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Drug Class Update Focused for Pelvic pain and Dysmenorrhea: GnRH Agonists and Antagonists

Date of Review: April 2026

Date of Last Review: 12/2021 (GnRH agonists); 2/2023 (GnRH antagonists)
Dates of Literature Search: 06/20/2023 – 01/06/2026

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Review medications approved to manage pelvic pain and dysmenorrhea to confirm Oregon Health Plan (OHP) Fee for Service (FFS) polices align with Health Evidence Review Commission (HERC) Guidance for these conditions. With the implementation of the Benefit Plan Update (BUP) in January 2027, a pathway to coverage for medications to treat previously unfunded conditions will be necessary.

Plain Language Summary:
- Painful menstrual cramps, also known as dysmenorrhea, are experienced by many women during their reproductive years. Symptoms can include cramps, nausea, vomiting, diarrhea, dizziness, and headaches. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or naproxen are the first treatments usually given for managing pain caused by dysmenorrhea. If these medicines do not relieve the pain, a hormonal birth control medicine may be prescribed. For some women, a hormonal intrauterine device (IUD) can be used to treat painful periods.
- Some types of dysmenorrhea can be caused by endometriosis or uterine fibroids and can also cause infertility, or difficulty getting pregnant.
- Fibroids are solid growths that form on the outside, or the inside, or in the walls of the uterus. Fibroids are usually noncancerous (benign), but they can cause heavy menstrual bleeding, pelvic pressure, frequent urination, and lower back pain.
- Endometriosis occurs when endometrium (the tissue lining the inside of the uterus) starts growing in other parts of the body such as on the ovaries, fallopian tubes, or bladder. Later in the menstrual cycle, this tissue may break down and shed the in the body. This can cause pain throughout the entire month. The most common symptoms of endometriosis include painful periods, pelvic pain between periods, and pain with sexual intercourse.
- The most common treatments to relieve pain associated with endometriosis and fibroids are hormone therapies, like birth control pills and gonadotropin-releasing hormone (GnRH) analogs. Hormone therapies are medicines that decrease the amount of estrogen in the body. Less estrogen will slow the growth of endometrial tissue and stop more lesions from forming outside the uterus. Less estrogen can also shrink fibroids, which makes it easier to remove them surgically.
- Certain kinds of birth control pills (such as estradiol combined with norethindrone), and medicines called GnRH analogs (leuprolide, elagolix, relugolix), stop the production of hormones that tell the ovaries to make estrogen, which decreases the amount of endometrial tissue that grows every month. Many women have lighter and shorter menstrual flows (periods) when they take birth control pills. Some GnRH analogs may create an artificial menopause, and

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monthly periods are prevented. The risk of bone loss when taking these medicines is very high, which prevents people from taking these medicines for longer than 24 months.

- OHP FFS pays for birth control pills when prescribed for adolescents and adults and they do not require prior authorization. Providers must explain to the Oregon Health Authority (OHA) why a patient needs a GnRH analog before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the comparative evidence assessing efficacy GnRH agonists and antagonists to other drug therapies for the treatment of moderate to severe pain associated with pelvic pain and dysmenorrhea?
2. What is the comparative evidence assessing safety of GnRH agonists and antagonists to other drug therapies for the treatment of moderate to severe pain associated pelvic pain and dysmenorrhea?
3. Are there any subgroups (based on age, race, ethnicity, comorbidities, disease duration, or severity) that would particularly benefit or be harmed from treatment with GnRH agonists or antagonists for pelvic pain or dysmenorrhea associated with endometriosis or uterine fibroids?

Conclusions:

- Since the last review, 3 systematic reviews[1-3] and 4 guidelines[4-8] have been published or updated to assess therapies used for management of primary dysmenorrhea, uterine fibroids, or endometriosis.
- In May 2025 the Society of Obstetrics and Gynecology Canada (SOGC) issued guidance for management of primary dysmenorrhea.[4]
    - Health care providers should offer NSAIDs or acetaminophen, administered with regular dosing regimens, as a first-line treatment for most women with primary dysmenorrhea unless contraindicated (strong recommendation, high-quality evidence).[4]
    - Continuous or extended use combined hormonal contraceptives are recommended for the treatment of dysmenorrhea (strong recommendation, high-quality evidence).[4]
- A 2025 Cochrane Review assessed the benefits and risks of medical treatments prior to surgery for uterine fibroids.[1] Pretreatment with GnRH analogs (i.e. leuprolide, goserelin, and triptorelin) may reduce uterine and fibroid volume compared to placebo and other medical therapies and probably increases preoperative hemoglobin levels, but probably also increases the number of adverse events (low certainty evidence).[1] Blood transfusions and operation time during hysterectomy may be reduced with GnRH analogs compared to placebo with fewer women experiencing postoperative morbidity (low certainty evidence).[1]
- Canada's Drug Agency (CDA) Canadian Drug Expert Committee (CDEC) recommends that the GnRH antagonist, relugolix-estradiol–norethindrone acetate, be reimbursed for the management of heavy menstrual bleeding associated with uterine fibroids in patients (2025).[5]
- The National Institute for Health and Care Excellence (NICE) recommends relugolix–estradiol–norethindrone as an option for treating moderate to severe symptoms of uterine fibroids (2022) or endometriosis in adults of reproductive age (2024).[6,7]
- A 2023 Cochrane Review assessed the effectiveness of GnRH agonists (goserelin, leuprolide, nafarelin, and triptorelin) in the treatment of painful symptoms associated with endometriosis.[2] For relief of overall pain, there may be a slight decrease in favor of treatment with GnRH agonists compared to placebo or oral or injectable progestogens (low certainty evidence).[2] The effects on alleviating pain are uncertain when comparing GnRH agonists with danazol or intra-uterine progestogens.[2] There may be a slight increase in adverse effects when women are treated with GnRH agonists, compared to placebo (very low certainty evidence).[2]
- A 2025 Cochrane Review evaluated the harms and benefits of progestogens in the treatment of endometriosis-associated pain symptoms.[3] In individuals with endometriosis, oral progestogens compared with placebo likely reduce overall pain and dysmenorrhea and may reduce pelvic pain (moderate certainty

evidence) .[3] Compared with other hormonal suppression strategies (i.e., oral contraceptives, GnRH agonists), the evidence is less certain due to the small number of studies for each comparison and outcome.[3]

- The European Society of Human Reproduction and Embryology (ESHRE) guidance for management of endometriosis was updated in February 2022.[8] Treatment should begin with NSAIDs/analgesics and/or hormonal treatments (combined oral contraceptives, progestogens).[8] Second-line treatments include a GnRH agonist (i.e., leuprolide) or GnRH antagonists (i.e., elagolix, relugolix).[8] Strength of recommendations and quality of evidence are as follows:
    - Women may be offered NSAIDs or other analgesics (either alone or in combination with other treatments) to reduce endometriosis-associated pain (weak recommendation; very low-quality evidence).[8]
    - It is recommended to prescribe women a combined hormonal contraceptive (oral, vaginal ring or transdermal) to reduce endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain (strong recommendation; low-quality evidence).[8]
    - It is recommended to prescribe GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (strong recommendation; low-quality evidence).[8]
    - Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypo-estrogenic symptoms (strong recommendation; moderate-quality evidence).[8]
    - It can be considered to prescribe GnRH antagonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (weak recommendation; moderate-quality evidence).[8]
- New Food and Drug Administration (FDA) safety alerts for GnRH agonists are presented in **Table 3**.
- There is insufficient evidence that any subgroups (based on age, race, ethnicity, comorbidities, disease duration, or severity) that would particularly benefit or be harmed from treatment with GnRH agonists or GnRH antagonists for pelvic pain or dysmenorrhea associated with endometriosis or uterine fibroids.

Recommendations:

- No changes to the PDL are recommended based upon recent published guidelines and systematic reviews.
- Modify PA criteria for GnRH agonists and GnRH antagonists to align with HERC guidance.
- After evaluation of drug costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy:

- A drug class update that reviewed drugs for management of endometriosis and uterine fibroids was presented to the Pharmacy and Therapeutics (P & T) committee in December 2021. The committee accepted a recommendation to implement new prior authorization (PA) criteria for GnRH analogs to evaluate GnRH antagonists (e.g., relugolix, elagolix), separately from GnRH agonists (e.g., leuprolide). PA criteria are presented in **Appendix 5**.
- The GnRH antagonists were last reviewed by the P & T committee at the February 2023 meeting. At that time, PA criteria were revised for relugolix, estradiol, and norethindrone combination therapy to include management of moderate to severe pain associated with endometriosis in premenopausal women in addition to management of heavy menstrual bleeding associated with uterine fibroids (**Appendix 5**).
- The pediatric formulation of leuprolide is the only preferred GnRH agonist on the preferred drug list (PDL). All other GnRH agonists and antagonists are non-preferred on the PDL and are presented in **Appendix 2**.

Background:

The HERC has issued guidance for the management and treatment of pelvic pain and dysmenorrhea, which are not currently funded diagnoses.[9] The complete guidance is presented in **Appendix 1.** For management of dysmenorrhea a hysterectomy may be indicated if a 6-month trial of NSAIDs and hormonal therapeutic

options are ineffective or contraindicated. Hormonal options include: a) contraceptives, progesterone-containing IUD, or injectable hormone therapy or b)GnRH analogs or danazol.[9] For diagnostic magnetic resonance imaging (MRI) or surgical management of pelvic pain syndrome, a 6-month trial of NSAIDs and a) oral contraceptives, progesterone-containing IUD, or injectable hormone therapy or b) GnRH agonists or danazol must be proven ineffective or contraindicated.[9]

Dysmenorrhea

Dysmenorrhea, or painful menstruation, is experienced by many female assigned at birth people in their reproductive years.[10] Dysmenorrhea is characterized by severe, painful, cramping in the lower abdomen that is often accompanied by sweating, headaches, nausea, vomiting, muscle cramps, and diarrhea.[11] Primary dysmenorrhea is defined as painful menstruation in the absence of pelvic pathology.[11] Secondary dysmenorrhea is due pelvic pathology such as endometriosis, adenomyosis, pelvic inflammatory disease, congenital anatomic abnormalities, or uterine fibroids.[11] Primary dysmenorrhea is a result of the cyclooxygenase pathway producing increased leukotrienes and prostaglandins.[12,13] The increased prostaglandins cause uterine contractions that restrict blood flow and lead to the production of metabolites that stimulate pain receptors.[12] The diagnosis of primary dysmenorrhea is made more often in adolescents and young women with estimates ranging from 67% to 90% for those aged 17–24 years.[11] In general, increased severity of dysmenorrhea has been suggested to relate to age, smoking, earlier age at menarche, nulliparity, longer and heavier menstrual flow, and family history of dysmenorrhea.[11]

First-line treatment options for primary dysmenorrhea include NSAIDs, acetaminophen, and/or hormonal contraception.[4] Nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen effectively manage dysmenorrhea by decreasing prostaglandin levels via inhibition of cyclooxygenase-mediated production.[14] The NSAID should be started with the onset of symptoms or menses and continued through day 2 or 3 of the menstrual cycle.[13,14] Hormonal contraception includes combined estrogen-progestin products (oral pills, transdermal patches, and vaginal rings) and progestin-only options (implant, injection, IUD, and oral pills). Hormonal agents inhibit proliferation of the endometrial lining, which decreases leukotriene and prostaglandin production.[14] Choice of treatment order depends on the clinical needs and preferences of the patient.[13]

Uterine Fibroids

Uterine fibroids (i.e., leiomyomas) are benign, hormone-dependent, smooth muscle tumors of that arise primarily in 3 regions of the uterus (submucosal, intramural, and subserosal) in women of reproductive age.[15] Although they are often asymptomatic, uterine fibroids can cause excessive menstrual bleeding, pelvic pain, and other symptoms that seriously affect a woman's quality of life.[16] Normal menstrual blood loss has been defined as 30 mL to 40 mL per menstrual cycle, while heavy menstrual bleeding has been defined as greater than 80 mL blood loss per cycle.[17] Other fibroid symptoms include infertility, increased urinary frequency or incontinence, constipation, abdominal bloating, dyspareunia, and fatigue (due to anemia from heavy bleeding).[16] The evaluation of fibroids is based mainly on the patient's presenting symptoms: abnormal menstrual bleeding, bulk symptoms (i.e., abdominal protrusion, constipation or urinary frequency), pelvic pain, or findings suggestive of anemia.[15] Fibroids are sometimes found in asymptomatic women during routine pelvic examination or incidentally during imaging.[15]

In the United States, an estimated 26 million women between the ages of 15 and 50 have uterine fibroids.[16] Uterine fibroids account for nearly 30% of all hysterectomies among American women ages 18–44 years.[16] Factors that are associated with an increased risk of uterine fibroids include premenopausal status, family history, nulliparity, hypertension, and obesity.[18] On average, Black women are younger at onset of fibroids, and have larger and more numerous tumors, and are more likely to be anemic and have surgical interventions for fibroids.[16] These observed differences are likely due to inequities in social determinants of health as well as implicit and explicit bias among the medical community.[19] In addition, differences in social determinants of health such as limitations on access to quality education, jobs, stable housing, safe neighborhoods, nutritious foods, and health insurance are associated with inequitable uterine fibroid treatment among Black women.[20,21] Racial disparities in treatment, such as higher rates of hysterectomy and myomectomy (compared with nonsurgical therapy) and open

hysterectomy (compared with minimally invasive approaches) have been reported among Black women compared with White women.[20] The prevalence of uterine fibroids does not appear to be higher among Hispanic and Asian women as compared with White women, but data are far more limited for these populations.[20]

The alkaline hematin technique, which involves chemically measuring the blood content of used sanitary products, is considered the gold standard for menstrual blood loss determination and has traditionally been used to diagnose heavy menstrual bleeding.[22] Normal menstrual blood loss has been defined as 30 mL to 40 mL per menstrual cycle, while heavy menstrual bleeding has been defined as greater than 80 mL blood loss per cycle.[17] The alkaline hematin method directly measures the volume of menstrual blood loss by comparing hematin from menstrual products against calibration curves created from a simultaneous venous blood sample.[23] The alkaline hematin laboratory testing of blood stained sanitary products has been utilized as a primary endpoint in a number of trials evaluating heavy menstrual bleeding with the levonorgestrel-releasing IUD, oral contraceptives, and leuprolide.[24] The FDA has found this test to be somewhat more objective than a pictorial bleeding assessment which directs the study participant to grade their volume of bleeding by comparing their sanitary products to pictures of sanitary products that have undergone some degree of saturation with known quantities of blood.[24]

Symptomatic fibroids may require medical or surgical intervention.[16] Surgical treatment includes hysterectomy, myomectomy, uterine artery embolization, and magnetic resonance–guided focused ultrasound surgery.[15] The 3 medications that have FDA-approval for managing fibroid-related bleeding are the GnRH agonist, leuprolide acetate[25] and the 2 GnRH antagonists combined with add-back hormonal therapy (i.e., elagolix and relugolix).[26,27] Several medications including oral contraceptives, levonorgestrel-releasing IUD (LNG-IUD), and tranexamic acid are used to manage heavy menstrual bleeding associated with fibroids. The 2021 American College of Obstetricians and Gynecologists (ACOG) practice bulletin recommended treatment options to reduce bleeding due to uterine leiomyomas include GnRH antagonists, LNG-IUD, oral contraceptives, and tranexamic acid.[28] Medications that reduce bleeding and leiomyoma size include the GnRH agonists and selective progesterone receptor modulators (ulipristal, mifepristone).[28] Selective progesterone receptor modulators are not FDA-approved for management of bleeding due to fibroids.[3] A summary of the ACOG recommendations is presented in **Table 1.**

Table 1. Medical Management of Uterine Fibroids[28]

Medication (BRAND NAME)	Availability	Notes
Combined Estrogen-Progestin Contraceptives	Oral, vaginal ring, transdermal patch	Off-label use of hormonal contraceptives
High Dose Oral Progestogens	Oral, implants, injections	Off-label use of oral progestogens
Levonorgestrel (MIRENA)	Intrauterine device	Limited evidence for efficacy in treating fibroid-associated pain, effective in reducing bleeding associated with fibroids.
Tranexamic Acid	Oral	Contraindicated in patients at risk for thrombosis
Progesterone Receptor Modulators (Ulipristal, Mifepristone)	Oral	Not approved by the Food and Drug Administration for fibroid bleeding. Ulipristal use is restricted due to hepatic toxicity.
Elagolix-Estradiol-Norethindrone (ORIHANN)	AM oral dose: Elagolix 300 mg plus estradiol 1 mg and norethindrone 0.5 mg PM oral dose: Elagolix 300 mg	Maximum duration of therapy: 24 months
Relugolix-Estradiol-Norethindrone (MYFEMBREE)	Once daily oral dose: Relugolix 40 mg plus estradiol 1 mg and norethindrone 0.5 mg	Maximum duration of therapy: 24 months
Leuprolide Depot Suspension (LUPRON-DEPOT)	Intramuscular injection	Maximum preoperative duration of therapy: 3 months prior to surgery

Slow-release injectable leuprolide acetate received FDA approval in 1999 for preoperative management of patients with anemia caused by uterine fibroids.[29] Leuprolide for this indication is limited to 3 months of use. The recommended dosing regimens for uterine fibroids are 3.75 mg once a month for 3 months or a single 11.25 mg injection.[29] These regimens were found to increase hematocrit by 6% or more and hemoglobin by 2 g/dL or more in 77% of study participants at 3 months of therapy.[30] Although not listed as part of the indication, some clinicians found that the reduction in size of fibroids from leuprolide acetate treatment resulted in less surgical blood loss and less need for blood transfusions.[30] Leuprolide acetate is also FDA approved for management of endometriosis-associated pain and several non-gynecologic indications.[29,31]

Elagolix and relugolix are GnRH receptor antagonists. Both drugs competitively bind to pituitary GnRH receptors, blocking binding of endogenous GnRH with reversible, dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which then decreases estradiol and progesterone production.[32,33] Elagolix and relugolix are available as oral products and are formulated with low-dose hormonal add-back therapy to limit hypoestrogenic side effects such as hot flushes, increased mean serum lipid levels and bone mineral density (BMD) loss.[28] Elagolix in combination with estradiol and norethindrone acetate (ORIAHNN), received FDA-approval in May 2020 for the treatment of fibroid-related heavy menstrual bleeding in premenopausal women.[26] In May 2021 a comparable preparation, relugolix with estradiol and norethindrone acetate (MYFEMBREE), was approved by the FDA for the for the same indication.[27] Due to the risk of menopausal symptoms and reduction of BMD, both medications should only be taken for a maximum duration of 24 months.

According to 2018 NICE guidance, women with heavy menstrual bleeding associated with fibroids can start combined hormonal contraceptives containing estrogen and a progestogen to reduce menstrual blood loss.[34] This is an off-label use of oral contraceptives. Levonorgestrel-releasing IUDs have been found to decrease heavy menstrual bleeding in patients with and without uterine fibroids.[28] However, rates of IUD expulsion are higher in patients with uterine fibroids compared with patients without fibroids (11% versus 0 to 3%).[28] The risk of expulsion may be particularly increased in patients with uterine fibroids that distort the uterine cavity.[28] There is insufficient evidence to support the use of a levonorgestrel-IUD for the treatment of uterine fibroid symptoms other than bleeding.[35]

Tranexamic acid is an oral nonhormonal antifibrinolytic agent FDA-approved for the treatment of cyclic heavy menstrual bleeding in females of reproductive potential.[36] Women who cannot or do not wish to take hormonal contraceptives may prefer this treatment. Tranexamic acid 1,300 mg three times a day can be taken for up to 5 days during monthly menstruation to reduce bleeding.[36] Due to the risk of thrombosis, tranexamic acid is contraindicated in patients at risk for thromboembolic disease or when used concomitantly with hormonal contraceptives.[36] Efficacy of tranexamic acid in women with fibroid-associated heavy menstrual bleeding has not been established.[28]

<u>Endometriosis</u>

Endometriosis is caused by the growth of endometrial-like tissue which implants outside of the uterus on the ovaries, fallopian tubes, bladder, or bowel.[37] The growth is estrogen dependent, and endometrial tissue proliferates and sheds with the menstrual cycle.[37] The chronic inflammation and scarring results in chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility. It is estimated that 1 in 10 women between the ages of 15-49 may experience endometriosis with the highest incidence among those between 25 and 29 years of age.[5] Quality of life and work productivity are negatively impacted by endometriosis pain.[6] Epidemiologic studies have concluded that women with early menarche (<10 years old), with more frequent menstrual cycles (<28 days), family history of endometriosis, and longer menstrual flows (>5-6 days) are at higher risk for endometriosis.[5]

There are several non-specific assessment scales that have been used to measure patient response to medical treatment intervention. The Patient Global Impression of Change (PGIC) is a general tool used to evaluate the overall health status as perceived by the patient using a seven-point single-item scale ranging from 'very much worse' to 'very much improved'. [14] The PCIG has been applied as a valid tool in many clinical trials of analgesics but it lacks ability to reflect degrees of change within specific domains.[14] For pain assessment, the visual analogue or verbal rating scale is a numeric rating scale which ranges from a score of 0 (no pain symptoms) to 10 (worst pain imaginable).[15] The ease of administration and scoring allows this tool to be used in a variety of settings, however, it may not be appropriate for low literacy patients.[15] A similar pain assessment tool commonly used is the Brief Pain Inventory (BPI) which has the added benefit of assessing both pain severity and interference it has on various aspects of daily activities.[16] Pain and/or symptom scales that have been developed specifically for endometriosis often have substantial limitations, inconsistencies, or lack validation.[16] A specific tool known as the Biberoglu and Behrman (B&B) Scale is patient-reported symptom assessment tool for dysmenorrhea, chronic pelvic pain, dyspareunia, as well as pelvic tenderness and induration.[16] The B&B is graded on a scale from 0 to 3 (or 4 for dyspareunia) with higher scores representative of more symptoms.[16] However, several organizations including the National Institutes of Health have indicated that the B&B has never been validated nor administered consistently.[16] Quality of Life (QoL) assessment tools such as the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the European Quality of Life in 5 Dimensions (EQ-5D) have been developed for use in many medical conditions, but there has not been a strong correlation found between QoL and pain intensity with use of these scales in endometriosis patients.[16] The Endometriosis Health Profile (EHP) is a disease-specific instrument used to assess the quality of life in women with endometriosis.[16] The EHP-5 is a shorter version of the EHP-30.[16] Both explore the same five core dimensions including pain, control and powerlessness, emotional well-being, social support, and self-image.[16] The EHP-30 has been validated for use in women with endometriosis, while the EHP-5 has not. [16]

The goal of endometriosis management is to prevent disease progression and improve patient's quality of life.[38] Although available medical and surgical treatments have been shown to decrease the severity and frequency of patient symptoms, none appear to offer a cure or long-term relief.[38] Medical therapy for endometriosis is based on the observation that ectopic tissue is hormonally responsive.[39] Drugs that suppress ovulation have been found to be beneficial in managing the pain associated with endometriosis.[39] Danazol, an anabolic steroid which inhibits gonadotropin secretion, was the first FDA-approved agent for endometriosis, but its usefulness has been undermined by a significant adverse effect profile.[40] Current first-line therapies to manage pain associated with endometriosis are continuous combined oral contraceptives (COCs) or progeestogens.[41] Oral contraceptives have been shown to suppress gonadotropin secretion and estrogen biosynthesis.[40,42] Most of the data supporting the use of COCs in managing endometriosis pain is observational.[41]

Second-line therapeutic options for pain associated with endometriosis are GnRH agonists administered with hormone therapy or in combination with a LNG-IUD.[41] Gonadotropin-releasing hormone agonists (i.e. goserelin, leuprolide, and nafarelin) initially stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), resulting in a temporary increase of ovarian steroidogenesis.[39] However, continuous administration of GnRH agonists in women results in suppression of gonadotropin secretion and decreased steroidogenesis of estrogen.[40,42] Goserelin and nafarelin are FDA-approved for up to 6 months of continuous use for treatment of pelvic pain caused by endometriosis while leuprolide is FDA-approved for a maximum duration of 12 months.[40] The 12-month treatment limitation is due to concern about the significant bone loss that occurs with GnRH agonist therapy. Add-back therapy or the simultaneous use of estrogen and progestin, progestin alone, or progestin plus a bisphosphonate may alleviate some of the GnRH agonist side effects including bone loss.[41]

The GnRH antagonist, elagolix is indicated to manage moderate-to-severe pain associated with endometriosis and is FDA-approved as a once-daily low dose (150 mg) or a twice-daily high dose (200 mg).[32] However, due to hypoestrogenic-induced declines in BMD, treatment should be maintained for a maximum duration of 24 months for the low-dose regimen (6 months in patients with moderate hepatic impairment) and 6 months for a high-dose regimen.[32] Relugolix combination therapy (40 mg relugolix, 1 mg estradiol, and 0.5 mg norethindrone) received FDA approval for management of pain associated with endometriosis

in 2022.[33] Use of relugolix combination therapy should be limited to 24 months due to the risk of continued bone loss that may not be reversible.[33] **Table 2** outlines the pharmacotherapies used for management of symptoms associated with endometriosis.

Table 2. Medications for Management of Endometriosis[43]

Drug Name (BRAND NAME)	**Formulation**	**Safety Precautions (Boxed Warning in Bold)**
Combined estrogen/progestogen contraceptives	Oral, vaginal ring, transdermal patch	**- Cigarette smoking increases the risk of serious cardiovascular events, particularly in women over 35 years of age** -Increased risk of gall bladder disease
Danazol (DANOCRINE)	Oral Capsule: 50 mg, 100 mg, 200 mg	**-Thrombotic events including strokes** **-Peliosis hepatis and benign hepatic adenoma** **-Intracranial hypertension** **-Use in pregnancy is contraindicated** -Lipoprotein changes -Androgen effects
Gonadotropin Releasing Hormone Agonists		
Goserelin acetate (ZOLADEX)	Subcutaneous Implant: 3.6 mg	-Hyperglycemia -Loss of BMD -Hypoestrogenism -Serum lipid changes -Use in pregnancy is contraindicated
Leuprolide acetate (LUPRON-DEPOT)	Intramuscular depot Injection: 1-month: 3.75 mg 3-month: 11.25 mg	-Loss of BMD -Use in pregnancy is contraindicated -Maximum duration of therapy for endometriosis is 12 months due to concerns of BMD loss.
Nafarelin acetate (SYNAREL)	Nasal Spray: 200 mcg/actuation	-Loss of BMD -Worsening depression -Hypoestrogenism -Serum lipid changes -Use in pregnancy is contraindicated
Progestogens		
Medroxyprogesterone acetate (DEPO-SUBQ PROVERA) (DEPO-PROVERA)	Subcutaneous Depot Injection: 104 mg Intramuscular injection: 150 mg	-**Loss of BMD** -Ocular disorders (sudden loss of vision, or sudden onset of proptosis, diplopia, or migraine) -Ectopic pregnancy -Menstrual bleeding irregularities -Use in pregnancy is contraindicated
Etonogestrel (NEXPLANON)	Subdermal Implant: 68 mg	-History of thrombosis -Active liver disease -History of breast cancer -Use in pregnancy is contraindicated
Norethindrone Acetate	Oral Tablet: 5mg	-Ocular disorders (sudden loss of vision, or sudden onset of proptosis, diplopia, or migraine) -Worsening depression

		-Increased risk for thrombosis -Bleeding irregularities -Ectopic pregnancy -Adverse effects on lipid metabolism -Use in pregnancy is contraindicated
Medroxyprogesterone (PROVERA)	Oral Tablet: 10 mg	-**Cardiovascular disorders and breast cancer** -Active liver disease -Use in pregnancy is contraindicated
Levonorgestrel (MIRENA)	Intrauterine device: 52 mcg	-Breast cancer -Uterine cancer -Active liver disease - Use in pregnancy is contraindicated
Gonadotropin-Releasing Hormone Antagonists		
Elagolix (ORILISSA)	Oral Tablet: 150 mg, 200 mg	-Decreased BMD -Suicidal ideation -Hepatic transaminase elevations -Use in pregnancy is contraindicated
Relugolix, Estradiol, and Norethindrone (MYFEMBREE)	Oral Tablet: relugolix 40 mg, estradiol 1 mg, & norethindrone 0.5 mg	-**Thromboembolic disorders and vascular events** -Decreased BMD -Breast cancer or other hormone-sensitive malignancies -Suicidal ideation and mood disorders -Hepatic impairment or transaminase elevations -Gallbladder disease or history of cholestatic jaundice -Hypertension -Menstrual bleeding irregularities -Use in pregnancy is contraindicated
Abbreviations: BMD = bone mineral density		

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane Review: Preoperative Medical Therapy Before Surgery For Uterine Fibroids

A 2025 Cochrane Review assessed the benefits and risks of medical treatments prior to surgery for uterine fibroids.[1] This was an update of a 2017 review. Literature was searched through August 2024.[1] Forty-one RCTs (n = 3,982) met inclusion criteria.[1] Thirty-six studies evaluated GnRH analogs (leuprolide, goserelin, and triptorelin) the comparators were no pretreatment (19 studies), placebo (9 studies), or other medical pretreatments (progestin, selective-progesterone receptor modulators [SPRMs], selective estrogen receptor modulators [SERMs; raloxifene], dopamine agonists, and estrogen receptor antagonists) (8 studies).[1] Five studies evaluated SPRMs versus placebo.[1] Most results provided low-certainty evidence due to poor reporting of randomization procedures, lack of blinding, imprecision and inconsistency. Some outcomes were not measured or did not have usable data.[1] The use of ulipristal acetate (an SPRM) was suspended in March 2025 because of an association with cases of liver failure.[1]

Compared to placebo or no treatment, GnRH analog pretreatment reduces uterine volume (mean difference [MD] −175.34 mL, 95% confidence interval [CI]−219.04 to −131.65; 13 studies, 858 participants; I^2 = 67%; low-certainty evidence) and fibroid volume (MD range 5.7 mL to 155.4 mL; 5 studies to heterogeneous to pool, 427 participants; low-certainty evidence), and probably increases preoperative hemoglobin (MD 0.88 g/dL, 95% CI 0.68 to 1.08; 10 studies, 834 participants; I^2 = 0%; moderate-certainty evidence).[1] However, there is probably a greater likelihood of adverse events with GnRH analogs (odds ratio (OR) 2.78, 95% CI 1.77 to 4.36; 5 studies, 755 participants; I^2 = 28%; moderate-certainty evidence). No usable data were available for preoperative bleeding.[1]

Duration of hysterectomy surgery may be reduced amongst women who receive GnRH analog treatment compared to placebo or no pretreatment (−9.59 minutes, 95% CI −15.9 to -3.28; 6 studies, 617 participants; I^2 = 57%; low-certainty evidence).[1] There were fewer blood transfusions with GnRH analogs compared to placebo or no pretreatment (OR 0.54, 95% CI 0.29 to 1.01; 6 studies, 601 participants; I^2 = 0%; moderate-certainty evidence) and less postoperative morbidity (OR 0.54, 95% CI 0.32 to 0.91; 7 studies, 772 participants; I^2 = 28%; moderate-certainty evidence).[1]

GnRH analogs may be associated with a greater reduction in uterine volume than other medical therapies (−47% compared to −20% and −22% with use of 5 mg and 10 mg ulipristal acetate, respectively; low-certainty evidence).[1] There may be little to no difference in bleeding reduction compared to ulipristal acetate 5 m (OR 0.71, 95% CI 0.30 to 1.68; 1 study, 199 participants; low-certainty evidence), and there is probably little to no difference in preoperative hemoglobin (MD −0.02, 95% CI −0.41 to 0.37; 242 participants; moderate-certainty evidence).[1] It is uncertain whether there is any difference in fibroid volume between GnRH analogs and cabergoline (MD 12.71 mL, 95% CI −5.92 to 31.34; 2 studies, 110 participants; I^2 = 0%; low-certainty evidence).[1] Adverse events such as hot flushes may be more likely with GnRH analogs (OR 2.83, 95% CI 1.68 to 4.77; 6 studies, 507 participants; I^2 = 59%; low-certainty evidence) compared to raloxifene, ulipristal, mifepristone, and cabergoline.[1]

In summary, pretreatment with GnRH analogs may reduce uterine and fibroid volume compared to placebo and other medical therapies (i.e., ulipristal, fulvestrant) and probably increases preoperative hemoglobin levels, but probably also increases the number of adverse events.[1] Blood transfusions and operation time during hysterectomy may be reduced, with fewer women experiencing postoperative morbidity.[1]

Cochrane Review: Gonadotropin-Releasing Hormone Agonists for Management of Endometriosis

A 2023 Cochrane Review assessed the effectiveness of GnRH agonists (goserelin, leuprolide, nafarelin, and triptorelin) in the treatment of painful symptoms associated with endometriosis.[2] Literature was searched through May 2022 for RCTs comparing GnRH agonists to progestogens, danazol, or placebo.[2] Seventy-two studies (n = 7355) met inclusion criteria.[2] The evidence was very low to low quality: the main limitations of all studies were serious risk of bias due to poor

reporting of study methods, and serious imprecision.[2] Five RCTs used placebo as the comparator, 29 RCTs used danazol, 3 RCTs evaluated LNG-IUDs, 7 RCTs included oral or injectable progestogens, and the rest of the trials evaluated different dosing regimens of GnRH agonists.[2] No studies comparing GnRH agonists to analgesics were identified.[2]

In trials comparing GnRH agonists to placebo, GnRH agonists may decrease overall pain, reported as pelvic pain scores (risk ration [RR] 2.14; 95% CI 1.41 to 3.24, 1 RCT, n = 87, low-certainty evidence), dysmenorrhea scores (RR 2.25; 95% CI 1.59 to 3.16, 1 RCT, n = 85, low-certainty evidence), dyspareunia scores (RR 2.21; 95% CI 1.39 to 3.54, 1 RCT, n = 59, low-certainty evidence), and pelvic tenderness scores (RR 2.28; 95% CI 1.48 to 3.50, 1 RCT, n = 85, low-certainty evidence) after 3 months of treatment.[2] Treatment with GnRH agonists may be associated with a greater incidence of hot flushes compared to placebo at 3 months of treatment (RR 3.08; 95% CI 1.89 to 5.01, 1 RCT, n = 100, low-certainty evidence).[2]

For women treated with either GnRH agonists or danazol, the effects were not different on relief of overall pain using a visual analog scale (MD -0.30; 95% CI -1.66 to 1.06, 1 RCT, n = 41, very low-certainty evidence), pelvic pain (MD 0.20; 95% CI -0.26 to 0.66, 1 RCT, n = 41, very low-certainty evidence), dysmenorrhea (MD 0.10; 95% CI -0.49 to 0.69, 1 RCT, n = 41, very low-certainty evidence), dyspareunia (MD -0.20; 95% CI -0.77 to 0.37, 1 RCT, n = 41, very low-certainty evidence), pelvic induration (MD -0.10; 95% CI -0.59 to 0.39, 1 RCT, n = 41, very low-certainty evidence), and pelvic tenderness (MD -0.20; 95% CI -0.78 to 0.38, 1 RCT, n = 41, very low-certainty evidence) after 3 months of treatment.[2] For pelvic pain (MD 0.50; 95% CI 0.10 to 0.90, 1 RCT, n = 41, very low-certainty evidence) and pelvic induration (MD 0.70; 95% CI 0.21 to 1.19, 1 RCT, n = 41, very low-certainty evidence), the complaints may decrease slightly after 6 months of treatment with GnRH agonists, compared to danazol.[2]

The studies that compared GnRH agonists to LNG-IUDs found very low-certainty evidence for differences on effect on overall pain relief after 6 months of treatment (MD -0.76, 95% CI -1.62 to 0.10, I^2 = 22%, 3 RCTs, n = 58).[2] Seven studies were identified which compared GnRH agonists with oral or injectable progestogens, however, only one study reported relief of overall pain, after 3 months of treatment with either GnRH agonists or oral progestogens. There may be an improvement in overall pain, reported as pelvic pain (MD -2.50, 95% CI -3.55 to -1.45, 1 RCT, n = 261, low certainty of evidence) and dyspareunia (MD -2.10, 95% CI -2.83 to -1.37, 1 RCT, n = 261, low certainty of evidence) after 3 months of treatment, in favor of oral progestogens compared to GnRH agonists.[2] There may be a decrease of vaginal bleeding seen in women treated with GnRH agonists, compared to oral progestogens (RR 0.33, 95% CI 0.23 to 0.48, 1 RCT, n = 242, low certainty of evidence).[2] Also, there may be less weight gain in women treated with GnRH agonists instead of oral progestogens (RR 0.31, 95% CI 0.10 to 0.92, 1 RCT, n = 242, low certainty of evidence).[2]

In summary, for relief of overall pain, there may be a slight decrease in favor of treatment with GnRH agonists compared to placebo or oral or injectable progestogens.[2] The effects on alleviating pain are uncertain when comparing GnRH agonists with danazol or intra-uterine progestogens.[2] There may be a slight increase in adverse effects when women are treated with GnRH agonists, compared to placebo.[2] Most of the evidence cited in this review was very low to low certainty due to a wide range of outcome measures and a wide range of outcome measurement instruments.[2]

Cochrane Review: Progestogens For Pain Symptoms Associated With Endometriosis

A 2025 Cochrane Review evaluated the harms and benefits of progestogens in the treatment of endometriosis-associated pain symptoms.[3] Literature was searched through October 2024 for RCTS that compared progestogens to placebo, other medications, or different progestogen doses.[3] Thirty-three RCTs (n=5,059) met inclusion criteria, 13 RCTs were assessed as having a low risk of bias.[3] Studies assessing the LNG-IUD were ineligible, as a separate Cochrane review assessed the evidence for this intervention.[44] The LNG-IUD Cochrane review found no high-quality evidence to support the use of LNG-IUD in management of endometriosis symptoms.[44]

Eight RCTs compared oral progestogens to placebo and determined oral progestogens probably reduce overall pain measured on a visual analogue scale (VAS; MD −2.58, 95% CI −3.13 to −2.03; moderate certainty), and probably reduce dysmenorrhea at 3 months (RR 0.21, 95% CI 0.07 to 0.70, moderate certainty), but may have little to no effect on pelvic pain at 3 months (RR 0.7, 95% CI 0.29 to 1.69; low certainty).[3] There is probably little to no difference between the interventions in study withdrawal due to adverse effects (RR 2.36, CI 0.74 to 7.52, moderate certainty) and cumulative side effects (RR 1.18, 95% CI 0.94 to 1.46, moderate certainty).[3]

Oral progestogens were compared with oral contraceptives in 4 RCTs and found no differences on improving pelvic pain measured on a VAS (MD 0.38, 95% CI −0.46 to 1.22, moderate certainty).[3] There was very low-certainty evidence about the effect of oral progestogens versus oral contraceptives on dysmenorrhea at 12 months (MD −0.57, 95% CI −1.29 to 0.15).[3] There may be little to no difference between oral progestogens and oral contraceptives in study withdrawal due to adverse effects (RR 0.75, 95% CI 0.27 to 2.07, low certainty), and there is probably little to no difference in cumulative side effects (RR 1.13, 95% CI 0.8 to 1.60, moderate certainty).[3]

Ten RCTs compared oral progestogens compared with GnRH agonists and showed very little or no difference on overall pain measured on a VAS (MD −0.01, 95% CI −0.30 to 0.28), risk of pelvic pain (RR 1.12, 95% CI 0.80 to 1.59), dysmenorrhea (RR 1.45, 95% CI 0.71 to 3.00), and study withdrawal due to adverse effects (RR 0.9, 95% CI 0.34 to 2.43).[3] All these outcomes had low-certainty evidence.[3] The risk of cumulative side effects was probably higher with oral progestogens (RR 1.44, 95% CI 1.11 to 1.86, moderate certainty) compared to GnRH agonists.[3]

In 2 RCTs comparing depot progestogens versus GnRH agonists, depot progestogens reduce dysmenorrhea risk slightly (RR 0.93, 95% CI 0.89 to 0.97, high certainty) but may have little to no effect on pelvic pain (RR 0.96, 95% CI 0.87 to 1.07, low certainty).[3] The interventions may be similar in study withdrawal due to adverse effects (RR 1.41, 95% CI 0.24 to 8.32, low certainty), but the risk of cumulative side effects is probably lower with depot progestogens (RR 0.03, 95% CI 0.01 to 0.11, moderate certainty).[3] One RCT compared depot progestogens to a GnRH antagonist and found depot progestogens may have little to no effect on pelvic pain (RR 0.85, 95% CI 0.7 to 1.03, low certainty), dysmenorrhea (RR 0.85, 95% CI 0.7 to 1.03, low certainty), and cumulative adverse effects (RR 1.04, 0.95 to 1.14, low certainty).[3] Study withdrawal due to side effects is likely higher with depot progestogens (RR 2.02, 95% CI 1.04 to 3.94, moderate certainty) compared to GnRH antagonists.[3]

In summary, in individuals with endometriosis, oral progestogens compared with placebo likely reduce overall pain and dysmenorrhea and may reduce pelvic pain.[3] Compared with other hormonal suppression strategies, the evidence is less certain due to the small number of studies for each comparison and outcome.[3]

After review, 13 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[45-50] wrong study design of included trials (e.g., observational),[51] comparator (e.g., no control or placebo-controlled),[52-57] or outcome studied (e.g., non-clinical).[58]

New Guidelines:

Primary Dysmenorrhea Guidance

Society of Obstetrics and Gynecology Canada: Primary Dysmenorrhea

In May 2025 the SOGC issued guidance for management of primary dysmenorrhea.[4] Non-steroidal anti-inflammatory drugs are more effective than placebo but have more gastrointestinal side effects.[4] All currently available NSAIDs are of comparable efficacy and safety (high-quality evidence).[4] Dysmenorrhea responds favorably to the inhibition of ovulation. Combined hormonal contraceptives suppress ovulation and endometrial tissue growth, thereby decreasing menstrual

blood volume and prostaglandin secretion with subsequent decreases in intrauterine pressure and uterine cramping.[4] Observational studies consistently demonstrate a lower prevalence of dysmenorrhea among individuals who use combined hormonal contraceptives.[4]
Specific recommendations include:

- Health care providers should offer NSAIDs or acetaminophen, administered with regular dosing regimens, as a as first-line treatment for most women unless contraindicated (strong recommendation, high-quality evidence).[4]
- Continuous or extended use combined hormonal contraceptives are recommended for the treatment of dysmenorrhea (strong recommendation, high-quality evidence).[4]

Uterine Fibroid Guidance

Canada's Drug Agency: Reimbursement Recommendation: Relugolix-Estradiol-Norethindrone for Uterine Fibroids

CDA published a review of relugolix combination therapy for management of uterine fibroids in August 2025.[5] The CDA has not been able to make a reimbursement recommendation for elagolix combination therapy in management of uterine fibroids as the manufacturer has not filed a submission with the agency. Evidence from 2 clinical trials demonstrated that more patients receiving relugolix combination therapy experienced a meaningful reduction in menstrual blood loss after being on treatment for 6 months compared to patients receiving placebo.[5] More patients receiving relugolix combination therapy had an improvement in anemia, pain, and health-related quality of life (HRQoL) compared to patients receiving placebo.[5] However, it is unclear if patients on the medication are able to avoid surgery over the long term.[5]

The committee reviewed the longer-term evidence from the extension studies that suggested treatment effects were maintained for reduced menstrual blood loss volume and patient-reported symptom severity and improved HRQoL (up to 104 weeks total treatment) and anemia based on hemoglobin levels (up to 52 weeks total treatment).[5] There were limitations with the study designs, a large number of discontinuations, and a potential selection bias for patients who respond to and tolerate the drug that increase the uncertainty of the longer-term results.[5] The CDA noted that clinical guidelines recommend nonhormonal drugs (NSAIDs, antifibrinolytics) or hormonal therapies (combined hormonal contraceptives, progestins, depot medroxyprogesterone and LNG-IUDs) for management of abnormal uterine bleeding in premenopausal women.[5]

- The CDA's Drug Expert Committee recommends that relugolix-estradiol–norethindrone acetate be reimbursed for the management of heavy menstrual bleeding associated with uterine fibroids in patients in the premenopausal stage only if these conditions are met:
    - Patients in the premenopausal stage and aged 18 years or older with confirmed uterine fibroids and heavy menstrual bleeding.[5]
    - The maximum duration of initial authorization is 6 months.[5]
    - For renewal after initial authorization, the physician must provide proof of clinical response, defined as reduction in menstrual blood loss volume, reduction in pain, improvement in hemoglobin (in patients with anemia), or improvement in health-related quality of life.[5]
    - Reimbursement for relugolix combination therapy should be discontinued upon occurrence of any of the following: successful surgery or procedure, plans for pregnancy, menopause, or a meaningful decline in BMD.[5]

National Institute for Health and Care Excellence: Relugolix–Estradiol–Norethindrone For Treating Symptoms Of Uterine Fibroids

NICE published guidance for the use of relugolix-estradiol-norethindrone combination therapy for treating moderate to severe symptoms of uterine fibroids in October 2022.[6] NICE guidance on heavy menstrual bleeding recommends that, when there is no identified cause and fibroids are less than 3 cm in diameter, pharmacological treatments include non-hormonal (tranexamic acid, non-steroidal anti-inflammatories) and hormonal medicines (LNG-IUD, combined hormonal contraception, cyclical oral progestogens).[6] If pharmacological treatment is unsuccessful or declined, or symptoms are severe, then surgical options (endometrial ablation, hysterectomy) are offered.[6] When fibroids are 3 cm or more in diameter, uterine artery embolization is another option before surgery.[6] Ulipristal

acetate and myomectomy (a surgical option) are only considered if other surgical options and uterine artery embolization are unsuitable, declined or unsuccessful.[6] Pretreatment with injectable GnRH agonists before hysterectomy and myomectomy is considered if uterine fibroids are causing an enlarged or distorted uterus.[6] Relugolix combination therapy has shown to be effective in reducing menstrual blood loss volume associated with uterine fibroids compared to placebo.[6] There is no evidence directly comparing relugolix–estradiol–norethindrone acetate with GnRH agonists.[6]

- Relugolix–estradiol–norethisterone acetate is recommended as an option for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age.[6]

Endometriosis Guidance

National Institute for Health and Care Excellence: Relugolix–Estradiol–Norethindrone For Treating Symptoms Of Endometriosis

In November 2024 NICE updated guidance for diagnosis and management of endometriosis.[59] No changes were made to first-line treatment recommendations which include a short-term trial (3 months) of acetaminophen or NSAIDs.[59] If first-line treatment is ineffective, hormonal treatment (the combined oral contraceptive pill or progestogen) should be offered to women with suspected, confirmed or recurrent endometriosis.[59] If medical treatment is not effective, GnRH antagonists are recommended as second line options. NICE has not developed guidance for the use of elagolix in managing symptoms of endometriosis but has issued guidance for the use of relugolix combination therapy. Clinical trial evidence shows that relugolix combination therapy reduces pain compared with placebo.[7] Relugolix combination therapy has not been directly compared in a clinical trial with usual treatment.[7] Indirect comparisons suggest that it is likely to reduce pelvic pain almost as well as GnRH agonists.[7] It is unclear how well relugolix-estradiol-norethindrone works compared with surgery.[7]

- Relugolix–estradiol–norethindrone is recommended as an option for treating symptoms of endometriosis in adults of reproductive age who have had medical or surgical treatment for endometriosis.[7]

European Society of Human Reproduction and Embryology: Endometriosis Guideline

The ESHRE guidance for management of endometriosis was updated in February 2022.[8] Treatment should begin with NSAIDs/analgesics and/or hormonal treatments (combined oral contraceptives, progestogens).[8] Second-line treatments include a GnRH agonist (i.e., leuprolide) or GnRH antagonists (i.e., elagolix, relugolix).[8] For the GnRH agonists, treatment is limited by their side effect profile and add-back therapy should be considered to prevent bone loss and hypoestrogenic symptoms.[8] Evidence is limited regarding GnRH antagonist dose or duration of treatment and the need for add-back therapy.[8] There are considerable side effects with GnRH antagonists, including the potential impact on bone density.[8] Aromatase inhibitors (i.e., letrozole, anastrozole) can be considered as second or third line treatment and must be combined with hormonal therapy in reproductive-aged women.[8] The guideline development group strongly believes that oral danazol should not be used unless no other medical therapy is available, due to its severe side effects (acne, edema, vaginal spotting, weight gain, muscle cramps, deepening of voice, increase in facial hair).[8] For this reason, danazol is no longer recommended as a medical treatment for endometriosis associated pain in the current guideline.[8]

Strength of recommendations and quality of evidence are as follows:

- Women may be offered NSAIDs or other analgesics (either alone or in combination with other treatments) to reduce endometriosis-associated pain (weak recommendation; very low-quality evidence).[8]
- It is recommended to offer women hormone treatment (combined hormonal contraceptives, progestogens, GnRH agonists, or GnRH antagonists) as one of the options to reduce endometriosis-associated pain (strong recommendation; moderate-quality evidence).[8]
- It is recommended to prescribe women a combined hormonal contraceptive (oral, vaginal ring or transdermal) to reduce endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain (strong recommendation; low-quality evidence).[8]

- It is recommended to prescribe GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (strong recommendation; low-quality evidence).[8]
- It is recommended that GnRH agonists and GnRH antagonists are prescribed as second-line (e.g., if hormonal contraceptives or progestogens have been ineffective) due to their side effect profile (good practice point based on clinical expertise).[8]
- Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms (strong recommendation; moderate-quality evidence).[8]
- It can be considered to prescribe GnRH antagonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (weak recommendation; moderate-quality evidence).[8]
- In women with endometriosis-associated pain refractory to other medical or surgical treatment, it is recommended to prescribe aromatase inhibitors, as they reduce endometriosis-associated pain. Aromatase inhibitors may be prescribed in combination with oral contraceptives, progestogens, GnRH antagonists, or GnRH agonists (strong recommendation; low-quality evidence).[8]

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts[60]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Goserelin	ZOLADEX	March 2023	Warnings/ Precautions	Depression: Depression may occur or worsen in women receiving GnRH agonists. Monitor and manage appropriately.
Relugolix	ORGOVYX	March 2023	Warnings/ Precautions	Relugolix is contraindicated in patients with severe hypersensitivity to relugolix or any of the product components. Hypersensitivity reactions, including pharyngeal edema and other serious cases of angioedema, have been reported in postmarketing in patients treated with relugolix. In the HERO study, patients treated with relugolix reported angioedema (0.2%). Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue relugolix and promptly seek medical care. Discontinue relugolix hypersensitivity reactions and manage as clinically indicated.
Triptorelin Pamoate	TRELSTAR	November 2023	Warnings/ Precautions	Metabolic Syndrome: The use of GnRH agonists may lead to an increased risk of metabolic changes such as hyperglycemia, diabetes, hyperlipidemia, and non-alcoholic fatty liver disease. Monitor for signs and symptoms of metabolic syndrome including lipids, blood glucose level and/or HbA1c and manage according to institutional guidelines.

				Cardiovascular Diseases: Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported in men. Monitor for cardiovascular disease and manage according to current clinical practice.
Triptorelin Pamoate	TRELSTAR	April 2024	Warnings/ Precautions	Convulsions: Convulsions have occurred in patients treated with GnRH analogs with or without a history of predisposing factors. Manage patients who experience convulsions according to institutional guidelines.
Triptorelin Pamoate Goserelin Histrelin Leuprolide	TRELSTAR, TRIPTODUR ZOLADEX VANTAS, SUPPRELIN LUPRON, FENSOLVI, CAMCEVI, ELI	September 2025	Warnings/ Precautions	Severe Cutaneous Adverse Reactions (SCARs), including Stevens Johnson syndrome/toxic epidermal necrolysis, occurred in patients treated with GnRH agonists. Interrupt treatment if signs or symptoms of SCARs develop. Permanently discontinue if SCARs are confirmed.
Leuprolide	LUPRON, FENSOLVI, CAMCEVI, ELIGARD	July 2023	Warnings/ Precautions	Postmarketing reports of convulsions have been observed in patients on leuprolide acetate therapy. These included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies, or tumors, and in patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above. Patients receiving a GnRH agonist who experience convulsion should be managed according to current clinical practice.

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Appendix 1: HERC Guidance for Management of Dysmenorrhea and Pelvic Pain Syndrome

GUIDELINE NOTE 59, DYSMENORRHEA[9]

Line 551

Hysterectomy for dysmenorrhea may be indicated when all of the following are documented (A-G):

A) Patient history of:
   1) No treatable conditions or lesions found on laparoscopic examination
   2) Pain for more than 6 months with negative effect on patient's quality of life
B) Failure of a six-month therapeutic trial with both of the following (1 and 2), unless there are contraindications to use:
   1) Hormonal therapy (a or b):
      a) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
      b) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
   2) Nonsteroidal anti-inflammatory drugs
C) Evaluation of the following systems as possible sources of pelvic pain:
   1) Urinary
   2) Gastrointestinal

3) Musculoskeletal

D) Evaluation of the patient's psychological and psychosexual status for nonsomatic cause of symptoms
E) Nonmalignant cervical cytology, if cervix is present
F) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
G) Negative preoperative pregnancy test unless patient is postmenopausal or has been previously sterilized

GUIDELINE NOTE 55, PELVIC PAIN SYNDROME[9]

Line 525

A) Diagnostic MRI may be indicated for evaluation of pelvic pain to assess for adenomyosis and to assist in the management of these challenging patients when all of the following are documented:
   1) Patient history of dysmenorrhea, pelvic pain or abnormal uterine bleeding for more than six months with a negative effect on her quality of life.
   2) Failure of a six-month therapeutic trial with both of the following (a and b), unless there are contraindications to use:
      a) Hormonal therapy (i or ii):
         i) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
         ii) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
      b) Nonsteroidal anti-inflammatory drugs
   3) An endovaginal ultrasound within the past 12 months that shows no other suspected gynecological pathology if diagnostic MRI shows > 12mm thickening of the junctional zone, the presumptive diagnosis of adenomyosis is fulfilled. See Guideline Note 39.

B) Hysterectomy for chronic pelvic pain in the absence of significant pathology may be Indicated when all of the following are documented (1-7):
   1) Patient history of:
      a) No treatable conditions or lesions found on laparoscopic examination
      b) Pain for more than 6 months with negative effect on patient's quality of life
   2) Failure of a six-month therapeutic trial with both of the following (a and b), unless there are contraindications to use:
      a) Hormonal therapy (i or ii):
         i) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
         ii) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
      b) Nonsteroidal anti-inflammatory drugs
   3) Evaluation of the following systems as possible sources of pelvic pain:
      a) Urinary
      b) Gastrointestinal
      c) Musculoskeletal
   4) Evaluation of the patient's psychological and psychosexual status for nonsomatic cause of symptoms
   5) Nonmalignant cervical cytology, if cervix is present
   6) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
   7) Negative preoperative pregnancy test unless patient is postmenopausal or as been previously sterilized

Appendix 2: Current Preferred Drug List

GnRH Agonists

Generic	Brand	Route	Form	PDL
leuprolide acetate	LUPRON DEPOT-PED	INTRAMUSC	KIT	Y
histrelin acetate	SUPPRELIN LA	IMPLANT	KIT	N
leuprolide acetate	LUPRON DEPOT	INTRAMUSC	SYRINGEKIT	N
leuprolide acetate	LUPRON DEPOT-PED	INTRAMUSC	SYRINGEKIT	N
leuprolide acetate	LEUPROLIDE DEPOT	INTRAMUSC	VIAL	N
leuprolide acetate	LUTRATE DEPOT	INTRAMUSC	VIAL	N
triptorelin pamoate	TRELSTAR	INTRAMUSC	VIAL	N
triptorelin pamoate	TRIPTODUR	INTRAMUSC	VIAL	N
nafarelin acetate	SYNAREL	NASAL	SPRAY	N
leuprolide acetate	LEUPROLIDE ACETATE	SUBCUT	KIT	N
histrelin acetate	SUPPRELIN	SUBCUT	KIT	N
leuprolide mesylate	CAMCEVI	SUBCUT	SYRINGE	N
leuprolide acetate	ELIGARD	SUBCUT	SYRINGE	N
leuprolide acetate	FENSOLVI	SUBCUT	SYRINGE	N
leuprolide acetate	LEUPROLIDE ACETATE	SUBCUT	VIAL	N

GnRH Antagonists

Generic	Brand	Route	Form	PDL
elagolix sodium	ORILISSA	ORAL	TABLET	N
elagolix sodium	ORILISSA	ORAL	TABLET	N
elagolix/estradiol/norethindrn	ORIAHNN	ORAL	CAP SEQ	N
relugolix/estradiol/norethindr	MYFEMBREE	ORAL	TABLET	N

Appendix 3 Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to January 05, 2026>

Uterine Fibroids

1	elagolix.mp.	187
2	DANAZOL/	2383
3	relugolix.mp.	225
4	Leuprolide/	3160
5	histrelin.mp.	137
6	Triptorelin Pamoate/	2056
7	Nafarelin/	327
8	Ethinyl Estradiol-Norgestrel Combination/	390
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	8454
10	Leiomyoma/	22103
11	9 and 10	394
12	limit 11 to (english language and humans and yr="2022 -Current")	50

Dysmenorrhea

Ovid MEDLINE(R) ALL <1946 to January 05, 2026>

1	elagolix.mp.	187
2	DANAZOL/	2383
3	relugolix.mp.	225
4	Leuprolide/	3160
5	histrelin.mp.	137
6	Triptorelin Pamoate/	2056
7	Nafarelin/	327
8	Ethinyl Estradiol-Norgestrel Combination/	390
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	8454
10	Dysmenorrhea/	5156
11	9 and 10	74
12	limit 11 to (english language and humans and yr="2022 -Current")	11

Endometriosis

Ovid MEDLINE(R) ALL <1946 to January 05, 2026>

1	elagolix.mp.	187
2	DANAZOL/	2383

3	relugolix.mp.	225
4	Leuprolide/	3160
5	histrelin.mp.	137
6	Triptorelin Pamoate/	2056
7	Nafarelin/	327
8	Ethinyl Estradiol-Norgestrel Combination/	390
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	8454
10	Endometriosis/	28410
11	9 and 10	1250
12	limit 11 to (english language and humans and yr="2022 -Current")	45

Appendix 4: Key Inclusion Criteria

Population	Females
Intervention	GnRH agonists and antagonists
Comparator	Oral contraceptives, progestogens, danazol
Outcomes	Pain relief, improved quality of life, and for fibroids, amount of menstrual blood lost
Timing	6 months
Setting	Outpatient

Gonadotropin-Releasing Hormone Agonists

Goals:
- Restrict use of gonadotropin-releasing hormone (GnRH) agonists to medically appropriate conditions funded under the Oregon Health Plan.
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:
- Up to 6 months

Requires PA:
- All GnRH agonists

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3.

Approval Criteria		
3. Will the prescriber consider switching to a preferred product, if appropriate? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Go to #4
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
5. Is the diagnosis central precocious puberty or other endocrine disorder?	**Yes:** Go to #6	**No:** Go to #7
6. Is the prescriber a pediatric endocrinologist?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh; deny for medical appropriateness.
7. Is the diagnosis gender dysphoria?	**Yes:** Approve for 1 year	**No:** Go to #8
8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Go to #11
9. Is the patient pregnant or actively trying to conceive?	**Yes:** Go to #10	**No:** Go to #11
10. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to # 11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Is this request for treatment of breast cancer or prostate cancer?	**Yes:** Approve up to 1 year	**No:** Go to #12
12. Is this request for leuprolide for the management of preoperative anemia due to uterine fibroids (leiomyoma)?	**Yes:** Approve for up to 3 months	**No:** Go to #13

Approval Criteria		
13. Is this request for management of moderate to severe pain associated with pelvic pain or endometriosis in a woman ≥18 years of age?	**Yes**: Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Has the patient tried and failed an adequate trial of at least 1 of the preferred endometriosis therapy options for at least 6 months including administration of combined hormonal contraceptives or progestins (oral, depot injection, ring, patch, implant, or intrauterine) alone? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the preferred therapy options?	**Yes:** Approve for 6 to 12 months, depending on selected medication. *Note maximum recommended duration of therapy for nafarelin and goserelin is 6 months. Leuprolide therapy should not exceed 12 months. If requesting continuation of therapy beyond FDA-approved duration, pass to RPh. Deny; medical appropriateness.	**No:** Go to #15 *Hormonal combination contraceptives or progestins do not require PA
15. RPh only: All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for conditions which are not outlined above is currently insufficient and should be denied for "medical appropriateness" If new evidence or guideline-recommendations are provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

P&T / DUR Review: *4/26 (DM); 8/23; 12/21; 3/19; 5/15*
Implementation: *6/1/26; 9/1/23; 1/1/22; 5/1/19*

Gonadotropin-Releasing Hormone Antagonists

Goal(s):

- Promote safe use of elagolix and relugolix/estradiol/norethindrone in people with endometriosis-associated pain
- Promote safe use of elagolix/estradiol/norethindrone and relugolix/estradiol/norethindrone for heavy menstrual bleeding associated with uterine fibroids (leiomyoma).

- Promote use that is consistent with medical evidence and product labeling.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:
- Initial: Up to 6 months
- Elagolix renewal: Up to 6 months for 150 mg daily dose with total cumulative lifetime treatment period not to exceed 24 months in patients with normal hepatic function. For patients with moderate hepatic impairment receiving 150 mg once daily, duration of therapy should not exceed 6 months. In patients receiving high dose elagolix therapy (200 mg twice daily), maximum treatment duration is 6 months.
- Elagolix/estradiol/norethindrone renewal: Up to 6 months for elagolix 300 mg dosed twice daily with a total cumulative treatment period not to exceed 24 months
- Relugolix/estradiol/norethindrone renewal: Up to 6 months for relugolix component 40 mg dosed once daily with a total cumulative treatment period not to exceed 24 months

Requires PA:
- Elagolix (ORLISSA)
- Elagolix/estradiol/norethindrone (ORIAHNN)
- Relugolix/estradiol/norethindrone (MYFEMBREE)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is this request for management of moderate to severe pelvic pain associated with endometriosis in a premenopausal patient?	**Yes**: Go to #6	**No:** Go to #12
6. Has the patient tried and failed an adequate trial of preferred first line endometriosis therapy options including administration of combined hormonal contraceptives or progestins (oral, depot injection, or intrauterine) alone? -or- Does the patient have a documented intolerance, FDA- labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness First-line therapy options such as combined hormonal contraceptives or progestins do not require PA
7. Is the patient taking any concomitant medications that are strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine, gemfibrozil, etc.), combined P-glycoprotein inhibitor and moderate CYP3A inhibitor (e.g., erythromycin), combined P-glycoprotein inducer and strong CYP3A inducer (e.g., rifampin)? Note: Elagolix levels are increased when co-administered with OATP1B1 inhibitors. Relugolix levels are increased when co-administered with inhibitors such as erythromycin and decreased when co-administered with inducers such as rifampin. Avoid combinations of these therapies due to drug interactions that can increase the risk of adverse reactions or decrease the efficacy of GnRH antagonists.	**Yes:** Deny; medical appropriateness	**No:** Go to #8

Approval Criteria		
8. Does the patient have a diagnosis of osteoporosis or related bone-loss condition? Note: In patients with major risk factors for decreased bone mineral density (BMD) such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of GnRH antagonists may pose an additional risk, and the risks and benefits should be weighed carefully.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Does the patient have severe hepatic impairment as documented by Child-Pugh class C?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B?	**Yes:** Go to #11	**No:** Approve for 6 months ***** FDA approved elagolix dosing for patients with normal liver function or mild liver impairment: 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months
11. Is the dose for elagolix 150 mg once daily or relugolix 40 mg /estradiol 1 mg/norethindrone 0.5 mg?	**Yes:** Approve for 6 months (cumulative lifetime treatment) ***** FDA approved elagolix dosing for moderate hepatic impairment: 150 mg once daily for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Is the request for elagolix/estradiol/norethindrone or relugolix/estradiol/norethindrone for management of heavy menstrual bleeding associated with uterine fibroids (leiomyomas)?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Has the patient tried and failed a trial of first line therapy options including at least 1 of the following for at least 6 months: a) hormone-releasing IUD OR b) continuous administration of combined hormonal contraceptives OR c) cyclic progestins OR d) tranexamic acid? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the first-line therapy options?	**Yes**: Go to #14	**No:** Pass to RPh. Deny; medical appropriateness First-line therapy options such as hormonal contraceptives, progestins, or tranexamic acid do not require PA
14. Does the patient have a diagnosis of osteoporosis or related bone-loss condition? Note: In patients with major risk factors for decreased bone mineral density (BMD) such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of GnRH antagonists may pose an additional risk, and the risks and benefits should be weighed carefully.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 6 months (cumulative, lifetime treatment)

Renewal Criteria		
1. Has the patient been receiving elagolix/estradiol/norethindrone for management of uterine fibroids or relugolix/estradiol/norethindrone for management of uterine fibroids or pain associated with endometriosis?	**Yes:** Go to #4	**No:** Go to #2
2. Has the patient been receiving therapy with elagolix 150 mg once daily for management of endometriosis?	**Yes:** Go to #3	**No:** Pass to RPh; Deny; medical appropriateness. (Elagolix 200 mg twice daily is limited to 6-month maximum treatment duration per FDA labeling)
3. Does the patient have moderate hepatic impairment as documented by Child-Pugh Class B?	**Yes:** Pass to RPh; Deny; medical appropriateness. (Elagolix 150 mg once daily is limited to 6-month maximum treatment duration in patients with moderate hepatic impairment per FDA labeling)	**No:** Go to #4
4. Has the patient's condition* improved as assessed and documented by the prescriber? *For endometriosis: has pain associated with endometriosis improved? For uterine fibroids: has patient experienced at least a 50% reduction in menstrual blood loss from baseline?	**Yes:** Approve for up to 18 months Document physician attestation received. Total cumulative treatment period not to exceed 24 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 4/26 (DM); 2/23; 12/21, 3/19,11/18
Implementation: 6/1/26; 4/1/23; 1/1/22; 5/1/19