kingdom Poor	**G1:** Computerized decision aid and information leaflet (74) **G2:** Information leaflet only (72)	**Primary:** total score on Decisional Conflict Scale **Secondary:** anxiety, quality of life, knowledge, treatment preferences	Decisional conflict was significantly reduced in G1 vs. G2 (adjusted difference 16.6 95% CI, 21.5 to 11.6, p<0.001). Anxiety declined slightly for both groups (p=NS). Quality of life and knowledge scores improved in both groups but more in G1 as compared to G2.
Vuorma et al., 2004[80, 85] Finland Poor	**G1:** Information booklet (184) **G2:** Usual care (179)	**Primary:** planned treatment at 3 months and actual treatment at 1 year General health status measured by RAND -36 **Secondary:** knowledge of treatment methods, satisfaction with communication anxiety and sexuality	Fewer women in G1 received newer treatments (minor surgery or LNG-IUS) (p=0.03); hysterectomy rates were similar in both groups. Most health status measures improved for both groups. At 3 months 18% of women in G1 and 8% in G2 had received prescription for oral medication (p=0.007). There were no differences between groups in anxiety, satisfaction, knowledge or sexual satisfaction.
Kennedy et al., 2002[81] United Kingdom Poor	**G1:** Interview and information booklet (300) **G2:** Information booklet only (296) **G3:** No intervention (298)	**Primary:** general health status measured using SF-36 **Secondary:** treatments received during followup, severity of menorrhagia, patient satisfaction	Health status measures improved for all three groups Treatment rate (81%) during study was similar for all three groups (p=0.17) but women in G1 were less likely to have a hysterectomy (OR 0.60 95% CI, 0.38 to 0.96). G1 were more satisfied in taking part in treatment decision and with results compared to G3.

Abbreviations: CI: confidence interval; OR: odds ratio; NS: nonsignificant.

KQ2. Harms of Interventions for Management of Abnormal Bleeding

Description of Included Studies and Sources of Information

Capturing useful information about potential harms of treatment for reproductive age women that is specifically applicable to interventions for abnormal bleeding is a challenge. A wide range of interventions are used to treat abnormal bleeding. Eleven interventions relevant to the primary care setting were identified for this report. They range from medications that are exceptionally familiar to providers such as nonsteroidal anti-inflammatory drugs to potentially less familiar or newer medications like exenatide (an injectable diabetes agent). Interventions also include those with widespread use and many indications, like oral contraceptive pills or acupuncture, as well as those specifically for the indication of abnormal bleeding like TXA.

We took a four step approach to structuring this key question about harms.

- Summarizing harms detected within clinical trials included in this review. This has limitations since many of the studies are small, with a range in size of 11 to 894 and a median

total study population of 64. Thus they are not well-suited to detecting events that are rare but may be serious or affect a specific subgroup of women.

- Compiling the key content of FDA documents and package inserts for specific products addressed in this review. This however lacks specificity as many of these products have multiple indications and the concerns may not be as applicable to the population of women with AUB or to the dose and duration of use for treating AUB.
- Searching for surveillance studies that aimed to examine risk of harm in large populations of individuals (i.e., 1600 or more) using the specific intervention. This last step was done using a separate search described in greater detail in methods. We prioritized summarizing results from harms surveillance studies of: metformin, exenatide, cabergoline, and LNG-IUS.
- Providing information about existing contemporary reviews and guidance on harms for common medications with broad indications. Like the second approach it is important to note that these extant literature reviews reflects varied indications and populations that may not be directly applicable to use for AUB.

The organization of this chapter includes evidence about harms from these sources in the following order:

- Harms identified in randomized trials included in this review.
- Harms flagged in FDA package inserts and regulatory proceedings.
- Harms investigated in large surveillance studies of metformin, exenatide, LNG-IUS, and TXA.
- Contemporary reviews that include review of harms

We present this summary of harms in the same order of key questions and intervention methods as the results for our key questions. Interventions for irregular uterine bleeding are present before those for heavy cyclic bleeding.

Key Points for Harms of Reviewed Treatments

- Metformin is associated with increased risk of gastrointestinal symptoms like diarrhea and abdominal pain. Symptoms can be reduced by slowly increasing the dose. Severe harms including lactic acidosis, serious hypoglycemia, and liver failure, studied among populations of adult diabetics, occur at incidence rates below 1 in 10,000 and may be as low as 1 in 100,000 person-years of exposure.
- Progestogens are associated with a number of common side effects of hormonal preparations including weight gain, fluid retention, abdominal pain, nausea, change in mood, and change in appetite. Each progestogen has different risk profiles with regard to deep venous thrombosis, risk is lower with progestogens alone compared to those medications that also contain estrogens.
- COCs have commonly recognized side effects that include edema, breast tenderness, nausea, headache, and skin changes. Known contraindications, including advancing age, smoking, and high risk of thrombosis, apply when considering use of COCs for irregular bleeding. Selected COC formulations may have lower risk of deep vein thrombosis than others.
- Cabergoline has few known distinct harms however, data is inadequate to assess risk in young women without elevated prolactin.

- LNG-IUS has few serious harms after insertion, with irregular bleeding, especially early after insertion being among the most common. Painful insertion occurs in roughly one procedure in 100, 3.2 percent are technically difficult, and uterine perforation occurs in 0.9 to 2.6 cases per 1000. The LNG-IUS is not associated with increased deep vein thrombosis risk.
- NSAIDs have common harms that include abdominal pain, nausea, gastritis, and lightheadedness/dizziness. Gastrointestinal bleeding is a serious side effect that relates to total dose and duration of use, however even short term use can increase risk, though the occurrence of the latter with lower doses intermittently is poorly characterized.
- TXA use is associated with headache, nasal and sinus symptoms, back pain, and abdominal pain in more than 10 percent of those taking the drug. Joint pain, muscle cramps, migraine, anemia and fatigue occur in more than five percent. Rare events are less well characterized and may include thrombosis, anaphylaxis, and visual disturbances. TXA is contraindicated in those with higher risk of thrombosis.
- Other than COCs, progestogens, and the LNG-IUS, the available data may not apply well to populations of young women using these treatments.

Detailed Summary

Harms Related to Metformin Use

Information about Metformin from Included Trials

Metformin was investigated in two placebo controlled trials[49, 50] and in two arms of a three arm trial in which two arms included metformin:[51] one metformin alone and another with combined oral metformin and exenatide weekly injections. Doses used in these studies, after an initial one week dose ramp up were 850 mg twice a day,[49] 500 mg three times each day,[50] and 1000 mg twice daily.[51] Combined, the three RCTs with four total metformin arms administered the drug to only 77 women, 20 of whom were also receiving another agent.[49-51] This provides insufficient power to detect events that occur at the level of one to five percent or lower that are typically of concern for harms. It also provides insufficient power to conclude that specific symptoms were statistically more common among those treated than among the 33 women who received placebo in two studies.[49, 50] Women receiving metformin did report gastrointestinal symptoms, including diarrhea, abdominal pain, and nausea at higher absolute numbers than those in the placebo or exenatide only groups,[50, 51] and the study reporting withdrawals[49] documented three times more women on the active drug withdrew from the trial for side effects (15 of 45 compared to 5 of 47; $p<0.05$).

Information about Metformin from FDA Documents and Package Inserts

Increased gastrointestinal complaints are consistent with the documented side effects listed in the package insert for metformin which include: diarrhea, nausea/vomiting, flatulence, indigestion, and abdominal discomfort as events that are the most common and expected to occur in more than five percent of those who initiate the drug.[86] Of note, it is recommended that the dose be increased gradually over one week or more precisely because these effects are common and can be reduced by gradual introduction of the drug. The most serious known side effect of metformin is lactic acidosis which occurs when lactate accumulates in the blood and decreases

blood pH. The package insert includes a boxed warning for this concerning effect.[86] Little is known about how common lactic acidosis might be among reproductive age women, with PCOS and not type 2 diabetes, similar to those in the study or for whom the intervention might be considered as part of primary care management of irregular uterine bleeding.

Information about Metformin from Large Datasets

Our literature search aimed at identifying publications designed to investigate harms, required more than 1,600 exposed individuals, or for case-control analyses, case identification consistent with a base population of more than 1,600. We identified four publications focused on metformin harms.[87, 88, 89, Lewis, #768]

The Toxic Exposure Surveillance System (TESS) database of the American Association for Poison Control Centers provided data from 1996 through 2000 for accidental and intentional over ingestion and unintentional misuse of metformin for 4,072 cases[87] Fifty-nine percent were women and the majority was adults. Children under twelve had few serious side effects and no deaths. Among adults, harms were evenly distributed across ages with a trend for more serious outcomes in the elderly. In all groups lactic acidosis was rare (1.6%) and hypoglycemia at 2.8 percent was more common that previously reported. Given all individuals had unintended or/higher that therapeutic doses, they also observed elevated creatinine levels, an increased anion gap, hypotension and coma among those hospitalized.

The first publication focused on harms of intended use was published in 2003 to assess incidence of serious acute liver injuries in patients on hypoglycemic agents.[88] The population comprised the 171,264 members of five health maintenance organizations receiving oral diabetes medications. They identified 35 cases of acute liver failure, not known to be attributable to another cause. Incidence per 1000 person years of use was not statistically meaningfully different by medication used, after adjusting for other comorbidities and confounders. Overall occurrence was roughly 1 case per 10,000 person years in this population of all adult diabetics.[88]

In 2008, an analysis using the U.K. General Practice Research Database undertook an analysis of the risk of lactic acidosis and hypoglycemia among 50,048 type 2 diabetics using oral medications.[89] The average age of patients included in the analysis was 60.7 ± 11.7 and 54.8 percent were women. They determined the incidence rate of lactic acidosis was 3.3 per 100,000 person years among metformin users and 4.8 per 100,000 person years among those on sulfonyl ureas. The adjusted odds ratios for both lactic acidosis and severe hypoglycemic episodes were significantly higher for those on sulfonyl ureas than metformin with a more than two-fold elevation in risk. However this analysis also did not include individuals taking metformin for indications other than diabetes.

A retrospective cohort of more than 44,169 diabetic patients in a prepaid health plan followed for an average of 4.2 years evaluated use of endoscopy.[90] The exposure of interest was defined by prescription of specific diabetes medications and the outcome of interest was lower gastrointestinal tract endoscopy including flexible sigmoidoscopy and colonoscopy. The analysis was undertaken in part out of concern that therapy with metformin, with attendant risk of GI side effects, could increase use of lower tract endoscopy. Forty-seven percent of participants were women with an average age of 66. The authors found that rates of endoscopy were higher among all groups of diabetics on medications, including those using insulin. Taking into account the precision of the estimates, there was no evidence that metformin led to excess use compared to other medications either in the window immediately after initiation or with chronic use. Over the

higher use of endoscopy may simply reflect greater screening and prevention vigilance among these patients with a chronic disease. No comparison is offered to rates among diabetics controlled with diet and exercise alone.

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Information about Metformin from Systematic Reviews

Estimates for withdrawals related to inability to tolerate the drug in included trials are consistent with meta-estimate in the AHRQ systematic evidence review on *Screening and Management of Obesity in Adults* which reported a risk ratio of 3.92 (95% CI, 1.23 to 12.57) for withdrawals in metformin treated groups compared to placebo in trials aimed at weight loss and not diabetes management.[91] The report likewise found excess complaints of GI symptoms but was not able to quantify risk finding evidence about harms insufficient to inform care.[91]

Similar to the surveillance data, a Cochrane pooled analysis of comparative data from 347 trials found an upper limit of 4.3 cases of lactic acidosis per 100,000 patient years among metformin-treated diabetic patients; the analysis indicated no significant difference in mean treatment levels or net change from baseline for lactate for metformin users as compared with users of other therapies represented in the included trials. This review also notes that the only evidence for lactic acidosis associated with metformin use is based on approximately 330 cases reported in the literature.[92] The 2011 AHRQ comparative effectiveness review on *Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update* included 140 trials with a meta-analysis.[93] Across all data sources in their review, the reviewers concluded there was high grade evidence that metformin was associated with greater occurrence of gastrointestinal side effects alone and in combination with other diabetes medications than with other agents alone or in combinations that did not include metformin. Nonetheless the overall safety profile and effectiveness of metformin led to the conclusion was the first line agent of choice for initial management of type 2 diabetes. The authors take care to point out that even among trials for a chronic condition like type 2 diabetes, longer term surveillance for harms does not exceed two years. As in diabetes, women with abnormal bleeding might wish to consider chronic treatment and the literature to assess safety of continued use for any indication is scant.

Within a number of reviews of oral diabetes agents[94, 95] metformin is typically found to have a favorable safety profile when compared to other medications and is often noted to be first line therapy in part for this reason. Relative safety in the context of other options for treating diabetes is not directly applicable to use for improving menstrual cycle regularity, however there are no

physiologic reasons to expect that younger individuals without diabetes would experience greater risk.

Harms of Exenatide Use

Information about Exenatide from the Included Trial

A single RCT in this review investigated exenatide, finding that alone it was less effective than metformin, but that when combined the results were superior to either agent alone for improving cycle regularity in women with PCOS.[51] Exenatide is injected weekly and is generally administered as a second agent among those with diabetes that is insufficiently controlled on a single agent. The trial included in this review allocated women with PCOS to three groups: 1000 mg of metformin twice daily, exenatide 10mcg per day, or both.[51] Nausea, diarrhea, and bloating were more common in the arms taking metformin. No harm was more common in the exenatide group except injection site pain or bruising which was de facto restricted to groups using exenatide. Comparisons across groups of 20 are underpowered to detect differential harms across groups or to detect more rare and potentially serious harms.

Information about Exenatide from FDA Documents and Package Insert

The package insert for exenatide notes that hypoglycemia is a common adverse effect but does not specify what proportion of those prescribed the drug might experience low blood sugar.[96] Events that occurred in two percent or more of new users of exenatide when added to a regimen with metformin or a sulfonyl urea include: nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia, asthenia which is a lack of strength or energy, gastroesophageal reflux, and increased sweating. Postmarketing experience includes reports of: injection-site reactions; generalized pruritus and/or urticaria; macular or papular rash; angioedema; anaphylactic reaction; International normalized ratio (INR) increased with concomitant warfarin use sometimes associated with bleeding; nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension; abdominal pain; eructation; constipation; flatulence; acute pancreatitis; hemorrhagic and necrotizing pancreatitis sometimes resulting in death; dysgeusia; somnolence; altered renal function, including increased serum creatinine; renal impairment; worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis); kidney transplant and kidney transplant dysfunction; and alopecia (Byetta Package Insert, 2011).[96]

Information about Exenatide from Large Datasets

Surveillance studies have all focused on acute pancreatitis which is suspected of being a rare but important side effect. Two analyses in large patient pools did not identify an association,[97, 98] while a third publication with data from the FDA post marketing surveillance database did see increased risk for both exenatide and another drug with similar but not identical mechanism, sitagliptin.[99]

The two claims-based analyses relied on large databases of health plan enrollees: The Ingenix Research Datamart[97] and the Normative Health Information database.[98] The first examined 27,966 individuals who began exenatide and 16,276 who started sitalgliptin.[97] During one year of followup, acute pancreatitis occurred in 0.13 percent of those on exenatide and 0.12 percent of those on sitagliptin. In adjusted models, relative to comparison cohorts within the health plan the relative risk of acute pancreatic was 1.0 for both groups with confidence bounds

from 0.6 to 1.7 and 0.5 to 2.0, respectively. The second analysis included 25,719 new users of exenatide compare to 234,536 new users of other diabetes medications.[98] The groups differed in important ways including more obesity and concomitant diabetes medications among those using exenatide. In adjusted models to control for these and other factors, there was no increase in use for current or recent use but an elevation in risk for past use. This was compared with a matched case-control analysis that found no association for any category of current, recent, or past use. This is compatible with those with past use having unknown additional comorbidity or discontinuing use because of other serious health events. The authors conclude overall there was not increased risk of pancreatitis among those taking exenatide.

The FDA surveillance data compared adverse events for exenatide to those for other drugs in the database.[99] They found the odds of being on exenatide were more than 10 fold higher than among those on the control drug. Pancreatic cancer was almost three fold higher. The sole control for confounding was the use of those on other drugs in the registry as a comparator. The authors note that the FDA data is limited by incomplete data and reporting bias, notably they lack information about obesity and individual behaviors such as alcohol use and the risk models are not adjusted for these confounders.

Information about Exenatide from Systematic Reviews

Systematic reviews of diabetes medications, including the AHRQ report above on obesity treatment, a detailed comparative effectiveness review conducted by the United Kingdom's National Health Service, and a Cochrane analysis including exenatide, reveal gastrointestinal issues, particularly nausea and vomiting, and hypoglycemia as the most commonly observed side effects observed in those initiating therapy with this agent.[91, 100, 101]

Harms Related to Progestogen Use

Information about Progestogens from Included Trials

A single RCT included in this review investigated progesterone use for improving cycle regularity.[47] The two agents used in this comparative effectiveness trial were 20 mg of oral dydrogesterone, each day for ten days, or 90 mg of micronized progesterone gel vaginally every other day for ten days. The authors' intent was to demonstrate that both oral and vaginal administration improved cycle control which was the case compared to baseline. However power calculations did not indicate the equivalence band desired and the overall study was small (n=69). They report the only adverse events experienced were in the vaginal progesterone group and included one episode each of groin pain, ovarian cyst, and 5-kg weight gain. These events were too rare given the small study size to meaningfully assert comparability or excess of harms between groups. Six patients in each treatment group withdrew for the study without reasons given; which suggests there was not a large discrepancy in willingness to stay on study drug.

Progestogens used in studies in our review to treat abnormal cyclic bleeding included dydrogesterone,[47] MPA (both injectable and oral forms),[57, 59, 76]progesterone (vaginal gel, oral, or coil),[47, 71] and norethisterone (also known as norethindrone).[61, 67, 71, 77] Harms reported with this class of drug include: breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; headache; nervousness; dizziness; edema; increases or decreases in weight; change in cervical secretions; cholestatic jaundice, breast tenderness and galactorrhea; skin sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash; acne, alopecia and hirsutism; rash

(allergic) with and without pruritus; anaphylactoid reactions and anaphylaxis; depression; pyrexia; fatigue; insomnia; nausea; and somnolence.[102-105] Most studies reviewed were small and did not systematic compared adverse events across interventions groups. Progestogens in all but one case were a comparator that was hypothesized and found to perform less well that the intervention under study. The one exception was a direct comparison of two routes of delivery discussed above.[47] We have considered COCs and the LNG-IUS in their own section.

Information about Progestogens from FDA Documents and Package Inserts

We have summarized information for progestin only methods included in this review. The label for Crinone, the progesterone vaginal gel, reports adverse events seen in the three clinical studies for secondary amenorrhea in women taking either 4-percent or 8-percent strength Crinone along with estrogen and occurring in 5% or more of women.[103] These are given as: abdominal pain (5% in patients taking 4% strength, 9% in patients taking 8% strength, respectively); appetite increased (5%, 8%); bloating (13%, 12%); cramps not otherwise specified (19%, 26%); fatigue (21%, 22%); headache (19%, 15%); nausea (8%, 6%); back pain (8%, 3%); myalgia (8%, 0%); depression (19%, 15%); emotional lability (23%, 22%); sleep disorder (18%, 18%); vaginal discharge (11%, 3%); upper respiratory tract infection (5%, 8%); and pruitis in genital area (2%, 6%).[103] The package insert for vaginal progesterone gel includes a warning that "physicians should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis)."[103]

This profile of complaints is similar among smaller groups of women who receive the drug as part of treatment for infertility care. One of the specific agents studied among women with irregular menses, dydrogesterone, is not available in the United States. This compound has been associated with risk of onset of acute porphyria. Porphyria is a genetic condition in which individuals have a range of severities of defects in the enzyme pathways that produce heme. The insert advises prescribing only for compelling reasons. Our review team does not find evidence that other progestogens are associated with acute onset of porphyria symptoms.

The DMPA label[104] includes a warning to women who may become pregnant while using the drug or find themselves exposed to the drug during the first four months of pregnancy regarding the risk of hypospadias; the risk of hypospadias, usually 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure to these drugs.[104] Additionally, there have been undesirable effects at the site of injection, such as residual lump, change in skin color, or sterile abscess.[104]

Information about Progestogens from Large Datasets

The specific compounds used for irregular uterine bleeding or abnormal cycle bleeding were not addressed in large surveillance studies or in systematic review that compiled information about harms separate from their inclusion in COCs with the exception of DMPA.

As noted, we have not attempted to review the surveillance literature related to harms of oral contraceptives or specific progestogens in COCs. We did however seek large scale primary studies related to harms of progestin-only formulations such as DMPA. A Danish case-control study that included 64,548 women with fractures indicated an association of DMPA use with OR =1.44 (95% CI,1.01 to 2.06), this however was not adequately controlled for factors that may confound the relationship, such as the potentially increased use of DMPA among smokers or those with lower BMI which are both also associated with fracture risk.[106] A study in South

Africa, evaluated bone density in 3487 black, reproductive age women using injectable progestogens as contraception and reported decreased bone density by measurement of heel bone density; this effect was reversible within two to three years of discontinuing the injected progestogen across age categories of users.[107] These findings are compatible with data from smaller studies which they review well in their publication.

DMPA has been associated in observational studies with deep venous thrombosis,[108] however, intriguing work comparing those who use medications for menorrhagia has documented increased risk among women who use TXA, mefenamic acid, and norethisterone, suggesting that the increased risk of thrombosis may be an example of confounding by indication. Such confounding suggests that the reason for which the medication is administered itself increases risk of the adverse outcomes.[109] In a comprehensive study of 9262 DMPA users in Turkey conducted between 1996 and 2004, deep vein thrombosis was not observed.[110] The most common adverse effects reported were menstrual disturbances (80%), weight gain (10%), bloating, breast pain, headache, mood change, and sexual difficulties (each reported by more than 1%). More than one-third of women discontinued the method with the most common reasons for discontinuing other than desiring to conceive being irregular menses and side effects.

Information about Progestogens from Systematic Reviews

A Cochrane review examining the use of progestogens for the treatment of heavy menstrual bleeding found that progestogens had a generally better side effect profile than danazol, with lower incidence of side effects such as headache, weight gain, and skin changes; however, breast changes were relatively more common in the progestogens group.[111] In the context of evaluating progestin-only pills for contraception, another Cochrane review found inter-cycle bleeding and cycle irregularity to be some of the most common reasons for treatment discontinuation represented in included trials.[112]

Harms Related to Combined Oral Contraceptive (COC) Use

Information about COCs from Included Trials

Among women with irregular menses only one study treated with COCs. Davis and colleagues [48] assessed a triphasic pill in which the estrogen was ethinyl estradiol and the progestogen was norgestimate. Their trial among women with dysfunctional uterine bleeding, randomly assigned 201 women to the oral contraceptive arm or a placebo. No formal assessment of specific observed harms is provided. Four women in the treated and three in the placebo group discontinued use after adverse events. Sixteen percent of those on active drug and 19 percent of those receiving placebo withdrew prior to completion of the trial.

Our review included six RCTs examining COC use in women with abnormal cyclic bleeding.[48, 56, 58, 65, 78, 79] Due to the low power of these three medium sized RCTs and three small RCTs for detecting adverse events, reports of potential harms in these publications are largely limited to descriptive text rather than quantitative comparisons.

The two trials assessing the use of estradiol valerate and dienogest in women with AUB each found that nine to ten percent of women discontinued therapy with the COC regimen due to side effects.[78, 79] The type and incidence of adverse effects noted in these two studies of estradiol valerate and dienogest are similar to those noted in the package insert for this combination.[113]

One RCT assessing use of triphasic norgestimate-ethinyl estradiol observed adverse event-related discontinuation rates of approximately three to 4 percent of women in both the treatment group and the placebo group; authors do not provide detailed description of adverse events, noting that the incidence was low and comparable between the two groups.[48]

The trial examining therapy with ethinyl estradiol and norethindrone acetate reported that five women discontinued the study due to adverse events (approximately 25%), noting that the most comment events included intermenstrual bleeding, menstrual disorder, and headache.[58] The two studies involving use of ethinyl estradiol and levonorgestrel did not describe potential harms associated with treatment failure, other than noting the incidence of treatment failure.[56, 65]

Information about COCs from FDA Documents and Package Inserts

The package inserts are similar for all combined estrogen and progestogen oral contraceptive pills. The warning for combined pills notes:

> "Cigarette smoking increases risk of serious cardiovascular events from combined oral contraceptive (COC) use. This risk increases with age particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COC's should not be used by women who are over 35 years of age and smoke."[114-116]

Other serious harms associated with COCs include thrombophlebitis and venous thrombosis with and without embolism, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis, hypertension, gallbladder disease and benign liver tumors. A complete listing of package insert adverse events for this and other oral contraceptives reviewed in this report is included in Appendix N. Package inserts do not generally include information about the expected population incidence of these harms.

The majority of primary care providers and many women are aware of the most serious risks of COCs and of more common side effects such as edema, nausea, vomiting, skin changes, and gastrointestinal symptoms. Among more common side effects are also changes in cycle characteristics themselves including spotting/breakthrough bleeding, lack of menses, and change in characteristics of menstrual flow.

Adverse events for specific COCs studied for heavy menstrual bleeding in this review include Nordette-28® (0.03mg ethinyl estradiol and 0.15mg levonorgestrel). The package insert reports based on data from case control studies, the relative risk for superficial venous thrombosis is 3 times higher in users of the COC compared to nonusers; the risk of deep vein thrombosis or pulmonary embolism is 4 to 11 times higher, and 1.5 to 6 times higher in women predisposed to venous thromboembolic disease.[115] For users of low dose (i.e., less than 0.05 mg ethinyl estradiol) combination oral contraceptives, the incidence of deep-vein thrombosis and pulmonary embolism is up to 4 per 10,000 woman-years compared to 0.5 to 3 per 10,000 woman-years for nonusers, although this risk is less than that associated with pregnancy (reported to be six per 10,000 woman-years).[115] A large postmarketing study noted in the label information for Nordette reports a relative risk of thrombotic strokes ranging from three for normotensive users to 14 in women with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers using oral contraceptives, 2.6 for smokers who did

not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users, and 25.7 for users with severe hypertension.[115]

Label information on estradiol valerate and dienogest (Natazia®) reports two cases of myocardial infarction and two cases of rupture ovarian cyst from clinical trials, along with known serious risk of other cardiovascular events, vascular events, and liver disease (the estimated attributable risk of liver adenomas is 3.3 cases/100,000 COC users).[113] In clinical studies of the drug, 11.4 percent of women discontinued treatment due to an adverse reaction, most commonly: menstrual disorder (metrorrhagia, menorrhagia, menstruation irregular, genital hemorrhage, vaginal hemorrhage, dysfunctional uterine bleeding) (2.3%); mood changes (depression, mood swings, mood altered, depressed mood, dysthymic disorder, crying) (1.2%); acne (1.1%), headache (including migraines) (1.1%), and weight increased (0.7%).[113]

Postmarketing reports with Natazia include: venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, myocardial infarction and stroke); hypertension; gallbladder disease; hepatitis; hypersensitivity; fluid retention; hypertriglyceridemia; dizziness; chloasma; angioedema; erythema nodosum; erythema multiforme; vulvovaginal candidiasis; and gastrointestinal symptoms.[113]

Information about COCs from Large Datasets

More than a hundred publications about harms (and preventive effects) of COCs are available and full review was beyond the scope of this review. The systematic reviews featured below include contemporary pills formulations and their harms.

Information about COCs from Systematic Reviews

Two recent systematic reviews have identified significant increased risk of deep venous thrombosis among users of oral contraceptives, though the size of risk varied significantly among different COC regimens and appeared lowest for agents containing levonorgestrel or norgestimate.[117, 118] One Cochrane review has evaluated the potential association between combined oral contraceptive use and weight gain, finding insufficient evidence to make conclusions and noting the likelihood that there is no large association between COCs and increased weight during therapy.[119] Other Cochrane reviews have assessed the relative efficacy and safety of various oral contraceptive regimens; these reviews note variability in the type and incidence of adverse events among included studies and comment that adverse event reporting among these studies was generally of lower quality than expected, recommending better tracking of side effects in future studies as well as systematic capture of patient reasons for treatment discontinuation.[120-123] One of these reviews found that the incidence of discontinuation due to side effects was lower in triphasic-treated patients as compared to their monophasic-treated counterparts.[122] The one Cochrane review assessing the use of COCs in the setting of heavy menstrual bleeding identified only one small crossover trial, which did not include description of adverse events.[35]

Harms of Cabergoline

Information about Cabergoline from Included Trials

A single exploratory study, with 29 participants among whom 14 had PCOS and 15 were normal controls, randomly assigned 16 women to cabergoline and 13 to placebo for four months.[52] The authors did not report adverse events and all women completed the trial.

Information about Cabergoline from Package Insert

The package insert for this drug intended to treat elevated prolactin levels provides data about the risk of side effects in comparison to placebo in a four week study and compared to bromocriptine which is another medication for prolactinoma treatment.[124] In Table 19 we have summarized the incidence of cabergoline side effects that occurred in more than 5 percent of those on the drug, as well as 4 week experience of side effects among individuals on placebo. We did not identify large dataset analyses aimed at surveillance for harms.

Table 19. Percent of participants experiencing side effects reported in cabergoline trials

Side Effect	Placebo at 4 Weeks	Cabergoline at 4 Weeks	Cabergoline at 8 weeks
Nausea	20	27	29
Headache	25	26	26
Dizziness	5	15	17
Asthenia	10	9	6
Constipation	0	10	7
Abdominal pain	5	5	5
Somnolence	5	5	2
Fatigue	0	7	5
Depression	5	3	3
Hot flashes	5	1	3
Dyspepsia	0	2	5

Information about Cabergoline from Systematic Reviews

Several systematic reviews have explored the safety and efficacy of cabergoline for treatment of a range of conditions. Two Cochrane reviews on ovarian hyperstimulation syndrome and restless leg syndrome, respectively, each assessed a small pool of available trials, finding no significant difference in overall incidence of adverse events between cabergoline and comparators.[125, 126] A meta-analysis of dopamine receptor agonist use among individuals with Parkinson's disease found a relative risk of 6.38 (95% CI, 3.17 to 12.81) for moderate to severe valvular regurgitation;[127] a similar analysis of cabergoline use in hyperprolactinemia also found a significant increase in risk of valve regurgitation, though this echocardiographic finding in this patient population was clinically asymptomatic in all patients and participants were certain to be older and more frail than women who would use the treatment for irregular uterine bleeding.[128]

Harms of Lifestyle and Behavioral Interventions

Information across Sources for Diet and Exercise

The single RCT of diet and exercise intervention was conducted in teens with irregular menses and did not identify adverse effects.[53] One acupuncture trial included 34 women randomized to a walking regimen who reported no adverse events or injuries.[54] However it is important not to assume that lifestyle and behavioral interventions such as diet and exercise are without risks. The U.S. Preventive Services Task Force report on *Screening and Management of Obesity in Adults*[91] provides a clear and succinct description of the potential harms stating:

> Possible harms that could accrue from [these] interventions include bone loss and increased fracture risk, injuries from increased physical activity, decreased self-esteem from being labeled as obese or failure to lose weight, use of extreme or unhealthy dietary approaches, and weight cycling.[91]

Acupuncture

Information across Sources for Acupuncture

One study of acupuncture, that compared two strategies for selecting placemen of needles, did not discuss harms or withdrawals.[55] The other RCT reports only local redness or hematomas occurring in 10 percent of those receiving acupuncture in 14 sessions over 16 weeks.[54] Two women in the acupuncture group of 33 women reported other side effects which were dizziness and nausea, while the exercise and no intervention control group did not report any events.

A number of Cochrane reviews have explored the use of acupuncture for treatment of a variety of women's health issues, ranging from dysmenorrhea to endometriosis-related pain to induction of labor; across the board, these reviews found that potential harms of acupuncture have not been well studied and are often omitted from trial reports completely, noting that investigation of possible adverse effects is an important consideration for future research involving this therapeutic approach.[129-132]

Harms of the Levonorgestrel-Releasing Intrauterine System

Information about LNG-IUS from Included Trials

One trial did not provide any information about harms or adverse effects.[56] Two trials stated that there were no serious adverse effects related to either treatment.[61, 62] One trial with 39 subjects reported that one subject discontinued LNG-IUS therapy (5%) and five subjects discontinued cyclic COC (26%).[58] One trial reported side effects in a table, without comparative statistics.[60]

One trial with 145 subjects reported that no deaths or drug-related serious adverse events occurred during the study.[57] Six subjects in the LNG-IUS group (7%) and two in the oral MPA group (2%) discontinued treatment because of adverse events.[57] The LNG-IUS was expelled in four subjects (5%); two other subjects had the LNG-IUS removed due to adverse effects.[57] No uterine perforations or pregnancies were observed during the study.[57] Other adverse events were reported in a table, without comparative statistics.

One trial with 51 subjects reported 242 adverse events, 158 in the LNG-IUS group and 84 in the mefenamic acid group.[60] The LNG-IUS was expelled in two subjects (8%); one of these had chlamydial endometritis.[60]

Information about LNG-IUS from FDA Documents and Package Insert

In October 2009, the prescription label for the LNG-IUS available in the United States was updated though a process with the FDA.[133] This revision was made for the new indication: treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.[134]

According to the package insert, the most common (i.e., more than 10%) adverse reactions reported in clinical trials of LNG-IUS are: uterine/vaginal bleeding alterations (51.9%), amenorrhea (23.9%), intermenstrual bleeding and spotting (23.4%), abdominal /pelvic pain (12.8%), and ovarian cysts (12%).[133] The data provided reflect the experience with the use of Mirena brand LNG-IUS in the adequate and well-controlled studies for contraception (n=2,339) and heavy menstrual bleeding (n=80). For the treatment of heavy menstrual bleeding indication (n=80), the subjects included women aged 26 to 50 with confirmed heavy bleeding and exposed for a median of 183 treatment days of Mirena (range: 7 to 295 days).

The adverse reactions seen across the two indications overlapped, and are reported using the frequencies from the contraception studies. The less common (i.e., between 5% and 9% of users) adverse reactions are: headache/migraine (7.7%), acne (7.2%), depressed/altered mood (6.4%), menorrhagia (6.3%), breast tenderness/pain (4.9%), vaginal discharge (4.9%), and IUD expulsion (4.9%). Other relevant adverse reactions occurring in fewer than five percent of subjects include nausea, nervousness, vulvovaginitis, dysmenorrhea, back pain, weight increase, decreased libido, cervicitis/Papanicolaou smear normal/class II, hypertension, dyspareunia, anemia, alopecia, skin disorders including eczema, pruritus, rash and urticaria, abdominal distention, hirsutism and edema.[133, 135]

Information about the LNG-IUS from Large Datasets

Large scale surveillance for harms provides important information to patients to assure informed decisions about risks. This data includes information about complications with insertion. In the New Zealand monitoring system which includes 3519 insertions, difficult

insertions occurred in 3.6 percent of procedures and were not well predicted by nulliparous status of noncontraceptive use of the IUD. Pain on insertion occurred for one percent of patients and one half of one percent of attempts to insert could not be completed.[136, 137] Uterine perforation rates in three large datasets ranged from 0.9 to 2.6 cases per 1,000.[136, 138, 139] Authors of each of these studies, as well as those of another report from four national pharmacovigilance centers in Europe confirm, that perforations may not consistently be associated with painful insertions and that only a small portion (less than 10%) are recognized at the time of the insertion.[140]

In surveillance data, the LNG-IUS in not associated with increased risk of deep vein thrombosis,[108] including in more than 8 million women years of observation among Danish women.[141] The anecdotally reported complaint of hair loss is supported by a single study in New Zealand by surveying women in the national registry. They found five cases of alopecia (two recovered, one not, and two still unknown) and estimated incidence to be 1.8 per thousand users.[138]

Information about the LNG-IUS from Systematic Reviews

Systematic reviews report adverse events similar to those noted in the package insert,[133] with weight gain, bloating, acne, nausea and breast pain as the most commonly observed side effects; these reviews also comment on the risk of spontaneous device expulsion.[142-144]

Harms of NSAIDs

Information about NSAIDs from Included Trials

Three trials did not provide any information about harms or adverse effects.[65, 70, 71] Two trials reported there were no serious side effects.[72, 74] Another trial reported treatment discontinuations among one person receiving mefenamic acid and one person receiving norethisterone after the third cycle.[67] A table of adverse events was presented in this study with no comparative statistics, though abdominal pain was reported in 18 percent and 20 percent of both mefenamic acid and norethisterone groups.

In one trial,[60] there were 242 adverse events noted, with 158 in LNG-IUS group and 84 in the mefenamic acid group. There were two significant adverse events in this study, one with hypertension in a patient with a history of hypertension, and one with chlamydia endometriosis resulting in IUS expulsion. Of note, a smaller proportion of patients reported abdominal pain with mefenamic acid (7.7%) compared to LNG-IUS (32%), though significance was not reported in the table of adverse events.

In another trial,[63] 18 patients stopped treatment, four of 26 on TXA, three of 23 on mefenamic acid, and 11 of 27 on ethamsylate, of which three, one, and four respectively were due to an unwanted events of nausea, headache and dizziness. Of note, an improvement in dysmenorrhea was reported by 13 percent of patients (n=3) in the mefenamic group, 19 percent of patients (n=5) in the tranexamic group and 4 percent (n=1) of patients in the ethamsylate group.

One of the trials[74] reported nausea and GI disturbances in nine (16.4%) and eight (14.5%) and leg cramps in seven (12.7%) and 12 (21.8%) cases among those receiving TXA and TXA with mefenamic acid, respectively.

One trial reported no treatment discontinuations,[68] but treatment with TXA caused nausea, dizziness, numbness, restless legs and headache and in three women vomiting and difficulty swallowing. Flurbiprofen caused tiredness, stomach pains and nausea.

In one trial,[64] one person discontinued mefenamic acid due to severe skin rash and itching and in another trial[66] one person on mefenamic acid complained of gastritis. In another trial,[69] one patient had epigastric distress and four patients had nausea and vomiting on meclofenamate. However, the severity of dysmenorrhea ($p<0.006$), backache ($p<0.02$), and headache ($p<0.002$) were significantly less for patients taking meclofenamate than placebo, there was no difference in nausea or vomiting.

One trial[72] reported any side effects in 18 patients with naproxen and 15 patients with mefenamic acid, 13 patients had gastrointestinal symptoms (nausea, diarrhea, abdominal discomfort, and anorexia) on naproxen and six on mefenamic acid. Central nervous system symptoms (light headedness, dizziness, tiredness, and headache) were reported by six and five patients, respectively on mefenamic acid and naproxen.

One trial[73] reported no significant differences in nausea, depression, breast symptoms and other symptoms between mefenamic acid and placebo. However there was significant reductions in abdominal pain ($p<0.001$), headache ($p<0.001$) and diarrhea ($p<0.008$) among those taking mefenamic acid compared to placebo.

Information about NSAIDs from FDA Documents and Package Inserts

As a class, NSAIDs carry a risk of serious harms from cardiovascular thrombotic events, myocardial infarction, stroke, renal effects, and hepatic effects, along with gastrointestinal ulceration, bleeding and perforation. All drugs in this class have a boxed warning for cardiovascular and gastrointestinal risk. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately one percent of patients treated for three to six months, and in about two to four percent of patients treated for one year, with trends continuing with longer duration of continuous use.[145-148] Labels note that even short-term therapy is not without risk with this drug class.

In general, NSAIDs have been commonly associated with harms including: edema; abdominal pain; constipation; diarrhea; dyspepsia/ heartburn; elevated liver enzymes; flatulence; GI bleeding; nausea; vomiting; body weight changes; headache; nervousness and other manifestations of central nervous system stimulation (e.g., anxiety, insomnia, increased reflexes, tremor); symptoms associated with central nervous system inhibition (e.g., amnesia, asthenia, depression, malaise, somnolence); rash; changes in vision; dizziness/ vertigo; tinnitus; and signs and symptoms suggesting urinary tract infection.

More harms information on specific drugs is limited in the package inserts, for many of the reasons given in the above discussion. In controlled studies of meclofenamate, approximately four percent of the patients had diarrhea severe enough to require discontinuation of the drug.[146] See Appendix M for more complete information from individual package inserts.

Information about NSAIDs from Systematic Reviews

A pooled analysis of trials in a systematic review of NSAIDs for the treatment of dysmenorrhea found that mild neurological and gastrointestinal adverse events reported at significantly greater frequency by those receiving NSAIDs as compared with those receiving placebo.[149] Another recent review underscores the risk of various gastrointestinal complaints and

notes that the cardiovascular effects of the traditional NSAIDs are poorly understood and warrant further research;[150] an increased risk of nonfatal myocardial infarction was also observed in a recent systematic review and meta-analysis.[151]

Harms of Tranexamic Acid

Information about TXA from Included Trials

Within studies included in our review, similar numbers of participants withdrew from TXA and placebo or other treatment groups[75, 76] No thrombotic events were reported in the participants treated with TXA and no deaths occurred during the study. Serious adverse events reported in the TXA groups of trials included allergic reactions, headaches, and other symptoms such as tachycardia, acute bronchitis, hypoglycemia, and posttraumatic stress disorder, the later judged to be unrelated to study treatment. There was no significant difference in the percentage of side effects reported, comparing TXA to placebo. In particular, the frequency of gastrointestinal-related adverse events was similar between groups. One included trial had no withdrawals or side effects reported,[68] another reported no serious adverse effect[77] and another did not provide any information about harms or adverse effects.[63]

Information about TXA from FDA Documents and Package Insert

The companies, Xanodyne Pharmaceuticals and Ferring Pharmaceuticals, that manufacture TXA, Lysteda®, received FDA approval after submitting research findings and other data in 2009. The manufacturer conducted two placebo-controlled randomized trials; the second of which has been published.[75] The first trial randomized 304 women and compared two doses of TXA (1950 mg and 3900 mg given daily for up to five days during each menstrual period) versus placebo over three cycles.[152] The data provided to the FDA for safety included these two pragmatic cluster RCTs and two uncontrolled phase three trials, and a single QT-interval phase two study. In total, these five studies described 12,169 treatment cycles, but among them only 234 women received the current recommended therapeutic dose of the medication.[153] Overall, the nature and number of adverse events did not raise any significant safety concerns. There were no venous thromboembolic events in subjects taking TXA. There were no adverse effects on vision, or ocular safety concerns. There was no effect on the QT-interval. No drug-drug interactions studies were conducted. The total number of subjects in clinical trials who received TXA was considered low for evaluation of harms and drug safety. The FDA also reviewed evidence from a database for a different formulation of TXA that included 40 cases of possible venous thromboembolism over five years (none in the United States), with 40 percent of these events occurring with intravenous use of the drug, and for different indications (not heavy menstrual bleeding).[152] The review utilized by the FDA also documented associated instances of retinal venous and arterial occlusion and ligneous conjunctivitis.[152]

In April 2011, the prescription label and package insert for the formulation of TXA available in the United States was updated.[152] According to the current label, the most common adverse reactions reported in clinical trials of TXA were headache (50.4%), nasal and sinus symptoms (25.4%), back pain (20.7%), abdominal pain (19.8%), musculoskeletal pain (11.2%), arthralgia (6.9%), muscle cramps and spasms (6.5%), migraine (6%), anemia (5.6%), and fatigue (5.2%); comparative statistics between active drug and placebo were not provided.[152]

Information about TXA from Large Data Sets and Postmarketing Reports

We identified a single large surveillance study using the General Practice Database from the United Kingdom.[109] The case-control analysis of deep vein thrombosis reported increased odds of TXA use among cases (OR=3.20; 95% CI, 0.65 to 15.78) and note lack of precision of the estimates based on sparse use of the medication. This report examining drugs used for heavy menstrual bleeding found that all common treatments for menorrhagia were associated with deep vein thrombosis risk and raised the question of confounding by indication, meaning that characteristics of the women being treated (abnormal bleeding patterns) rather than the drugs themselves might be the causal component.[109]

Based on U.S. and worldwide postmarketing reports, the following have been reported in patients receiving TXA for various indications: nausea, vomiting, and diarrhea; allergic skin reactions; anaphylactic shock and anaphylactoid reactions; impaired color vision and other visual disturbances; dizziness; and thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction).[152] There postmarketing reports of venous and arterial thrombotic events included women who had used TXA concomitantly with combined hormonal contraceptives.

In consideration of the information reviewed, the FDA issued contra-indications and precautions about TXA advising clinicians not to prescribe TXA to women who are known to have the following conditions: active thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism, or cerebral thrombosis); a history of thrombosis or thromboembolism, including retinal vein or artery occlusion; an intrinsic risk of thrombosis or thromboembolism (e.g., thrombogenic valvular disease, thrombogenic cardiac rhythm disease, or hypercoagulopathy). Four precautions are noted: 1) concomitant therapy with tissue plasminogen activators may decrease the efficacy of both medications; 2) the risk of venous thromboembolism and arterial thromboses may increase further when hormonal contraceptives are administered with TXA, of particular concern in women who are obese or smoke cigarettes, especially smokers over 35 years of age; 3) TXA is not recommended for women taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates because the risk of thrombosis may be increased; patients should be instructed to report visual and ocular symptoms promptly and the medication should be stopped pending a complete ophthalmic evaluation, including dilated retinal examination, to exclude the possibility of retinal venous or arterial occlusion.[152]

Information about TXA from Systematic Reviews

A 2012 review of the efficacy of TXA in treating heavy menstrual bleeding is compatible with this review, finding mild to moderate adverse effects reported in included studies; gastrointestinal effects most common and no reports of thromboembolic events in the ten studies evaluated.[154] A Cochrane review conducted a combined analysis the efficacy and safety of TXA and etamsylate as antifibrinolytics used to treat heavy menstrual bleeding; emphasizing the short duration of the included studies, they comment that no increase in adverse events was observed with use of these agents.[155] Two systematic reviews of TXA use in orthopedic surgery recently found no increased risk of thrombotic events in their pooled data analyses.[156, 157] It is important to note that the trials included in these reviews are similar to those in this review in that they are underpowered to detect rare but important harms.

Decision Aids

There are no harms associated with using decision aids other than time invested by patient and clinician if the decision aid is ineffective and informing patients about important care options.

Summary

Pharmaceutical agents, procedures and devices, and even diet and exercise have potential complications. While contraceptive methods have typically been well-characterized in the broadly applicable population of women reproductive age women, there may be characteristics associated with abnormal bleeding that modify the risk profile of these interventions when restricted to women with indications related to AUB. Women and their care providers will need to weigh individual risk profiles, desire for contraception, and treatment strategies in order to balance the management of symptoms with minimization of risk. This may be especially so when choosing medications, such as those typically used for diabetes management, that are less well-studied in this population.

Discussion

Key Findings

State of the Literature

We identified 1723 nonduplicate publications through the search process, with 205 proceeding to full text review (Figure 2). Thirty-eight publications were included that reported on 36 separate randomized controlled trials (RCTs) and 11 types of interventions. These studies evaluated the levonorgestrel-releasing intrauterine system (LNG-IUS) (seven studies),[56-62] nonsteroidal anti-inflammatory drugs (NSAIDs) (13 studies),[64-67, 69-73] tranexamic acid (TXA) (six studies),[63, 68, 74-77] combined oral contraceptives (COCs) (three studies),[48, 78, 79] metformin (three studies),[49-51] exenatide (one study),[51] progestogens (one study),[47] cabergoline (one study),[52] acupuncture (two studies),[54, 55] lifestyle/behavioral changes (one study),[53] and patient decision aids (three studies)[81, 82, 85] using at least one comparator or placebo arm.

A number of these studies compared the intervention of primary interest to a progestogen, such as medroxyprogesterone (MPA). These studies were not considered important contributions to evidence about the effectiveness of progestogens for treatment since in each case the hypothesis was that the progestogen would be inferior to the intervention being studied. Though we report the outcomes for progesterone comparisons to other interventions we have not separately summarized the effectiveness of progestogens. One trial evaluated two routes of progestogen and was treated as a study evaluating progesterone for symptom management. [47]

The quality of the included studies tended to be fair (eight studies)[49, 55, 57, 61, 64, 72, 73, 77] or poor (22 studies).[47, 50, 51, 53, 54, 56, 58-60, 62, 63, 65-68, 70, 71, 74, 76, 81, 82, 85] In part this followed from the difficulty of blinding participants to intervention status. For instance no LNG-IUS studies included sham insertion or a sham LNG-IUS string placement in the endocervical canal along with placebo medication in both groups, though this would be required to achieve complete masking of intervention groups. Likewise it can be challenging to mask outcome assessors to group status when women and providers assess outcomes. An unmasked participant is counted in the scoring as an unmasked assessor when the outcome is self-reported or self-collected. While this is rigorous and appropriate in the evaluation of risk of bias in RCTs, it may be an inappropriately strict criterion to apply, for studies in which menstrual products are collected for measurement of blood loss or in which biological markers such as hemoglobin or hematocrit levels are also assessed. Understanding this context can inform interpretation of the literature.

Effectiveness of Interventions for Abnormal Bleeding

KQ1A. Management of Irregular Uterine Bleeding

A number of available interventions suitable for use in primary care have preliminary evidence of effectiveness for improving the regularity of menses. Only metformin has demonstrated effectiveness in more than one RCT with a total of 175 women with polycystic ovaries participating in each of three studies. One study suggests adding exenatide to metformin treatment can enhance effectiveness. No head-to-head comparison trials are available to inform choices among medication types for management of irregular uterine bleeding.

Progesterone

Vaginal and oral progesterone were studied in a single trial among women clinically classified as having dysfunctional uterine bleeding.[47] In this RCT both routes of administration improved cycle regularity with 92 percent and 85 percent of participants respectively achieving regular bleeding by the third cycle of use. Effects were comparable but the trial was not powered to show equivalence or noninferiority.

Combined Oral Contraceptives

A triphasic oral contraceptive was also studied in a single RCT among women with irregular uterine bleeding.[48] This trial included women with both short and long intervals between bleeding episodes and with both heavy and normal amounts of bleeding. The outcomes are provided in aggregate and not presented by initial bleeding characteristics. Overall 68 percent of women taking the COC achieved excellent or good cycle control compared to 26 percent of those receiving a placebo.

Metformin and Exenatide

Metformin was an active treatment arm in three RCTs conducted among women with polycystic ovarian syndrome (PCOS), two comparing outcomes to a placebo group[49, 50] and one comparing metformin only, exenatide only, and both[51]. In each case compared to baseline or placebo, metformin was effective for improving the regularity of bleeding over a number of months. When combined with exenatide the effect was greater than either alone in the study of 60 women with PCOS that compared all three approaches.[51]

Cabergoline

In a very preliminary investigation of this drug indicated for treatment of prolactinomas, cabergoline was associated with return of regular menses in three of eight women in the treated group compared to none of the six receiving placebo.[52] All women in the study had PCOS and normal prolactin levels.

Behavioral and Lifestyle Interventions

Among adolescents with PCOS, both a low-fat, calorie-restricted diet and a carbohydrate-restricted diet in conjunction with 30 minutes of aerobic activity three days a week resulted in more regular menses among those who lost weight.[53] This single small study did not present outcomes by the diet group to which participants were randomized. Presumably there was not clear difference, meaning there is no evidence to guide choice of dietary intervention. A single trial of acupuncture also included an exercise control group at the same intensity as the diet and exercise trial.[54] This group has a 42 percent improvement in regularity of menses. We did not find evidence comparing diet to exercise directly.

Complementary and Alternative Medicine

Two studies of acupuncture with different underlying hypotheses and different methods (conventional acupuncture and low frequency electroacupuncture) found benefit for a specific style of acupuncture when compared to no intervention or alternate placement of acupuncture needles.[54, 55] By 32 weeks in the trial of electroacupuncture for PCOS, women who received acupuncture had a 121 percent improvement in cycle regularity while those who exercised only

had a 42 percent improvement which was statistically comparable in this small trial.[54] Both acupuncture and exercise were superior to placebo in this trial. In the trial of two differing placements of needles, women who received treatment for "mind tranquilizing and menstruation promotion" had greater improvements (no treatment failures among 21 women) compared to those receiving traditional placement (n=16) for "delayed menses" among whom 19 percent did not have improvements.[55]

KQ1B. Management of Abnormal Cyclic Bleeding

The LNG-IUS, various NSAIDs, and COCs are effective for reducing the amount of menstrual bleeding and in some instance have been shown to have additional positive effects. Each category of intervention is described below.

Levonorgestrel-Releasing Intrauterine System

All seven studies of the LNG-IUS support that it is an effective intervention for reduction of heavy menstrual bleeding.[56-62] Evidence suggests the device reduces the volume and duration of bleeding, improves iron status, and can be an acceptable substitute in some women for hysterectomy. It is superior in direct comparisons with COCs and NSAIDs and has not been compared to TXA.

Our analysis of LNG-IUS is consistent with prior systematic reviews. A 2001 systematic review of five RCTs reported mean MBL reductions were between 71 and 96 percent.[158] A 2005 systematic review identified ten RCTs comparing LNG-IUS with surgery or pharmaceutical treatments.[142] The odds ratio for the proportion unwilling to continue with treatment was 0.27 (95% CI, 0.10 to 0.67) in favor of LNG-IUS. The odds ratio for proportion of women satisfied with treatment was 2.13 (95% CI, 0.62 to 7.33).[142]

Nonsteroidal Anti-Inflammatory Drugs

In a total of 13 studies, NSAIDs, including mefenamic acid, naproxen, meclofenamate, and flurbiprofen, given at the onset of menses for up to five days reduce menstrual blood loss (MBL) by 20 to 59 percent.[60, 63-74] Studies have evaluated use for periods of one to six menstrual cycles. Our analysis of NSAIDs is consistent with a prior 2007 systematic review of NSAIDs,[33] that found NSAIDs were more effective than placebo at reducing bleeding, but less effective than TXA or LNG-IUS. There were no differences in reductions between NSAIDs and oral progestins, COC, and an older progesterone releasing intra-uterine system (Progestasert®). There were no differences seen between individual types of NSAIDs, specifically mefenamic acid and naproxen. The most recent study found similar reductions in pictorial blood loss assessment chart scores when NSAIDs were combined with TXA compared to TXA alone. NSAIDs reduce clinically significant MBL, but do not consistently reduce to clinically meaningful levels in all patients (less than 80 ml). There was considerable variability in response. Some patients had an increase in blood loss during treatment. NSAIDs do not regulate the pattern of menstruation nor provide contraception. NSAIDs do provide relief of dysmenorrhea. Therefore, for patients who desire both reduced MBL and relief from dysmenorrhea, but not contraception, and who do not have contraindications, NSAIDs can be considered for up to five days during menses.

Tranexamic Acid

Three of six RCTs of TXA demonstrate effectiveness of improving heavy bleeding.[63, 68, 74-77] TXA at a dose of 2.0 to 4.5 g per day for four to five days from onset of bleeding meaningfully reduces MBL by 40 to 60 percent in studies as long as one year. Both biologic and self-reported symptoms of bleeding severity are improved. Our analysis of TXA is consistent with prior systematic reviews of another formulation of TXA. A 1995 systematic review pooled results from seven trials and found a reduction in MBL of 46.7 percent (95% CI, 47.9 to 51.6%) with TXA.[159] A 2004 systematic review and meta-analysis of two RCTs of TXA versus placebo reported a mean MBL difference of −93.96 ml (95% CI, −151.43 ml to −36.49 ml), in favor of TXA treatment.[155]

Combined Oral Contraceptives

Though the volume of RCT literature examining use of COCs in women with abnormal uterine bleeding (AUB) is somewhat small given the frequency with which these agents are used as one of the first line therapies in women presenting with AUB symptoms, our analysis indicates these agents are associated with decreases in AUB among treated women. All five RCTs of COCs for the indication of heavy cyclic menstrual bleeding found benefit for reducing volume of menstrual bleeding,[56, 58, 65, 78, 79] two studies also identified improvements in related laboratory values such as hematocrit and ferritin[78, 79] and one study also found significant improvement in patient rating of overall health.[56] This conclusion is in line with 2010 recommendations by the American College of Obstetrics and Gynecology, which notes combined hormonal contraceptives as a "reasonable option for initial management of menorrhagia."[24] In the two head-to-head comparisons between COCs and LNG-IUS,[56, 58] reductions in heavy menstrual bleeding were documented in both treatment groups. Women with a LNG-IUS had somewhat greater benefit of LNG-IUS.

Decision Aids

Three studies investigated decisions aids to assist women seeking treatment for heavy cyclic bleeding in making informed decisions about care.[81, 82, 85] Their findings suggest that these tools do increase patient knowledge and enhance satisfaction with care. However overall decision aids did not result in choices that influence disease symptoms in directly measure ways. One study found fewer women who received the decision aid ultimately choose surgical referral and hysterectomy.[81] However this decision can not necessarily be linked to improvement in bleeding symptoms. Since there are no known harms associated with using decision aids, they may nonetheless be of interest to assure patients can compare and contrast options and feel secure in their choices.

Applicability

Applicability describes the extent to which study populations, interventions, and outcomes in this literature apply to the target group. Studies for this review were intended to provide information to inform primary care management of AUB, whether irregular or cyclic. To a large degree, through shaping of the methods for this review, we have engineered the report so that the included research is applicable to primary care of women in the United States. Our stricter criteria, narrowing findings to only symptomatic populations of reproductive age women with

chronic complaints of abnormal bleeding, comes at the cost of fewer studies being addressed. However, it assures that those studies that are included were explicitly designed to examine the effectiveness of the treatments for improving the outcomes of interest in the populations of interest. Applicability of the findings is therefore high.

For each intervention, it is important to note the following provisions. The results of this review apply for women:

- Who are reproductive age and state they have an irregular pattern of menstrual bleeding or heavy cyclic menstrual bleeding.
- Without abnormal findings on pelvic exam or on ultrasound report (fibroids, polyps).
- Without an IUD in place, and who are not pregnant or lactating,
- Who are healthy, and without renal impairment, hepatic impairment, intestinal disease, thyroid disease, abnormal cervical cytology, noncyclic bleeding, history or presence of significant medical problems (e.g., thromboembolic disease, coagulopathy, subarachnoid hemorrhage, endocrine disorders, or eye disease).
- For whom any additional clinically determined diagnostic and screening tests have be completed to rule out these and other causes of abnormal bleeding.
- Does not have any of the contraindications found in the Food and Drug Administration sources discussed in the main document and do not have risks of drug-drug interactions if they take multiple prescription medications.

Our review as not designed to guide evaluation of women with abnormal bleeding, rather to address what treatments have evidence of effectiveness once the diagnosis is established an primary care management is to be initiated.

Applicability of Literature about Interventions for Irregular Uterine Bleeding (KQ1A)

The literature about management of irregular uterine bleeding applies to women in primary care settings in the United States. Nine RCTs, three conducted in the United States, two in Italy, and one each in China, Sweden, Turkey, and the United Kingdom provide evidence about seven types of intervention. Enrolled populations were somewhat narrowly defined and had either a clinical diagnosis of dysfunctional uterine bleeding, or met research criteria for PCOS. As a result the findings are strictly applicable only to these groups of women. We describe the agents study within the two populations in which the research was conducted.

Use for Dysfunctional Uterine Bleeding (KQ1A)

Progesterone

The study about progesterone supplementation comparing vaginal to oral route for a ten day time period is applicable to primary care in the United States, as both routes are used in standard care in the United States to provide progesterone in order to organize a withdrawal bleed that will typically occur within days of completing the progestogen. One agent in this trial, oral dydrogesterone, is not available in the United States, related to risk of harms specific to this progestogen that are described in KQ2. This study is therefore a surrogate for oral versus vaginal administration of similar progestogen formulations such as MPA that are widely used in the United States for this purpose however it does not provide direct evidence to support use of other agents. The outcome of interest for this review was regularity of bleeding after treatment which

was provided for three menstrual cycles. Both groups had improvement however applicability for chronic use is unclear as no long-term followup of symptom control is available. Progesterone is often used in management of specific causes of abnormal bleeding such as PCOS however this study does not directly apply because the population was not addressed in this study. Progesterone can be used by women who wish to conceive.

Combined Oral Contraceptives

The single study, conducted in the U.S. study is directly applicable to primary care in the United States. The study population of 201 women is representative of the spectrum of complaints that may accompany chronic irregular uterine bleeding including menses that are widely separated in time whether light, normal, or heavy with regard to heaviness of bleeding, and includes women with closely space and unpredictable bleeding also without restriction on heaviness of bleeding. The intervention is a common version of triphasic combined oral contraceptive (Ortho Tri-Cyclen®) that provides direct evidence for its effectiveness and indirect evidence for other triphasic pills with similar dosing profiles. The evidence is less direct but likely applicable to monophasic pills of similar estrogen and progesterone content. It does not apply to progesterone-only COCs or to pills with estrogen doses lower than 0.035 mcg as used in this study. Comparison to placebo provides definitive evidence of benefit but does not provide information about how COCs compare to other strategies that might be used such as LNG-IUS or progestogens. The outcomes included those that are a priority of women seeking treatment for uterine bleeding and included cycle regularity, incidence of excessive bleeding, and overall rating of symptom improvement.[48] Harms and contraindications, as discussed in KQ2, are well-known to care providers and often to women themselves, and COCs are not applicable as a long-term strategy for women who wish to conceive.

Management of Polycystic Ovarian Syndrome (KQ1A)

Metformin and Exenatide

The three trials that investigated use of metformin are applicable to care in the United States and were conducted in the United States, two studies in Italy and another in the United Kingdom. The study in the United States compared metformin, to exenatide or both. These studies enrolled women with PCOS and fewer than expected normal menses. They investigated doses of metformin that are available in the United States (500 mg and 850 mg, administered by mouth twice daily). None of the studies used an extended release form which is now available so evidence related to that formulation is indirect. The outcome of interest for this review was menstrual frequency which was improved compared to placebo in tow trials. The only head-to-head comparison was metformin compared to exenatide or both. Both were superior to either alone for cycle control. The most common side effect which is gastrointestinal symptoms was identified in these studies and thus would be expected to apply to this typically younger group of women who do not have diabetes. Metformin can be used by women who wish to conceive and is safe in pregnancy. Based on other literature, it may enhance fertility. Little is known about exenatide and fertility and safety in pregnancy however it does not have contraceptive effects.

Diet and Exercise

The applicability of the single trial of diet and exercise is limited. It enrolled 24 adolescents with PCOS, 16 of whom completed the study and evaluated a low-fat, calorie-restricted diet or a

carbohydrate-restricted diet along with 30 minutes of anaerobic exercise three days a week. The trial did not provide an intention to treat analysis, comparing arms but did report that weight loss in either group improved cycle regularity. Behavioral changes can be applied in many populations and would be expected to have benefits. Thus evidence is insufficient to advise which dietary pattern is superior. Another arm of a single study found exercise 30 minutes each day, three days a week, was more effective than no intervention and as effective as acupuncture in improving cycle regularity.

Acupuncture

Two trials, one in Sweden and one in China, assessed acupuncture. Depending on the availability and the skill of acupuncturists available in communities, this intervention may not be broadly applicable in the United States. Both tradition acupuncture and electroacupuncture improved cycle regularity but this was assessed in essentially unblended trials. The outcomes examined were relevant to patient symptoms however were very poorly-described in one study in which the investigators applied categories like “cured” without clear definitions. Overall, literature is absent to inform choice of any of these modalities over another.

Applicability of Literature to Management of Abnormal Cyclic Bleeding (KQ1B)

Twenty-seven studies contributed evidence about interventions for management of abnormal cyclic bleeding focused predominantly on effectiveness for reducing the amount of bleeding among women with heavy menstrual bleeding. Overall these RCTs are applicable to primary care in the United States. Four were conducted in the United States, (including two multi-country trials); eight studies were conducted in the United Kingdom, four studies in Canada (including two multi-center studies), three in Australia (including one multi-center trial), two each in Finland and India. A single study was conducted in each of the following countries: Egypt, Netherlands, Sweden, and Turkey.

Levonorgestrel-Releasing Intrauterine System

Overall, the study findings for LNG-IUS from this review apply to women in the primary care settings in the United States. One trial was conducted in three countries: United States, Canada, and Brazil; two trials in the United Kingdom; and the remainder in Egypt, Canada, Turkey, and Finland. The settings are not substantially different from a primary care setting in the United States. However a limitation is that adolescent women and women with obesity were not included in the RCTs populations, but could be candidates for whom direct evidence is not provided by trials. Enrolled populations met our inclusion criteria and like others used direct measures of volume of bleeding that would be replaced in clinical care with patient self-report. The LNG-IUS is available in the United States. The intervention dosage was the same for all seven trials and is that currently marketed: 52 mg levonorgestrel, initial release rate 20 mcg per 24 hours. The LNG-IUS must be inserted by a provider. The details of the insertion procedure must be understood and practiced to safely provide this treatment in a primary care setting. The comparator differed among the five trials: two trials utilized a combined oral contraceptive pill, three trials utilized progestogen by oral or intramuscular route, one trial compared an NSAID, and one trial assigned the patients in the control group to continue their pre-existing medical treatment for excessive uterine bleeding or symptoms of dysmenorrhea, or both. None of the

trials compared LNG-IUS with TXA. The primary outcome of the trials was change in blood loss which directly addresses the primary symptom for which women typically seek treatment. One study used the proportion of women who cancelled their prior decision to undergo hysterectomy as the primary outcome measure (which favored the IUS). Timing of assessment of outcome varied among the trials: one trial reported after one menstrual cycle, three trials reported after three menstrual cycles, four trials reported after six menstrual cycles, and two trials reported after 12 months. The latter are more informative for a device intended to be in place for five years.

Nonsteroidal Anti-Inflammatory Drugs

The 13 RCTs examining NSAIDs and included in this review are applicable to United States populations. The studies were conducted in seven countries including Australia (2), Canada (1), India (2), the Netherlands (1), Sweden (1), the United Kingdom (5) and the United States (1). In some trials, women were excluded who were on hormonal medications, had menorrhagia related to IUD, or who were taking NSAIDs or steroids. Therefore, results of these studies are applicable to women with no contraindications to NSAIDs, including underlying hepatic, renal, or thyroid disease, stomach ulcers, or asthma and no drug sensitivity.

The specific NSAID varied and included mefenamic acid in 11 trials, naproxen in two trials, flurbiprofen in one trial, and meclofenamate in one trial. One trial evaluated mefenamic acid in conjunction with TXA. For each NSAID, dose and duration did not vary greatly, with usually up to five days duration of use. The most commonly used dose of mefenamic acid was 500 mg three times a day starting at the onset of menses. One trial initiated mefenamic acid five days prior to onset of menses through cessation of bleeding. Another trial used 500 mg at onset of menses followed by 250 mg every six hours for three to five days. Mefenamic acid at a dose of 250 mg three times a day from onset menses for five days was used when combined with TXA in one trial. Naproxen was evaluated with initial loading doses of 500 to 550 mg then 250 to 275 mg every six hours for five days or until 24 hours after cessation of heavy bleeding. Meclofenamate was studied at a dose of 100 mg three times a day from onset of menses for duration of six days or until cessation. Flurbiprofen was studied at a dose of 100 mg twice a day from onset of menses for duration of five days. Each of these doses is available for prescription in the United States. Notably the literature lacks RCTs about ibuprofen which is likely the most common prescription and over-the-counter NSAID used for heavy bleeding and dysmenorrhea.

Outcomes for the trials in this review included documentation of objective blood loss. This is not applicable in routine clinical care and subjective assessment of MBL is nearly always used as the criteria for initiating and determining success with NSAIDs. NSAIDs are also effective in reducing dysmenorrhea, and therefore patients with both heavy cyclic menstrual bleeding and dysmenorrhea or headaches may desire NSAIDs.

Tranexamic Acid

The literature about TXA for management of abnormal cyclic bleeding applies well to women in primary care settings in the United States (one trial was conducted in the United States, three in Europe and one in India). Enrolled populations met inclusion criteria and reviewed studies implemented exclusion of participants as described in the methods for this review. Because women with comorbidities are systematically excluded from these trials, we must note the studies apply to healthy women with heavy cyclic menstrual bleeding. While studies quantified the amount of bleeding at baseline, this is typically not feasible in clinical

populations and the patient's statement that menstrual bleeding is heavy would be more likely to be used as a criterion for consideration of this therapy. The formulation of TXA used in the included studies (Lysteda®) is the same that is currently available in the United States. The intervention dosage differed among the five trials, but was in the range of 2 to 4.5 grams per day for four to five days. Treatments compared to TXA in these trials did not include LNG-IUS or COC regimens. This modestly limits applicability since these would be among the usual intervention considered in real-world clinical settings. The primary outcome of the trials was change in blood loss which is typically the most pertinent symptom for women. The timing of assessments of outcomes varied among the trials but was generally short: two trials reported after two menstrual cycles, four trials reported after three menstrual cycles, one trial reported after six menstrual cycles. No trials reported use of for a year or more of therapy. This limits understanding of applicability for chronic use of this agent. Reporting of adverse events was not adequate for an assessment of harms and in the context of short followup in trials, this prevents consideration of risks.

Combined Oral Contraceptives

The findings of this review are applicable to women visiting a primary care setting for management of heavy, cyclic uterine bleeding. The included RCTs were conducted in the United States (one study), Canada (two studies), Australia (one study), multiple sites in Europe (one study), and Egypt (one study) in outpatient clinical care settings. Known contraindications to use of COCs and abnormal findings during diagnostic work-up (e.g., fibroids or other endometrial pathology) were commonly employed as exclusion criteria in the identified studies and these diagnostic exclusions are applicable in the general primary care setting as well. Study participants were all older than 18, and had normal range body weights so no evidence directly informs symptom management or safety in younger adolescents or obese patients. COCs were compared to placebo in three studies and LNG-IUS in two studies. Both participants in the COC group and LNG-IUS had improvements from baseline, but the LNG-IUS was superior to COC. In comparison to mefenamic acid, COCs were superior. The outcomes assessed were those of high relevance to patients and included measured MBL, measures of blood counts and iron reserves, and participant and clinician assessment of symptoms.

Decision Aids

Use of decision aids is increasingly common and promoted in U.S. health care settings especially in clinical contexts in which patient preference plays a strong role in selection of the treatment and prioritization of outcomes. Three studies of decision aids are included in this review. Two were conducted in the United Kingdom and one in Finland. They are somewhat applicable to U.S. care but may not directly apply given differences in payment structures for care and prescriptions as well as potential differences in clinical care norms. All three studies used information booklets mailed to patients prior to their appointments and one added a computerized decision tool. The studies assessed outcomes like general health status, quality of life, and decisional conflict, as well as secondary outcomes like anxiety. None found benefit which may or may not reflect how similar approaches would be received in a U.S. health care context.

Final comments on applicability

Overall applicability of this literature was high. However, often women who are in trials do not reflect the full range of those with abnormal bleeding seen in primary care. Study participants were more likely to be normal weight, nonsmokers, with few, if any concomitant conditions. The interventions (except in the case of specific comparators as noted) are available in the same doses and formulation in the United States. Outcomes such as measured blood loss, self-reported symptom severity and days of bleeding are of direct relevance to women with abnormal bleeding. Our findings are sparse for outcomes which can be considered essential for a condition like AUB that are defined by symptoms. Important outcomes include satisfaction with response to treatment, definitive assessments of whether or not the women considered their complaint resolved, and whether they wished to continue the same treatment or add additional treatments. Followup in general was brief, so they findings may not apply well to management of a chronic condition like abnormal bleedings. This makes findings about assessments of harms challenging since use of interventions over extended periods may have different risk profiles from short timeframes like one to six cycles.

Summary of Strength of Evidence and Findings

Overall the evidence to answer key questions about the management of AUB, did not reach standards for high strength of evidence for any intervention. This was particularly true in the literature relevant to treatment of women with irregular uterine bleeding. Combined oral contraceptives, as represented in a single good placebo controlled trial with a total of 201 participants, documented effectiveness. The treatment effect was large and combined these factors provided moderate evidence of benefit. Use of metformin is supported by low strength of evidence predominately related to small trials with somewhat limited quality. For the remainder of the interventions investigated for management of irregular uterine bleeding, there is insufficient evidence that follows from single or lower quality studies, or both. The strength of evidence tables that follow summarize the total number of studies and within those studies the number of women who received the specific intervention. The tables also provide the assessment of the risk of bias, consistency of findings across trials, directness of the evidence that treatment improves the symptom, and precision of the estimated provided by the literature.

Table 20. Strength of evidence for improving menstrual regularity (KQ1A)

Intervention Quality: Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence	Notes
Progestogen Poor: 1(69)[47]	High	NA	Direct	Imprecise	Insufficient	Data not analyzed by arm just comparison to baseline
COC Good: 1(101)[48]	Low	NA	Direct	Precise	Moderate	Cycle control improved for 87% in ITT analysis
Metformin Poor: 2(31)[50, 51] Fair: 1(45)[49]	Medium	Consistent	Direct	Imprecise	Low	Cycle control improved, drop-out rates high in treated
Exenatide Poor: 1(20)[51]	High	NA	Direct	Imprecise	Insufficient	Single trial arm, superior to metformin alone when added
Cabergoline Good: 1(8)[52]	Low	NA	Direct	Imprecise	Insufficient	Small pilot
Diet Poor: 1(24)[53]	High	NA	Direct	Imprecise	Insufficient	Data not analyzed by arm, no ITT
Exercise Poor: 1(34)[54]	High	NA	Direct	Imprecise	Insufficient	No controlled comparisons
Acupuncture Poor: 1(33)[54] Fair: 1(23)[55]	High	Consistent	Direct	Imprecise	Insufficient	Small studies, preliminary evidence of benefit, no masking

For management of heavy cyclic bleeding the literature was more robust. Combined oral contraceptives are supported by high strength of evidence for the purpose of decreasing MBL. The LNG-IUS, various NSAIDs, and TXA are also effective for reducing the amount of measured menstrual bleeding and are each supported by moderate strength of evidence. Of note, in head-to-head comparisons with statistically significant differences, the LNG-IUS has one trial each showing superiority to NSAIDs, two showing superiority to COCs, and two showing superiority to progestogens. COCs were superior in one trial compared to an NSAID. TXA was also superior to an NSAID, and when combined with an NSAID was superior to TXA alone. Most of these interventions have been shown to have additional positive effects, typically including shorter duration of bleeding and improvement is symptoms when participants used standardized scoring systems to report on treatment response.

Table 21. Strength of evidence for improving heavy menstrual bleeding (KQ1B)

Intervention Quality: Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence	Notes
LNG-IUS Poor: 5(173)[56, 58-60, 62] Fair: 2(104)[57, 61]	Medium	Consistent	Direct	Precise	Moderate	71% reduction in bleeding
NSAID Poor: 7(141)[63, 65-68, 70, 71] Fair: 3(129)[64, 72, 73, 83] Good: 1(32)[69]	Medium	Consistent	Direct	Imprecise	Moderate	20 to 59% reduction in bleeding

Intervention Quality: Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence	Notes
TXA Poor: 4(202)[63, 68, 74, 76] Fair: 1(25)[77] Good: 1(123)[75]	Medium	Consistent	Direct	Precise	Moderate	40 to 45% reduction in bleeding
COC Poor: 3(90)[56, 58, 65] Good: 2(269)[78, 79]	Low	Consistent	Direct	Precise	High	Reduced bleeding, improved iron measures
Progesterone Poor: 1(50)[76] Fair: 1(21)[77]	High	Consistent	Direct	Imprecise	Insufficient	Comparator in trials that favored the other intervention, little benefit

Implications for Clinical and Policy Decisionmaking

This review highlights the variety of options that can be effective for management of abnormal bleeding. We hope it serves to encourage care providers and women to consider the full range of potentially helpful interventions. This review may help to underscore the fact that contraceptive options like LNG-IUS and COCs are a proven option, while widening consideration to include agents like metformin for women with PCOS and TXA for those with heavy bleeding. Clinicians may be also be alerted to the some of the constraints of the literature for these specific populations and proceed with more information to guide decisions and to discuss likely side effects and potential harms.

Since these conditions are not typically life-threatening but are chronic, problematic, and can be embarrassing and costly in terms of lost productivity, the primary health system and policy challenge is to recognize that failure to address AUB is unnecessarily diminishing women's quality of life and function. Cost differences are unlikely to drive choices among many of these interventions, though initial costs of long term treatments like the IUS can be disincentives if up-front cost to the patient is high. Likewise for newer drugs, like TXA, decisions about eligibility and copays could influence uptake and continued utilization of an effective medication. All the interventions described, with the exception of exenatide, cabergoline, and acupuncture, are likely to be covered by most payors for these indications. For the treatments noted that have not yet proven effectiveness in large well-conducted studies this will need to be addressed with high quality research before policy decisions can be recommended.

Limitations of This Comparative Effectiveness Review

In this review we focused tightly on primary care interventions for two specific patterns of abnormal bleeding (irregular and cyclic). While this approach was identified by our team, Key Informants and Technical Expert Panel (TEP) as an area of the literature that would benefit from evidence synthesis, our focus does prevent comparison to second line therapies that may be used by subspecialists for women who have failed primary care treatment and prevents examination of how these medications fair when compared to surgical options. The latter category of study is fairly small, and for broader perspective, there are a number of reviews within the last five to 10 years that provide more sweeping information about these interventions. For the reader's

convenience, Appendix M lists these reviews and related practice guidelines and summarizes the conclusions that are relevant to the focus of this review.

We have also restricted this review to publications in English. Based on review of abstracts (generally available in English) and on the expertise of our team and TEP, we do not feel that this biases the review for assessment of the IUS and medications because few studies were omitted, and larger, higher quality trials are typically published in the English language literature. The sole domain that may be fundamentally under-represented because of this strategy is complementary and alternative medicine which includes interventions such as herbal remedies, acupuncture, and massage therapy. We also restricted interventions to those that had been studied in randomized trials. This limits the degree of context that we can provide from observational studies about factors such as predictors of treatment success or effect modifiers. However, it is uncommon for observational studies to meet criteria sufficient to influence the assessment of strength of evidence when there are trials available, so this restriction is unlikely to have influenced the overall findings of this review.

Limitations of the Evidence Base

Throughout the report we have endeavored to point out limitations specific to the included populations, comparisons, and quality of the literature. Recent improvements in unifying nomenclature and formalizing consensus definitions for the clinical groupings of bleeding abnormalities[9] will likely continue to have a positive influence on the ability to properly interpret the findings of individual studies, to identify groups of studies with comparable methods and to aggregate results.

Methodologic Limitations

Recurring methodologic recommendations include a need for:

- Larger RCTs, appropriately powered for direct head-to-head comparison of treatment options in which loss of participants in minimize and intention-to-treat analyses are uniformly conducted.
- Detailed attention to operational criteria for defining the bleeding pattern under study and for methods used to define inclusion and exclusion.
- Clear and definitive operational definitions of outcomes that include, indeed prioritize, patient-reported, condition-specific quality of life and satisfaction measures over durations of time compatible with treatment of a chronic condition.
- Study populations that match the characteristics of those who present with AUB in primary care settings. This includes teens, perimenopausal women, heavier women, and women with common comorbidities such as diabetes and hypertension.
- More effective mechanisms of masking participants, researchers, and providers to intervention status. This may include need to develop sham procedures to mimic intrauterine IUD insertion and to provide a sham “string” to confirm placement should a patient of provider check status. (Of note the IUD is effective without a string and string-less insertion is also an option for research where placement can be confirmed by ultrasound.)
- Studies designed to assess treatment trajectory and cost. Such studies could randomize women to distinct treatment pathways and track the rate of conversion from one

treatment to another for inadequate symptom control or sequence addition of measures, so that the effectiveness of combining multiple intervention methods can be assessed.
- An overall shift towards effectiveness from efficacy, moving beyond the level of proof of concept that is required for drug and device approval to a deeper level that can better inform care, cost considerations and policy.

Ongoing Research

We identified four ongoing studies that may add to our understanding of the relative safety and efficacy of different regimens for treatment of AUB (additional details provided in Appendix P). Two currently funded trials are exploring the effect of a pretreatment regimen, one employing misoprostol and one using norethindrone acetate, on short and long term bleeding outcomes among women undergoing placement of an LNG-IUS for treatment of heavy menstrual bleeding. A large postmarketing surveillance study of the Mirena® LNG-IUS is also underway in Kazakhstan, with a planned enrollment of 1700 participants, potentially contributing additional safety information to this body of literature. The utility and safety of new investigational agent, a selective progesterone receptor modulator (CDB-2914) that has shown promise for reducing bleeding in studies involving women with fibroids, is also currently being assessed in a study involving women with AUB.

Future Research Needs

While the number of informative studies that could be designed is likely limitless, we have listed examples, grouped by indication and intervention, of types of studies that could resolve current and pressing gaps in knowledge.

Irregular Uterine Bleeding

- Development of a body of literature that examines benefits of exercise and weight loss focused on improving bleeding patterns in women with irregular bleeding that results from failed ovulation.
- Continued investigation of the role that insulin sensitizing and glycemic control agents like metformin and exenatide have on improving irregular bleeding patterns.
- Carefully controlled trials of complementary and alternative medicine interventions like acupuncture for improving menstrual regularity.
- RCTs specifically designed to assess both the heaviness and the interval of bleeding in women with irregular bleeding, which could include approaches shown to have benefit for heavy cyclic bleeding.

Abnormal Cyclic Bleeding

- Investigate the epidemiology and natural history of heavy menstrual bleeding in representative primary care populations.
- Across specific interventions, additional research and analysis is needed to determine which individuals are most likely to respond to which interventions. This could develop from personalized medicine approaches, from better understanding of the mechanisms underpinning AUB, or from predictive modeling in large datasets.

- Assess the acceptability and cost-effectiveness of various treatments in the primary care setting in the United States including LNG-IUS, NSAID, COCs and TXA.
- Determine the most valid and accurate indirect measures of MBL that can be used in primary care settings and that correlate with objective direct measures.

Progesterone Containing Intrauterine Devices Including the LNG-IUS

- Establish a registry of LNG-IUS users in the United States for extended followup of potential harms and preventive effects (e.g., reduced risk of endometrial cancer, anemia).
- Extend postmarketing surveillance to assure safety when used in teens and nulliparous patients.
- Examine costs in light of whether the treatment simultaneously resolves bleeding complaints and provides contraception.

Nonsteroidal Anti-Inflammatory Drugs

- Directly compare classes of NSAIDs including commonly available over-the-counter preparations.
- Conduct long-term effectiveness studies to determine if treatment effects are durable or wane over time.
- Model the costs of treatment with varied NSAID dosing strategies.
- Determine if "pre-loading" in the days before onset of menses significantly reduces menstrual bleeding alone and in combination with NSAIDs after onset of menstrual bleeding.

Combined Oral Contraceptives

- Conduct direct comparisons of COCs with other AUB management strategies to better understand the relative merits of treatment options.
- Examine costs in light of whether the treatment simultaneously treats complaints and provides contraception.

Tranexamic Acid

- Establish a registry of TXA users and exploit existing large payer datasets to examine long-term followup for both effectiveness beyond six months, and incidence of rare/uncommon adverse effects.

Conclusions

Women who have problematic irregular or heavy cyclic menstrual bleeding have a number of treatment options available that are supported by systematic review of the research literature. These include high strength of evidence that COCs can improve menstrual regularity for women with irregular bleeding patterns. Metformin is supported by moderate strength of evidence for improving cycle regularity especially among women with PCOS. This provides both a contraceptive and a noncontraceptive option for irregular menses. Other interventions like progestogens are associate with statistically and clinically meaningful improvements from baseline patterns, however the overall evidence is insufficient from well-designed, larger studies with ability to directly compare treatment arms rather than only pre-post measures within groups.

Multiple interventions for heavy cyclic bleeding are supported by evidence that they reduce MBL. These include strong evidence that COCs are effective and moderate strength of evidence that LNG-IUS, NSAIDs, and TXA reduce bleeding relative to baseline, decrease total volume of bleeding when comparisons are made across treatment groups, and when measured, decrease days of bleeding. In direct comparisons LNG-IUS is superior to NSAIDs. TXA is superior to NSAIDs and TXA combined with an NSAID was superior to TXA alone. Results from COC and NSAID comparisons suggest comparable effectiveness. Not all women who are treated with any of these interventions that can be effective will improve. Across agents data are sparse to evaluate long-term improvements and risk of harms.

Limitations include a predominance of small, short trials lacking standard terminology and diagnostic criteria for identifying and including women with AUB. Tools for collecting outcome data are crude (collection of sanitary products) and may contribute to a high rate of attrition. Biologic outcomes, like measured blood loss and hemoglobin or hematocrit levels, may neglect the importance of patient-reported outcomes that assess whether symptoms are considered resolved by women themselves. Nevertheless, the variety of effective options suggests many women can achieve symptom relief and will have available to them choices that address both symptoms and contraceptive or fertility desires, as well as potentially improving other symptoms like menstrual cramping.

Abbreviations and Acronyms

ARHQ	Agency for Healthcare Research and Quality
CER	Comparative Effectiveness Review
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COC	Combined oral contraceptive
GnRH	Gonadotropin-releasing Hormone
HRQoL-4	Health related quality of life survey-based questionnaire
IM	Intramuscular
kg	Kilogram
KQ	Key Questions
LHRH	Luteinizing Hormone-releasing Hormone
LNG-IUS	Levonorgestrel-releasing intrauterine system
MBL	Menstrual blood loss
mcg	Microgram
MeSH	Medical Subject Heading
MIQ	Menorrhagia Impact Questionnaire
mmol	Millimolar
MPA	Medroxyprogesterone acetate
N	Number
NS	Non-significant
OR	Odds ratio
PBLAC	Pictorial Blood Loss Assessment Chart
PCOS	Polycystic ovary syndrome
PICOTS	Population, Interventions, Comparators, Outcomes, Timing, Settings
RCT	Randomized Controlled Trials
SOE	Strength of Evidence
TEP	Technical Expert Panel

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