



# Effective Health Care Program

## Primary Care Management of Abnormal Uterine Bleeding

### 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 women aged 36 to 40.<sup>1,2</sup> 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 5<sup>th</sup> and 95<sup>th</sup> percentiles, are:<sup>3-7</sup>

- Frequency of menses within a 24- to 38-day window
- Regularity (i.e., cycle-to-cycle variation) within 2 to 20 days
- Duration of flow from 4 to 8 days
- Blood loss volume from 5 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 or changes in sexual activity,

#### Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

and frustration with costs of sanitary protection. Collectively, the effects of troublesome bleeding reduce quality of life and drive desire for information about causes and treatment options.<sup>1,8</sup>



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 (e.g., fibroids, polyps), cancer and precancerous changes in the cervix or uterus, coagulation defects, and systemic disease. The 2011 International Federation of Gynecology and Obstetrics (FIGO) classification recommends a structured history followed by uterine evaluation.<sup>9</sup> In the research setting, the alkaline hematin method is the preferred technique for direct measurement of total menstrual blood loss (MBL). The pictorial blood loss assessment chart is a semi-quantitative tool for uniform reporting of bleeding as represented by the degree of saturation of sanitary pads and tampons. Diagnostic tools and evaluation strategies are not within the scope of this review;<sup>10,11</sup> however, the review captures the operational definitions used by researchers and addresses applicability of the findings to contemporary practice.

## Terminology

Nomenclature to classify AUB has evolved steadily over the past several decades.<sup>12</sup> 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. 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.<sup>12</sup> The resulting challenge was that practitioners and researchers applied different exclusions before selecting interventions or enrolling patients. Over time, these differences in terminology and use of operational definitions resulted in inconsistent application of diagnostic terms.<sup>4,12-14</sup>

Recent international consensus recommendations, formally adopted by FIGO in 2010 and published in 2011, more consistently align terminology by creating two major groupings (i.e., discrete structural vs. nonstructural) for causes of bleeding.<sup>9,15,16</sup> The FIGO classification includes nine categories of abnormal bleeding arranged according to the acronym PALM-COEIN:<sup>9,15</sup> 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).

If we map the intended focus of this comparative effectiveness review to the FIGO classification, we are addressing the COEIN groups that are characterized as “ovulatory dysfunction” (AUB-O), “endometrial hemostatic dysfunction” (AUB-E), and “not yet classified” (AUB-N) abnormal bleeding. However it is crucial to note that direct measures of ovulation are not employed in most available literature and endometrial samples for classification are even rarer, except when used to rule out malignancy. Indeed much remains to be explained about the pathophysiology of the very common and problematic complaint of unpredictable and/or heavy bleeding. In summary, the relevant population for this review includes nonpregnant women from menarche to menopause who have had abnormal bleeding (scant or heavy) for 3 months or longer that is not attributed to structural abnormalities, coagulation defects, systemic illnesses, or medications.

While some reviews further subdivide women experiencing AUB into age groups,<sup>17</sup> 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.<sup>18</sup> 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.<sup>19</sup> 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.

## Therapies

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 irregular and abnormal cyclic menstrual bleeding and lacked an overall awareness of current evidence on effectiveness of treatment options for AUB.<sup>20</sup>

Current recommendations for medical 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.<sup>21-26</sup> 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.<sup>2,21</sup>

## Scope and Key Questions

The relevant population for this review includes nonpregnant women from menarche to menopause who have had AUB for 3 months or longer, that is not attributed

to structural abnormalities, coagulation defects, systemic illnesses, or medications. 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
<b>Population:</b>	<p>Nonpregnant women from menarche to menopause who have had abnormal bleeding for 3 months or longer whose bleeding is not caused by structural abnormalities, coagulation defects systemic disease, cancer, or medication.</p> <p>Two specific subtypes of abnormal bleeding will be the focus:</p> <ul style="list-style-type: none"> <li>• <i>Irregular uterine bleeding</i>: problem bleeding (frequent or infrequent) of 3 months or greater duration, excluding regular cyclic/menstrual patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, coagulation defects, and related systemic disease.</li> <li>• <i>Abnormal cyclic uterine bleeding</i>: problem bleeding of 3 months or greater duration, excluding irregular and unpredictable patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, coagulation defects, and related systemic disease.</li> </ul>
<b>Interventions:<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• Medical therapies <ul style="list-style-type: none"> <li>– Nonsteroidal anti-inflammatory drugs</li> <li>– Antifibrinolytics</li> <li>– Oral hormone treatments (e.g., oral contraceptives, progestogens)</li> <li>– Levonorgestrel-releasing intrauterine system</li> <li>– Vaginal ring contraceptive device</li> </ul> </li> <li>• Behavioral strategies (e.g., stress reduction, weight reduction, exercise)</li> <li>• Complementary and alternative medicine therapies (e.g., acupuncture, herbal medicine)</li> </ul>
<b>Comparator:</b>	Direct comparison among interventions listed above or comparison to placebo.
<b>Outcomes:</b>	<ul style="list-style-type: none"> <li>• Bleeding profile (e.g., amount, frequency, duration, pattern, symptom bother, hematocrit)</li> <li>• Quality of life including both general and bleeding specific measures</li> <li>• Pain related to bleeding</li> <li>• Sexual function as reported by sexual function measures, general measures of sexual activity, frequency and satisfaction</li> <li>• Patient satisfaction with outcomes and acceptability of treatment</li> <li>• Fertility</li> <li>• Time to conception</li> <li>• Additional interventions including concurrent and consecutive surgical and nonsurgical treatments</li> <li>• Harms<sup>b</sup> (e.g., thromboembolic events, emotional side effects, weight gain, short- and long-term harms)</li> </ul>
<b>Timing:</b>	Interventions initiated after symptoms present most months for 3 months or longer.
<b>Setting:</b>	Any clinical care setting.

PICOTS = population, intervention, comparator, outcome, timing, and setting

<sup>a</sup>Excluding surgical interventions and procedures such as endometrial ablation.

<sup>b</sup>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

### Key Question 1A

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

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

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 of Key Informants 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.

## Methods

### Literature Search

For Key Question (KQ) 1, 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 interventions for women with irregular or abnormal cyclic uterine bleeding. We excluded studies of women with AUB caused by coagulation defects, 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 J of the full report.

### Quality (Risk of Bias) Assessment

We assessed quality of RCTs using the Cochrane Collaboration Risk of Bias Tool,<sup>27</sup> 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 preestablished 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 I 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. Detailed study information is provided in evidence tables included in Appendix J of the full 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, and self-report using scoring systems including 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 12 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 1,775 titles and abstracts for screening; 219 publications were identified as potentially eligible for inclusion and were promoted for full-text review. We identified 41 publications from 39 unique studies that met criteria for inclusion. Ten studies included in the review addressed KQ1A; 31 publications representing 29 studies addressed KQ1B. We conducted a separate search and screening process for KQ2. We identified 2,730 titles and abstracts for screening. Of these, 788 references were promoted for full text review. Using predefined criteria, we found 25 publications about harms that were eligible for inclusion. We obtained package inserts for each KQ1 included drug intervention.

### Description of Included Studies (KQ1)

Thirty-nine included studies evaluated NSAIDs (13 studies),<sup>28-40</sup> the LNG-IUS (7 studies),<sup>28,41-46</sup> tranexamic acid (TXA; 7 studies),<sup>29,34,40,47-50</sup> COCs (6 studies),<sup>31,41,43,51-53</sup> contraceptive vaginal ring (1 study),<sup>54</sup> metformin (4 studies),<sup>55-58</sup> progestogens (1 study),<sup>59</sup> cabergoline (1 study),<sup>60</sup> lifestyle/behavioral changes (2 studies),<sup>61,62</sup> acupuncture (2 studies),<sup>61,63</sup> and patient decision aids (3 studies)<sup>64-66</sup> 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 6 months or less. Four of the studies addressing KQ1B included a followup of 1 to 2 years.

### KQ1A. Management of Irregular Uterine Bleeding

Ten RCTs addressed restoring menstrual regularity in those with irregular uterine bleeding. Three were conducted in the United States,<sup>51,57,62</sup> two in Italy,<sup>56,60</sup> two in Turkey,<sup>58,59</sup> and one each in China,<sup>63</sup> Sweden,<sup>61</sup> and the United Kingdom.<sup>55</sup> The studies ranged in size from 23 to 201 participants and examined the efficacy of metformin (4 studies),<sup>55-58</sup> progestogen (1 study),<sup>59</sup> triphasic birth control pills (1 study),<sup>51</sup> cabergoline (1 study),<sup>60</sup> diet and exercise (1 study),<sup>62</sup> and acupuncture (2 studies).<sup>61,63</sup> The majority compared treatment to placebo or sham intervention; three included comparisons of effectiveness of two interventions. Two studies were classified as good

quality,<sup>51,60</sup> two studies as fair quality,<sup>55,63</sup> and six studies as poor quality.<sup>56-59,61,62</sup>

### **Metformin and Exenatide**

Metformin was an active treatment arm in four RCTs conducted among women with PCOS. Two RCTs compared metformin outcomes to a placebo group,<sup>55,56</sup> one compared metformin to N-acetyl-cysteine,<sup>58</sup> and one three-armed study compared metformin only, exenatide only, and both.<sup>57</sup> In each case, compared with baseline or placebo, metformin was effective for improving the regularity of bleeding over a number of months.<sup>55,56,58</sup> Combination therapy improved cycle frequency better than metformin or exenatide alone in 60 women with PCOS.<sup>57</sup>

### **Progestogens**

Vaginal micronized progesterone and oral dydrogesterone were studied in a single trial among women clinically classified as having dysfunctional uterine bleeding.<sup>59</sup> 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.

### **COCs**

A triphasic oral contraceptive was also studied in a single RCT among women with irregular uterine bleeding.<sup>51</sup> 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 with 26 percent of those receiving a placebo.

### **Cabergoline**

In a very preliminary investigation of cabergoline,<sup>60</sup> a drug indicated for the treatment of prolactinoma, treatment over 6 months was associated with return of regular menses in three of eight women compared with 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 3 days a week resulted in more regular menses among those

who lost weight.<sup>62</sup> 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<sup>61</sup> 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 calculated by 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 with no intervention or alternate placement of acupuncture needles.<sup>61,63</sup> By 32 weeks in the trial of electroacupuncture for PCOS,<sup>61</sup> 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 3 cycles,<sup>63</sup> women who received treatment for “mind tranquilizing and menstruation promotion” had greater improvements (no treatment failures among 21 women) compared with 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 31 publications representing 29 studies addressing nonsurgical interventions for the management of abnormal cyclic uterine bleeding. The interventions evaluated in the studies included the LNG-IUS (7 studies),<sup>28,41-46</sup> NSAIDs (13 studies),<sup>28-40</sup> TXA (7 studies),<sup>29,34,40,47-50</sup> COCs (5 studies),<sup>31,41,43,52,53</sup> and contraceptive vaginal ring (1 study).<sup>54</sup> We also identified three studies that evaluated decision aids for the management of AUB.<sup>65-67</sup> Included studies described nonsurgical interventions and compared these interventions to another intervention (17 studies),<sup>28,29,31,33,34,37,38,40-45,48,49,54,58,67</sup> placebo (9 studies),<sup>30,32,35,36,39,47,50,52,53</sup> or usual care (4 studies)<sup>46,64-66</sup> 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 29 included studies, 4 studies were assessed as good quality,<sup>35,47,52,53</sup> 8 as fair quality,<sup>30,38,39,42,45,49,50,54</sup> and 17 as poor quality.<sup>28,29,31-34,36,37,40,41,43,44,46,48,64-66</sup>

### LNG-IUS

LNG-IUS was an effective intervention for reduction of abnormal cyclic uterine bleeding in all seven of the identified studies.<sup>28,41-46</sup> Five studies that measured menstrual blood loss (MBL) directly from collected sanitary materials documented 70 to 87 percent reductions in bleeding when comparing treated women with their baseline.<sup>28,41-43,45</sup> 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. A single study among women scheduled for hysterectomy found that LNG-IUS users were more likely to cancel their surgery compared with women in the usual care group.<sup>46</sup>

### NSAIDs

In 13 studies, NSAIDs including mefenamic acid, naproxen, meclufenamate, and flurbiprofen given at the onset of menses for up to 5 days reduced MBL when compared with baseline.<sup>28-40</sup> NSAIDs are effective when compared with placebo.<sup>35,39,68</sup> Overall, 6 of 13 studies provided statistical comparisons to baseline only. Evidence is equivocal, one trial each, showing NSAIDs are similar in effectiveness or superior to oral norethisterone.<sup>33,37</sup> When measured, specific NSAIDs have been shown to reduce blood loss by 20 to 59 percent.<sup>28-31,33-35,38-40,68</sup> 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 reductions between NSAIDs and oral norethisterone or COCs. 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 with TXA alone.<sup>40</sup>

### TXA

All seven RCTs including TXA treatment demonstrated effectiveness for improving heavy bleeding.<sup>29,34,40,47-50</sup> TXA at a dose of 1.95 to 4.5 grams per day for 4 to 5 days from the onset of bleeding led to a clinically significant reduction in MBL, ranging from a 26 to 54 percent decrease in studies lasting up to a year. Both biologic and self-reported symptoms of bleeding severity were improved. In comparison to progestogens (norethisterone and medroxyprogesterone acetate), 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.

### COCs

Five RCTs included groups treated with COCs.<sup>31,41,43,52,53</sup> Measured reduction in bleeding was from 43 to 69 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.<sup>31</sup> Two placebo-controlled studies found COCs effective for reducing menstrual bleeding and days of bleeding.<sup>52,53</sup> In the two head-to-head comparisons between COCs and LNG-IUS,<sup>41,43</sup> reductions in heavy menstrual bleeding were documented in both treatment groups. Women with a LNG-IUS had greater benefit.

### Contraceptive Vaginal Ring

A single RCT compared the efficacy of the contraceptive vaginal ring to norethisterone in 95 women with abnormal cyclic uterine bleeding. The treatments were equally effective, reducing the patient-reported bleeding score by 67 percent in the contraceptive vaginal ring group and by 70 percent in the norethisterone group.<sup>54</sup>

### Decision Aids

Three studies investigated decision aids to assist women seeking treatment for heavy cyclic bleeding in making informed decisions about care.<sup>64-66</sup> 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.<sup>65</sup> 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. Twelve 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., 1,600 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 uterine bleeding first, followed by those for abnormal cyclic uterine 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.<sup>55-57</sup> This is compatible with the package insert.<sup>69</sup> 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.<sup>70</sup>

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.<sup>57</sup> The package insert suggests hypoglycemia is the most serious side effect,<sup>71</sup> and large scale surveillance studies have not confirmed initial

concerns that pancreatitis was more common among those treated.<sup>72,73</sup> 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.<sup>74-76</sup>

### **Progesterone**

Route of progestogen administration was compared in one comparative effectiveness trial for women with irregular menses.<sup>59</sup> 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.<sup>33,37,42,44,45,48,49</sup> The progesterone-releasing intrauterine system is separately reviewed below.

Progestogens, like depot medroxyprogesterone acetate (DMPA), and vaginal micronized progesterone 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. Package inserts also note potential dangers of exposure to high doses in pregnancy.<sup>77</sup>

A surveillance study has linked DMPA to increased future rate of fractures (though analyses were not controlled for key confounders like smoking and body mass index),<sup>78</sup> while another large study showed recovery of normal bone density within 2 to 3 years of ceasing use.<sup>79</sup> Some data suggest use of progestogens is associated with increased risk of deep venous thrombosis, though other 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.<sup>80</sup> Reviews and meta-analyses confirm common side effects, including progestogens being a cause of irregular bleeding.<sup>81</sup>

### **COCs**

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.<sup>82-85</sup> 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 alerted to factors that increase risk of complications such as 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.<sup>6,86</sup>

### **Cabergoline**

The sole study of cabergoline in this review was exploratory with 14 women with PCOS and 15 normal controls.<sup>60</sup> 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 found no difference in overall risk of harms for cabergoline compared with placebo,<sup>87,88</sup> however a review of use for Parkinson's patients revealed increased valvular heart disease on echocardiogram with few symptomatic individuals.<sup>89,90</sup> The applicability of this data to young women with irregular menses is very limited.

### **LNG-IUS**

Participants in the included trial of use of the LNG-IUS for abnormal cyclic uterine 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 expulsion are expected to occur in approximately 5 percent or more of women using this treatment, as reflected in package inserts.<sup>91,92</sup> Surveillance studies provide good estimates from large registries of users. Difficult insertions occur in 3 to 4 percent of women, with painful insertion occurring in about 1 percent.<sup>93,94</sup> Risk of uterine perforation is between 0.9 and 2.6 per 1,000 users and the majority are not recognized at the time of insertion.<sup>94-97</sup> Nulliparous status and noncontraceptive 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 1,000 users.<sup>95</sup> The LNG-IUS is not associated with increased risk of deep vein thrombosis in more than 8 million person-years of observation.<sup>98-100</sup> Systematic reviews match package insert and surveillance data also noting that expulsion occurs in 5 to 16 percent of women.<sup>81,84,101,102</sup>

### **Contraceptive Vaginal Ring**

In the single trial of the contraceptive vaginal ring included in this review, the incidence of nausea, headache, and breast tenderness was comparable in both treatment groups during three cycles of treatment. The contraceptive vaginal ring users were less likely to report breakthrough bleeding than women taking norethisterone. Local events, including vaginal discomfort, vaginitis, foreign body sensation and coital problems were reported more frequently in ring-users, but no one discontinued treatment due to adverse events. Product materials note that the contraceptive vaginal ring is contraindicated in cigarette smokers over age 35 due to increased risk of venous thromboembolism. A 15-year cohort study that included over 38,000 person-years of contraceptive vaginal ring use reported an elevated adjusted relative risk of 2.5 (95% CI, 1.4 to 4.4) for thrombotic stroke and 2.1 (95% CI, 0.7 to 6.5) for myocardial infarction compared with women (over 9 million person-years) who had not used hormonal contraception.<sup>98</sup> Systematic reviews have noted that the risk of venous thromboembolism for the contraceptive vaginal ring was elevated and similar to COCs.<sup>103</sup>

### **NSAIDs**

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.<sup>104-106</sup> Upper gastrointestinal bleeding occurs in approximately 1 percent of patients treated for 3 to 6 months and at higher rates with longer use.<sup>105-107</sup> However, the majority of use assessed in this way is chronic, daily use. Product materials 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 were more common in those treated than among placebo users.<sup>108</sup> The available reviews note additional investigation is required to clarify potential cardiovascular risks.<sup>109,110</sup>

### **TXA**

Within studies in our review similar numbers of participants withdrew from TXA treatment arms as from

placebo and comparison groups.<sup>47,48</sup> 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.<sup>111</sup> 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.<sup>112</sup> Joint pain, muscle cramps and spasms, migraine, anemia, and fatigue occur in more than 5 percent of users. Post-marketing reports have identified thrombosis, allergic reactions including anaphylaxis, and visual disturbances.<sup>112</sup> 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.<sup>113-116</sup> 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

The strength of evidence tables (Table B and Table C) 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.

Overall the evidence to answer KQs about the management of AUB did not reach standards for high strength of evidence for any intervention from the literature relevant to treatment of women with irregular uterine bleeding (Table B). COCs, as represented in a single good quality placebo controlled trial with 201 participants, documented effectiveness.<sup>51</sup> The treatment effect was large with improvement in bleeding patterns reported for more than 80 percent of women taking COC compared with 45 percent for the placebo group. Combined, these factors provided moderate evidence of benefit. Use of metformin is supported by low strength of evidence predominantly 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 and/or lower quality studies.

For management of heavy cyclic bleeding, the literature was more robust (Table C). 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,<sup>28</sup> two showing superiority to COCs,<sup>41,43</sup> and two showing superiority to progestogens.<sup>42,44,45</sup> COCs were equivalent in one trial compared with an NSAID.<sup>31</sup> TXA was also superior to NSAIDs,<sup>29,34</sup> and when combined with an NSAID was superior to TXA alone.<sup>40</sup> Most of these interventions have been shown to have additional positive effects, typically including shorter duration of bleeding and improvement in symptoms when participants used standardized scoring systems to report treatment response.

### Applicability

Applicability describes the extent to which results observed in published studies from this review are likely to reflect the expected outcomes when an intervention is applied to broader populations in real-world conditions. Studies for this review were intended to provide information to inform primary care management of irregular or cyclic AUB. In shaping the methods for this review, we 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 intrauterine device in place, and who are not pregnant or lactating;

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

<b>Intervention Quality: Studies Assigned to Intervention)</b>	<b>Risk of Bias</b>	<b>Consistency</b>	<b>Directness</b>	<b>Precision</b>	<b>Overall Strength of Evidence<sup>a</sup></b>	<b>Findings Comparisons</b>
<i>Progestogen<sup>b</sup></i> Poor: 1(69) <sup>59</sup>	High	NA	Direct	Imprecise	Insufficient	Not analyzed by arm
<i>COC<sup>c</sup></i> Good: 1(101) <sup>51</sup>	Low	NA	Direct	Precise	Moderate	Cycle control improved: <sup>d</sup> 87% COC vs. PBO, p<0.001 <sup>51</sup>
<i>Metformin<sup>e</sup></i> Poor: 3(81) <sup>56-58</sup> Fair: 1(45) <sup>55</sup>	Medium	NA	Direct	Imprecise	Low	Delay to first ovulation: <sup>f</sup> 24 days MET vs. PBO, p=0.02 <sup>55</sup>
<i>Exenatide<sup>g</sup></i> Poor: 1(20) <sup>57</sup>	High	NA	Direct	Imprecise	Insufficient	Small, poor quality trial
<i>Cabergoline<sup>h</sup></i> Good: 1(8) <sup>60</sup>	Low	NA	Direct	Imprecise	Insufficient	Cycle control improved: <sup>i</sup> 100% CBG vs. PBO, p=NR <sup>60</sup>
<i>Diet<sup>j</sup></i> Poor: 1(24) <sup>62</sup>	High	NA	Direct	Imprecise	Insufficient	Not analyzed by arm
<i>Exercise<sup>k</sup></i> Poor: 1(34) <sup>61</sup>	High	NA	Direct	Imprecise	Insufficient	Not analyzed by arm
<i>Acupuncture<sup>l</sup></i> Poor: 1(33) <sup>61</sup> Fair: 1(23) <sup>63</sup>	High	NA	Direct	Imprecise	Insufficient	Menstrual regulation: <sup>m</sup> 86% MP-ACU > R-ACU, p<0.05 <sup>63</sup>

CBG = cabergoline; COC = combined oral contraceptive; MET = metformin; MR-ACU = menstruation-promoting acupuncture; NR = not reported; PBO = placebo; R-ACU = routine acupuncture

<sup>a</sup>Overall strength of evidence assessment based on good and fair quality studies only.

<sup>b</sup>Oral dydrogesterone (n=35) vs. 8% vaginal micronized progesterone (n=34).

<sup>c</sup>Triphasic norgestimate-ethinyl estradiol vs. placebo (n=100).

<sup>d</sup>Subject assessment.

<sup>e</sup>Poor quality studies: metformin vs. N-acetyl cysteine (n=50), exenatide (n=20), or placebo (n=12); Fair quality study: metformin vs. placebo (n=47).

<sup>f</sup>Mean days to ovulation.

<sup>g</sup>Compared with metformin (n=20) or metformin plus exenatide (n=20).

<sup>h</sup>Compared with placebo (n=6).

<sup>i</sup>Menstrual cyclicity restoration in oligomenorrhea or spontaneous menses in amenorrhea.

<sup>j</sup>Low-fat diet (n=12) vs. low-carbohydrate diet (n=12).

<sup>k</sup>Compared with acupuncture (n=33) or no intervention (n=17).

<sup>l</sup>Poor quality study: acupuncture vs. exercise (n=34) or no intervention (n=17); Fair quality study: mind tranquilizing acupuncture vs. routine acupuncture (n=17).

<sup>m</sup>Patients cured or markedly relieved.

- 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.

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

<b>Intervention Quality: Studies Assigned to Intervention)</b>	<b>Risk of Bias</b>	<b>Consistency</b>	<b>Directness</b>	<b>Precision</b>	<b>Overall Strength of Evidence<sup>a</sup></b>	<b>Findings<sup>b</sup> Comparisons</b>
<b>LNG-IUS</b> Poor: (173) <sup>28,41,43,44,46</sup> Fair: 2(104) <sup>42,45</sup>	Medium	Consistent	Direct	Precise	Moderate	71% and 94% reduction in MBL in 2 head-to-head studies  LNG-IUS > MPA, p<0.001 <sup>42</sup> LNG-IUS vs. NOR, p=NS <sup>45</sup>
<b>NSAID</b> Poor: 9(192) <sup>28,29,31-34,36,37,40</sup> Fair: 3(129) <sup>30,38,39,68</sup> Good: 1(32) <sup>35</sup>	Medium	Consistent	Direct	Imprecise	Moderate	28% to 49% reduction in MBL in 3 placebo controlled trials; 46% and 47% reduction in MBL in 1 head-to-head study (2 NSAID arms)  MFA vs. PBO, p=NR <sup>30</sup> p<0.001 <sup>39,35</sup> MFA vs. NPX, p=NS <sup>38</sup>
<b>TXA</b> Poor: 4(202) <sup>29,34,40,48</sup> Fair: 2(260) <sup>49,50</sup> Good: 1(123) <sup>47</sup>	Medium	Consistent	Direct	Precise	Moderate	26% and 40% reduction in MBL in 2 placebo controlled trials; 45% reduction in MBL in 1 head-to-head study  TXA vs. PBO, p<0.001 <sup>50,47</sup> TXA > NOR, p<0.001 <sup>49</sup>
<b>COC<sup>c</sup></b> Poor: 3(90) <sup>31,41,43</sup> Good: 2(269) <sup>52,53</sup>	Low	Consistent	Direct	Precise	High	64% and 69% reduction in MBL in 2 placebo controlled trials  COC vs. PBO, p<0.001 <sup>52,53</sup>
<b>Progestogen<sup>d</sup></b> Poor: 1(50) <sup>48</sup> Fair: 4(173) <sup>42,45,49,54</sup>	Medium	Inconsistent	Direct	Imprecise	Insufficient	20% increase to 87% reduction in MBL in 4 head-to-head studies  MPA < LNG-IUS, p<0.001 <sup>42</sup> NOR < LNG-IUS, p=NS <sup>45</sup> NOR < TXA, p<0.0001 <sup>49</sup> NOR vs. CVR, p=NS <sup>54e</sup>
<b>CVR</b> Fair: 1(48) <sup>54</sup>	Medium	NA	Direct	Imprecise	Insufficient	67% reduction in MBL <sup>e</sup> in 1 head-to-head study  CVR vs. NOR, p=NS <sup>54</sup>

COC = combined oral contraceptive; CVR = contraceptive vaginal ring; LNG-IUS = levonorgestrel-releasing intrauterine system; MBL = menstrual blood loss; MCF = meclufenamate; MFA = mefenamic acid; MPA = medroxyprogesterone; NA = not applicable; NOR = norethisterone; NPX = naproxen; NR = not reported; NS = not significant; NSAID = nonsteroidal anti-inflammatory drug; PBO = placebo; TXA = tranexamic acid  
<sup>a</sup>Overall strength of evidence assessment based on good and fair quality studies only.

<sup>b</sup>Change in menstrual blood loss from baseline measured by the alkaline hematin method (unless otherwise noted) from good and fair quality studies.

<sup>c</sup>Ethinyl estradiol and levonorgestrel (n=71) or norethindrone and ethinyl estradiol (n=19) or estradiol valerate and dienogest (n=269).

<sup>d</sup>Medroxyprogesterone (n=177) or oral norethisterone (n=113) or depot medroxyprogesterone (n=44).

<sup>e</sup>Percent change in menstrual blood loss measured by the pictorial blood loss assessment chart.

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 is 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 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<sup>9</sup> 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 1 year. Populations need to become more representative of those seeking care (teens, heavier women, those with common comorbidities like diabetes) and need to 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 will benefit from these interventions. 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 have available choices that address both symptoms and contraceptive or fertility desires, as well as potentially improving other symptoms like menstrual cramping.

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## Full Report

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