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REVIEW

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# GnRH antagonists for the treatment of fibroids and adenomyosis, current evidence and future perspectives

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**ABSTRACT**

**Introduction:** Uterine fibroids and adenomyosis are common estrogen- and progesterone-dependent disorders associated with heavy menstrual bleeding, pelvic pain, anemia, and impaired quality of life. Although surgery remains widely used, there is an increasing demand for effective uterus-preserving medical therapies. Oral gonadotropin-releasing hormone (GnRH) antagonists have recently emerged as a novel therapeutic option, allowing rapid, reversible, and dose-dependent suppression of ovarian steroidogenesis.

**Areas covered:** This narrative, based on a targeted PubMed/MEDLINE literature search and review of major guideline documents published up to May 2026, summarizes the pharmacological properties, mechanisms of action, and clinical evidence regarding GnRH antagonists (elagolix, relugolix and linzagolix) in uterine fibroids and adenomyosis. Evidence from randomized controlled, extension studies, and emerging literature was critically reviewed, focusing on control of heavy menstrual bleeding, pain reduction, quality of life, safety, and the role of add-back therapy.

**Expert opinion:** GnRH antagonists represent a major advance in the medical treatment of uterine fibroids and are highly effective in controlling heavy menstrual bleeding. Their role in adenomyosis appears promising, although evidence remains limited. These agents should currently be considered suppressive rather than curative therapies, as symptoms often recur after discontinuation. Long-term integration into individualized treatment strategies will require further safety and comparative effectiveness data.

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## 1. Introduction

Uterine fibroids and adenomyosis are the two most prevalent benign uterine disorders encountered in gynecologic practice and are among the leading causes of abnormal uterine bleeding, pelvic pain, and impaired quality of life (QoL) in women of reproductive age [1–3]. Although traditionally considered distinct pathologies, these conditions share important clinical and biological features, including steroid hormone dependence, chronic symptom burden, and frequent indication for surgical intervention [4,5].

Uterine fibroids have a cumulative prevalence approaching 70% of women, although only approximately 25% become clinically significant and require intervention [2]. Adenomyosis has an overall prevalence of approximately 0.8% based on diagnostic coding, with incidence highest among women aged 41–45 years [3]. Notably, adenomyosis is present in nearly half of women undergoing hysterectomy for fibroid-associated abnormal uterine bleeding, highlighting the substantial overlap between these conditions [6]. In clinical practice, this overlap may be further complicated by the coexistence of endometriosis, creating a spectrum of estrogen-dependent gynecologic disorders in which abnormal uterine bleeding, dysmenorrhea, chronic pelvic pain, infertility, and impaired QoL may coexist and influence therapeutic decision-making [7]. Together, fibroids and adenomyosis account for a substantial proportion of hysterectomies worldwide, underscoring the persistent unmet need for effective, well-tolerated medical therapies capable of providing sustained symptom control while preserving the uterus [3,8].

Benign uterine disease has traditionally been treated by surgical approaches, including myomectomy or adenomyomectomy, hysterectomy, and, in selected cases, by interventional radiology techniques (such as uterine artery embolization or MR-guided focused ultrasound). While these interventions are highly effective, they are not suitable or desirable for all patients, particularly those wishing to preserve fertility or avoid invasive procedures. Medical treatments, including combined oral contraceptives, progestins, and

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**Article highlights**

- Oral GnRH antagonists enable rapid, reversible, and dose-dependent suppression of ovarian steroid production.
- In uterine fibroids, GnRH antagonists are highly effective in controlling heavy menstrual bleeding and improving anemia and quality of life.
- Add-back therapy is essential to mitigate hypoestrogenic side effects caused by GnRH antagonists and allow longer-term use.
- In adenomyosis, evidence is emerging, with promising effects on both bleeding and pain, but randomized controlled trials are still lacking.
- GnRH antagonists are best viewed as suppressive therapies rather than curative interventions, with symptom recurrence after discontinuation. Their role is likely to expand within personalized, uterus-preserving management strategies integrating medical and surgical approaches.
- Long-term safety, particularly regarding bone health, and cost-effectiveness remain key determinants of future positioning.

levonorgestrel-releasing intrauterine system (LNG-IUS), have been widely used to control bleeding and pain; however, their efficacy is often limited, especially in women with large fibroids or extensive adenomyosis [9,10]. Moreover, these therapies do not directly target the underlying endocrine drivers of disease activity.

In this context, modulation of the hypothalamic-pituitary-ovarian axis has emerged as a rational therapeutic strategy. Gonadotropin-releasing hormone agonists (GnRH-a) have long been used to induce a hypoestrogenic state and reduce fibroid size and menstrual bleeding, achieving amenorrhea in nearly 90% of patients and reducing uterine volume by 30 to 60% [9]. However, their clinical utility has been constrained by an initial flare effect resulting from gonadotropin surge, injectable administration, and the adverse consequences of profound estrogen deprivation, including vasomotor symptoms and bone mineral density (BMD) loss [11]. These limitations have historically restricted their use to short-term preoperative settings, typically limited to 3–6 months.

The development of oral GnRH antagonists represents a significant advance in the pharmacological management of hormone-dependent uterine disorders. By competitively blocking pituitary GnRH receptors, these agents induce rapid, reversible, and dose-dependent suppression of ovarian steroidogenesis without the flare phenomenon observed with agonists [12]. This pharmacological profile allows controlled endocrine modulation and supports the use of add-back strategies to preserve efficacy while improving tolerability [13,14].

In uterine fibroids, several oral GnRH antagonists, including relugolix combination therapy (Ryeqo® in Europe), linzagolix (Yselty® in Europe), and elagolix combination therapy, have been evaluated in phase II and III trials, demonstrating consistent efficacy in reducing HMB, improving anemia, and enhancing QoL [15]. By contrast, evidence in adenomyosis remains more limited and is mainly derived from smaller studies, although the underlying biological rationale and preliminary clinical findings are encouraging [16–18]. These differences highlight the need for a critical appraisal of the role of GnRH antagonists across benign uterine disease. While fibroids and adenomyosis share endocrine responsiveness, they differ in tissue architecture, symptom patterns, and treatment goals, raising important questions regarding the optimal use, duration, safety, and positioning of these agents within individualized medical and surgical treatment pathways.

This narrative review aims to provide a comprehensive, pharmacologically oriented evaluation of GnRH antagonists for the management of uterine fibroids and adenomyosis. We will examine their mechanisms of action, pharmacokinetic and pharmacodynamic properties, and the available clinical evidence, with particular emphasis on differences between the two conditions. Finally, we will offer an expert perspective on their current place in therapy, practical considerations for clinical use, and future directions in the evolving management of benign uterine disease.

The selection of references was guided by relevance, methodological rigor, and clinical significance, with literature sourced from PubMed, Embase, Scopus, and the Cochrane Library databases up to May 2026.

## 2. Biological rationale for GnRH antagonist therapy in uterine fibroids and adenomyosis

Uterine fibroids and adenomyosis, although they are distinct pathological entities, share a fundamental dependence on ovarian steroid hormones that provides the biological basis for endocrine-targeted therapies. Both conditions are characterized by an aberrant response of uterine tissues to estrogen and progesterone, resulting in altered cellular proliferation, extracellular matrix remodeling, inflammation, and vascular changes that ultimately drive symptom generation [19–21]. The pharmacological modulation of the hypothalamic-pituitary-ovarian axis, and specifically the suppression of circulating sex steroids, therefore, represents a rational strategy for the management of these disorders [5,6].

Uterine fibroids are benign monoclonal tumors arising from smooth muscle cells of the myometrium and are frequently associated with somatic mutations (most notably in the MED12 gene) that initiate tumorigenesis [22,23]. These mutations disrupt cyclin C-CDK8/19 kinase activity within the Mediator complex, leading to altered transcriptional regulation, enhanced extracellular matrix organization, and dysregulation of Wnt/β-catenin signaling [24,25]. However, while genetic alterations may trigger fibroid development, their subsequent growth and clinical behavior are largely governed by a hormonally responsive microenvironment [26,27]. Estrogen plays a permissive role in fibroid biology by upregulating progesterone receptor expression and enhancing cellular proliferation through activation of growth factor pathways, including insulin-like growth factor (IGF) and epidermal growth factor (EGF) signaling [26,28]. Progesterone, in turn, plays a central role in promoting fibroid growth by stimulating mitotic activity, inhibiting apoptosis, and enhancing extracellular matrix (ECM) deposition, which constitutes a substantial proportion of fibroid volume [19,26]. Progesterone acts through both genomic and non-genomic mechanisms via progesterone receptors (PRs) and membrane receptors (mPRs and PGRMCs) to activate signaling pathways that enhance tumor growth and survival [19]. Transforming growth factor-β (TGF-β) signaling is particularly relevant in this context, as it

drives fibrosis-like processes and contributes to the increased stiffness and bulk of fibroid tissue [19]. This intricate interplay between estrogen, progesterone, and local growth factors creates a self-sustaining environment that supports fibroid expansion and symptomatology, including HMB and pressure-related symptoms [26,29]. Importantly, fibroid tissues exhibit increased expression of steroid hormone receptors compared with adjacent myometrium, further amplifying their sensitivity to circulating hormones [26]. Progesterone promotes fibroid growth through paracrine signaling from mature leiomyoma cells to stem-progenitor cell populations that are deficient in estrogen receptor-α (ERα) and progesterone receptors, with the WNT/β-catenin pathway comprising a key component of this paracrine signaling system [27].

Suppression of ovarian steroid production through GnRH antagonists disrupts this hormonal milieu at multiple levels. By rapidly reducing circulating $E_2$ and progesterone concentrations, GnRH antagonists attenuate proliferative signaling, decrease ECM production, and induce a functional 'quiescence' of fibroid tissue [8,9,11]. Clinically, this translates into reduced menstrual bleeding (primarily through endometrial atrophy and decreased vascularity) and, in some cases, modest reductions in fibroid and uterine volume [8,9,11].

Adenomyosis is characterized by the presence of endometrial glands and stroma within the myometrium, accompanied by surrounding smooth muscle hypertrophy and hyperplasia [20,30]. Unlike fibroids, which are discrete lesions, adenomyosis often presents as a diffuse process, although focal adenomyotic nodules may mimic mass-like lesions on imaging. The pathogenesis of adenomyosis is complex and multifactorial, involving invagination of the basalis endometrium into the myometrium, tissue injury and repair mechanisms, and altered myometrial peristalsis [20,30]. At the molecular level, adenomyotic lesions demonstrate increased local estrogen production, partly mediated by upregulation of aromatase activity, as well as enhanced expression of estrogen and progesterone receptors [20,21,31]. Membrane progesterone receptors α and β, as well as estrogen receptor β (ERβ), are upregulated in adenomyosis compared to normal myometrium [31]. This results in a hyperestrogenic microenvironment that promotes glandular proliferation, angiogenesis, and neurogenesis. In parallel, progesterone resistance may impair progesterone's normal antiproliferative effects, further contributing to disease persistence.

Inflammation plays a central role in adenomyosis, with elevated levels of pro-inflammatory cytokines (IL-6, IL-8, IL-1β, TNF-α, IFN-γ), prostaglandins, and neurotrophic factors contributing to pain generation and abnormal uterine contractility. Both systemic and local immune changes have been described, including increased density of macrophages and lymphocytes in eutopic and ectopic endometrium, with elevated expression of toll-like receptors that are positively correlated with IL-6 and IL-8 production [32–35]. These alterations are associated with increased uterine volume, dysperistalsis, and HMB, reflecting both structural and functional disturbances [30,36]. The inflammatory microenvironment disrupts the immune barrier at the endometrial-myometrial junction, creating conditions hostile to embryo survival and contributing to infertility [37].

GnRH antagonists target several of these pathogenic mechanisms simultaneously. By suppressing ovarian steroid production, they reduce estrogen-driven proliferation and angiogenesis within adenomyotic foci [32]. In addition, decreased estrogen levels are associated with reduced inflammatory activity and prostaglandin production, contributing to improvements in dysmenorrhea and pelvic pain [32,33]. The induction of a hypoestrogenic state may also lead to partial regression of adenomyotic lesions and a reduction in uterine volume, although, as in fibroids, symptom relief often precedes or exceeds measurable structural changes.

The shared steroid dependence of fibroids and adenomyosis provides the conceptual framework for GnRH antagonist therapy; however, the degree of hormonal suppression required to achieve clinical benefit must be carefully balanced against the risk of hypoestrogenic adverse effects. Profound estrogen deprivation, as observed with GnRH agonists, is effective but associated with significant limitations, including vasomotor symptoms and BMD loss [38].

The introduction of oral GnRH antagonists has enabled a more nuanced approach based on dose-dependent suppression of ovarian function. Rather than inducing a complete hypoestrogenic state, these agents allow maintenance of circulating estradiol concentrations within a therapeutic 'window' sufficient to control symptoms while minimizing systemic side effects. This concept, often referred to as the estrogen threshold hypothesis, proposes that maintaining estradiol concentrations between 20 and 50 pg/ml (70 and 180 pmol/l) can reduce fibroid growth while minimizing hypoestrogenic adverse effects [39]. In clinical trials, median concentrations of estradiol remained above 20 pg/ml when GnRH antagonists were administered with 1 mg of estradiol and 0.5 mg of norethindrone acetate [39]. In this model, partial suppression of $E_2$ (typically in the range of approximately 30–60 pg/mL) appears sufficient to reduce endometrial proliferation and bleeding, attenuate fibroid-related signaling pathways, and modulate adenomyosis-associated inflammation, while preserving bone health and overall tolerability [11,40]. The concomitant use of add-back therapy with low-dose estrogen and progestin further stabilizes this balance, enabling extended treatment durations [11,40].

Despite their shared endocrine responsiveness, fibroids and adenomyosis exhibit important differences in tissue architecture and biological behavior that may influence their response to GnRH antagonist therapy. Fibroids, as well-circumscribed tumors with a substantial extracellular matrix component, may demonstrate limited volumetric reduction despite significant symptomatic improvement [8,9]. The response to GnRH antagonist therapy may also vary based on MED12 mutation status, with MED12 wild-type leiomyomas showing higher CDK8 activity and potentially different responses to hormonal suppression compared to MED12-mutant tumors [41]. In contrast, adenomyosis, as a diffuse and inflammatory condition, may show more variable structural responses, with symptom relief often driven by changes in uterine contractility and inflammatory signaling rather than lesion regression per se [30,36].

Overall, the biological rationale for GnRH antagonist therapy in uterine fibroids and adenomyosis is grounded in the

central role of ovarian steroids in the pathophysiology of these conditions, but its clinical translation requires an appreciation of the distinct yet overlapping mechanisms that characterize them.

## 3. Pharmacology and mechanism of action of GnRH antagonists

The introduction of orally active GnRH antagonists is a major advance in the pharmacological modulation of the hypothalamic-pituitary-ovarian axis [42]. Unlike earlier therapeutic strategies based on GnRH agonists, which induce an initial stimulatory 'flare' before receptor downregulation, GnRH antagonists exert an immediate and competitive inhibition at the level of the pituitary GnRH receptor [43]. This pharmacodynamic profile enables rapid, predictable, and dose-dependent suppression of gonadotropin secretion, with important implications for both efficacy and tolerability in the management of hormone-dependent uterine disorders.

GnRH antagonists bind competitively to GnRH receptors located on pituitary gonadotroph cells, thereby preventing endogenous GnRH from activating its receptor [43]. This results in an immediate reduction in luteinizing hormone and follicle-stimulating hormone secretion, without the transient increase in gonadotropins and sex steroids that characterizes GnRH agonist therapy. The absence of a flare effect is particularly relevant in clinical settings where rapid symptom control is desired, such as in women with severe HMB or anemia [44]. The downstream consequence of gonadotropin suppression is a reduction in ovarian steroidogenesis, leading to decreased circulating levels of estradiol and progesterone [45,46]. Importantly, this suppression is both rapid in onset (typically within hours to days) and fully reversible upon discontinuation, allowing flexible treatment strategies and facilitating individualized therapeutic regimens.

An important feature of oral GnRH antagonists is their ability to achieve dose-dependent suppression of ovarian function, in contrast to the more binary effect observed with GnRH agonists [45,46]. Lower doses may result in partial suppression of $E^2$, while higher doses approach near-complete ovarian suppression [45]. This pharmacological flexibility underpins the concept of tailoring therapy according to clinical needs, balancing symptom control against the risk of hypoestrogenic adverse effects. This paradigm shift (from complete suppression to controlled modulation) has enabled the development of treatment regimens that maintain circulating estradiol within a therapeutic window sufficient to inhibit endometrial proliferation and reduce fibroid- and adenomyosis-related symptoms, while preserving bone health and minimizing vasomotor symptoms. The integration of add-back therapy further refines this approach, allowing sustained treatment over extended periods [47].

Three oral GnRH antagonists have been most extensively investigated in the context of uterine fibroids and, to a lesser extent, adenomyosis: elagolix, relugolix, and linzagolix [40]. While sharing a common mechanism of action, these agents differ in pharmacokinetic profiles, dosing strategies, and approaches to add-back therapy.

Elagolix has a relatively short half-life (4 to 6 hours), necessitating twice-daily dosing in some regimens and enabling fine-tuned control of ovarian suppression [45,48–50]. Its pharmacodynamic effects are closely linked to dose, with higher doses achieving greater suppression of estradiol levels [45,46]. Elagolix is rapidly absorbed after oral dosing, reaching maximum concentrations at 1.0 to 1.5 hours [45,48]. Clinical use has largely been in combination with add-back therapy to mitigate hypoestrogenic effects during longer treatment durations [51].

Relugolix, in contrast, has a longer half-life (approximately 25 hours), which supports once-daily administration, and has been developed as a fixed-dose combination therapy with low-dose estradiol and norethindrone acetate. This formulation simplifies treatment by incorporating add-back therapy into a single tablet, promoting adherence and ensuring a consistent hormonal milieu.

Linzagolix offers a particularly flexible dosing strategy, with the potential for both full and partial suppression depending on the dose administered (100 mg or 200 mg once daily) [40]. Notably, lower-dose regimens (100 mg) may allow treatment without mandatory add-back therapy for limited durations, whereas higher doses (200 mg) are typically combined with hormonal add-back to support longer-term use [40].

Add-back therapy is a key component of longer-term GnRH antagonist regimens. Most combination regimens include low-dose estradiol with a progestin, typically norethindrone acetate, to reduce vasomotor symptoms, limit BMD loss, and protect the endometrium without substantially compromising control of bleeding or pain [47,52]. The safety implications of add-back therapy are discussed in detail below.

## 4. Clinical evidence of GnRH antagonists in uterine fibroids

The clinical development of oral GnRH antagonists for uterine fibroids has been supported by a robust body of phase II and III randomized controlled trials (RCTs) demonstrating consistent efficacy in reducing HMB, improving anemia, and enhancing QoL (Table 1). Across compounds, the primary therapeutic target has been the control of fibroid-associated HMB, typically defined as menstrual blood loss ≥ 80 ml per cycle, with responder analyses based on both absolute thresholds and percentage reductions. While differences in study design, dosing strategies, and add-back regimens complicate direct comparisons, a coherent pattern of efficacy and safety has emerged, supporting the integration of these agents into clinical practice [11].

The clinical efficacy of elagolix in uterine fibroids was established in the pivotal phase III Elaris UF-1 and UF-2 trials, which evaluated elagolix 300 mg twice daily in combination with add-back therapy (estradiol 1 mg and norethindrone acetate 0.5 mg once daily) and elagolix alone in premenopausal women with HMB associated with fibroids [53]. These randomized, double-blind, placebo-controlled studies enrolled a large population (412 women in UF-1 and 378 in UF-2). The primary endpoint (achievement of menstrual blood loss <80 ml and ≥50% reduction from baseline) was met in 68.5% of women in UF-1 and 76.5% in UF-2 receiving elagolix with add-

Table 1. Studies on GnRH antagonists in uterine fibroids.

| Drug | Study | Design | Population | Regimen | Treatment duration | Primary endpoint | Main efficacy findings | Safety / tolerability highlights | Main clinical message |
|---|---|---|---|---|---|---|---|---|---|
| Elagolix | Elaris UF-1 and UF-2 [53] | Two identical phase 3, randomized, double-blind, placebo-controlled trials in premenopausal women with fibroid-associated HMB | • UF-1 randomized 412 women<br>• UF-2 randomized 378 women | • ELX 300 mg twice daily + add-back therapy (estradiol 1 mg / NETA 0.5 mg once daily);<br>• ELX 300 mg twice daily | 6 months | Menstrual blood loss < 80 mL during final treatment month and ≥50% reduction from baseline | With ELX + add-back, the primary endpoint was achieved in 68.5% in UF-1 and 76.5% in UF-2, versus 8.7% and 10.0% with placebo. ELX alone achieved higher bleeding response rates (84.1% UF-1; 77.0%UF-2) | Hot flushes occurred more often than with placebo; hypoestrogenic effects, especially BMD loss, were attenuated by add-back therapy | Pivotal proof that oral GnRH antagonist effectively controls fibroid-related HMB; add-back therapy is crucial to improve long-term tolerability |
| Elagolix | Elaris UF-EXTEND [54] | Phase 3 extension study enrolling women rolling over from UF-1/UF-2; 433 enrolled, including 218 receiving up to 12 months of elagolix + add-back. | | ELX 300 mg twice daily plus add-back therapy; comparator analyses also included ELX alone during the extension program. | Up to 12 months total exposure | Same composite bleeding endpoint: menstrual blood loss < 80 ml in final month plus ≥ 50% reduction from baseline | Among women receiving ELX + add-back for up to 12 months, 87.9% met the primary endpoint, showing durability of bleeding control beyond the initial 6-month trials. | Most common adverse events with ELX + add-back were hot flush (6.9%), headache (5.5%), nausea (4.1%), and night sweats (3.2%). Mean BMD loss was significantly less with add-back than with ELX alone; the between-group lumbar spine difference was −3.3% points in favor of add-back. | Supports medium term durability of efficacy and confirms that add-back materially reduces skeletal toxicity during prolonged treatment. |
| Relugolix combination therapy | LIBERTY 1 and LIBERTY 2 [39] | Two replicate phase 3, randomized, placebo-controlled trials in women with symptomatic uterine fibroids and HMB. 388 women randomized in LIBERTY 1 and 382 in LIBERTY 2. | | Once-daily fixed-dose RLX combination therapy: RLX 40 mg + estradiol 1 mg + NETA 0.5 mg; placebo comparator; RLX monotherapy arm used for mechanistic/ safety context. | 24 weeks for the pivotal trials | Response defined as menstrual blood loss < 80 mL and ≥50% reduction from baseline over the last 35 days of treatment. | Response occurred in 73% of women in LIBERTY 1 and 71% in LIBERTY 2 with relugolix combination therapy, versus 19% and 15% with placebo. Six of seven key secondary endpoints improved, including amenorrhea-related bleeding measures, pain, distress from bleeding/pelvic discomfort, anemia, and uterine volume; fibroid volume did not significantly improve. | Overall adverse-event incidence was similar to placebo. BMD was preserved with relugolix combination therapy but decreased with relugolix monotherapy. | Demonstrated that a once-daily fixed-dose oral combination can deliver robust bleeding control while maintaining BMD, making long-term pharmacologic management more practical. |
| Relugolix combination therapy | LIBERTY randomized withdrawal study [56] | Phase 3 randomized withdrawal study after successful completion of LIBERTY 1/2 + long-term extension; responders at ~1 year were re-randomized to continue relugolix combination therapy or switch to placebo. 229 randomized; 228 treated. | | Continue relugolix combination therapy vs placebo; placebo relapse allowed open-label rescue | Up to 104 weeks total treatment exposure | Proportion maintaining menstrual blood loss < 80 mL through week 76; durability also assessed through week 104. | Through week 76, 78.4% on active therapy maintained blood loss < 80 ml vs 15.1% on placebo; at week 104, rates were 69.8% vs 11.8%. Placebo withdrawal led to relapse in 88.3% through week 104, with median time to relapse 5.9 weeks. | No new safety signals emerged in year 2; BMD remained stable from week 52 to week 104 in women continuing RLX combination therapy. | Strong evidence for durability during treatment and rapid recurrence after discontinuation, emphasizing that GnRH antagonists are principally suppressive rather than curative therapies. |

(*Continued*)

Table 1. (Continued).

| Drug | Study | Design | Population | Regimen | Treatment duration | Primary endpoint | Main efficacy findings | Safety / tolerability highlights | Main clinical message |
|---|---|---|---|---|---|---|---|---|---|
| Linzagolix | PRIMROSE 1 and PRIMROSE 2 [40] | Two identical phase 3, randomized, double-blind, placebo-controlled trials in women with symptomatic fibroids and HMB; 511women in PRIMROSE 1 and 501 in PRIMROSE 2 in the full analysis sets. | | Five masked groups: placebo; linzagolix 100 mg; 100 mg + add-back; 200 mg; 200 mg + add-back. Add-back = estradiol 1 mg + norethisterone acetate 0.5 mg. | 52-week program; primary efficacy at week 24 | Response = menstrual blood loss ≤ 80 mL and ≥50% reduction from baseline at 24 weeks. | In PRIMROSE 1, response rates were 56.4% (100 mg), 66.4%(100 mg + ABT), 71.4%(200 mg), and 75.5%(200 mg + ABT), vs 35.0% with placebo. In PRIMROSE 2, rates were 56.7%, 77.2%, 77.7%, and 93.9%, respectively, vs 29.4%with placebo. All active groups were significantly superior to placebo. | Up to week 24, hot flusheswere most frequent with 200 mg without add-back: 35% in PRIMROSE 1 and 32% in PRIMROSE 2; rates were lower (3–14%) in other groups. | Demonstrates a distinctive dose-flexible strategy: partial suppression at 100 mg may offer a non-add-back option for some women, whereas 200 mg + add-back maximizes bleeding efficacy. |
| Linzagolix | PRIMROSE 1/2 long-term extension and withdrawal [57] | Long-term extension/ withdrawal follow-up study | Participants continuing after phase 3 PRIMROSE program | Linzagolix with and without hormonal add-back in longer-term follow-up. | Extended follow-up through long-term study | Durability of bleeding control and long-term safety | Long-term efficacy maintenance reported | Long-term skeletal safety specifically assessed | Supportive long-term follow-up; pivotal efficacy evidence remains based on 2022 PRIMROSE trials |

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; ELX, elagolix; GnRH, gonadotropin-releasing hormone; HMB, heavy menstrual bleeding; NETA, norethindrone acetate; RLX, relugolix.

back therapy, compared with 8.7% and 10% in the placebo groups, respectively ($p < 0.001$ for both trials). Among women receiving elagolix alone (without add-back therapy), response rates were 84.1% in UF-1 and 77% in UF-2, demonstrating that add-back therapy does not compromise efficacy. Improvements were observed early in treatment and sustained over the duration of the trials. Secondary outcomes further supported clinical benefit. Elagolix-treated patients had significant improvements in hemoglobin levels, particularly among women with baseline anemia (hemoglobin ≤10.5 g/dl), with more than half achieving increases >2 g/dl at 6 months. Rates of amenorrhea were substantially higher in the active treatment groups (48.1% in UF-1 and 52.9% in UF-2) compared with placebo (4–5%). QoL measures showed marked improvement, with mean reductions in symptom severity scores of −33.2 to −41.4 points compared with −7.9 to −10.3 in placebo groups. Reductions in uterine and fibroid volume were modest and variable, reinforcing the concept that symptom control (particularly bleeding) is the primary therapeutic goal. Safety analyses highlighted the expected hypoestrogenic profile, with hot flushes being the most reported adverse event; however, the inclusion of add-back therapy significantly mitigated the extent of BMD loss compared with elagolix monotherapy. The efficacy of elagolix with add-back therapy was consistent across diverse subgroups, including variations in age, body mass index, race, ethnicity, baseline menstrual blood loss, fibroid location, and uterine and fibroid volume.

The Elaris UF-EXTEND phase 3 extension study evaluated the safety and efficacy of elagolix 300 mg twice daily with hormonal add-back therapy (estradiol 1 mg and norethindrone acetate 0.5 mg once daily) for an additional 6 months in women who completed 6 months of the same treatment in the preceding Elaris UF-1 and UF-2 trials, providing data on up to 12 months of continuous treatment. Among 218 women who received up to 12 months of elagolix with add-back therapy (mean age 42.4 years, 67.3% Black), 87.9% met the primary endpoint of both menstrual blood loss less than 80 mL during the final month and at least 50% reduction from baseline (95% CI 83.4–92.3). The treatment demonstrated sustained efficacy in reducing HMB associated with uterine leiomyomas throughout the extended treatment period. The most frequently reported adverse events were hot flush (6.9%), night sweats (3.2%), headache (5.5%), and nausea (4.1%). Importantly, the addition of hormonal add-back therapy significantly attenuated hypoestrogenic effects, with mean percent decreases in BMD from baseline to extension month 6 being significantly less with elagolix plus add-back therapy compared to elagolix alone (between-group difference in lumbar spine: −3.3, 95% CI −4.1 to −2.5). The study concluded that no new or unexpected safety concerns emerged with the additional 6 months of treatment, supporting the use of elagolix with add-back therapy for up to 12 months in this patient population [54].

The introduction of relugolix marked a significant therapeutic advance, particularly through the development of a once-daily fixed-dose combination of relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg. The efficacy and safety of this regimen were assessed in the phase III LIBERTY 1 and LIBERTY 2 trials, conducted in women with symptomatic uterine fibroids and HMB, with a primary endpoint broadly aligned with that used in the Elaris trials [39]. In both phase III trials, relugolix combination therapy demonstrated substantial efficacy, achieving responder rates of 73% in LIBERTY 1 and 71% in LIBERTY 2, compared with 19% and 15% in the placebo groups, respectively ($p < 0.001$ for both comparisons). The consistency of these results across studies and patient subgroups further reinforces the robustness of the therapeutic effect. As previously reported with elagolix, treatment was associated with a rapid and durable reduction in menstrual blood loss, and a notable proportion of patients achieved amenorrhea. Improvements in anemia were clinically relevant, with early increases in hemoglobin levels, an important consideration for women presenting with moderate or severe iron-deficiency anemia. Furthermore, relugolix combination therapy was associated with significant improvements in patient-reported QoL measures, including symptom severity and daily functioning, indicating a meaningful reduction in the impact of bleeding and pelvic pain on everyday life [39,55].

A major strength of the relugolix development program lies in the inclusion of long-term extension studies, which support the durability of efficacy together with a stable safety profile during prolonged therapy [56]. Among women treated with relugolix combination therapy for up to 52 weeks, 87.7% continued to meet responder criteria, with a mean reduction in menstrual blood loss volume of 89.9%, while 70.6% achieved amenorrhea. BMD remained largely preserved with add-back therapy, supporting the feasibility of longer-term treatment compared with earlier endocrine approaches [56]. The durability of this benefit was further confirmed in a randomized withdrawal study, in which 78.4% of women maintained menstrual blood loss below 80 mL at week 76 and 69.8% at week 104, compared with 15.1% and 11.8%, respectively, in the placebo group [55].

The fixed-dose combination approach offers practical advantages in clinical practice, particularly through once-daily oral administration and a simplified treatment regimen, which may support treatment adherence. However, the fixed-combination format provides less flexibility for individual adjustment of add-back components, which may be relevant in selected patients [11,13,39].

In the phase III PRIMROSE 1 and PRIMROSE 2 trials, linzagolix was evaluated at doses designed to achieve either partial (100 mg) or full (200 mg) estrogen suppression, with or without add-back therapy with estradiol 1 mg and norethisterone acetate 0.5 mg [40]. This dual-dose approach provides unique insights into the relationship between the degree of hormonal suppression and clinical outcomes. In the phase III PRIMROSE 1 and PRIMROSE 2 trials, all linzagolix treatment arms significantly outperformed placebo. In PRIMROSE 1, responder rates ranged from 56.4% with 100 mg monotherapy to 75.5% with 200 mg plus add-back therapy, compared with 35.0% with placebo. In PRIMROSE 2, responder rates ranged from 56.7% to 93.9% across the active treatment groups, versus 29.4% with placebo [40]. Higher-dose linzagolix regimens combined with add-back therapy achieved responder rates comparable to those observed with elagolix and relugolix, confirming class-wide efficacy in reducing HMB [40]. Lower-dose regimens

(100 mg), designed to achieve partial estrogen suppression without mandatory add-back therapy, also demonstrated meaningful reductions in menstrual blood loss, although with somewhat lower response rates [40]. This flexible dosing strategy highlights a key advantage of GnRH antagonists: the ability to individualize treatment intensity according to symptom severity, patient preferences, and tolerability. However, the trade-off between efficacy and hypoestrogenic side effects remains evident, with higher levels of suppression associated with increased risk of vasomotor symptoms (hot flushes in 32–35% with 200 mg alone versus 3–14% in other groups) and bone loss in the absence of add-back therapy [40].

Long-term extension studies confirmed that the benefits observed at 24 weeks were maintained through 52 weeks, with response rates of 55.0% to 89.9% depending on dose and add-back therapy [57]. BMD remained generally stable at week 52, and in women initially treated with linzagolix 200 mg alone through week 24, early bone loss improved after the introduction of add-back therapy from week 24 onward [57]. The onset of action was rapid, with a median time to achieving clinically significant HMB reduction of <4 weeks for most doses and as little as 3 days for 200 mg with or without add-back therapy [58].

As with other agents in this class, reductions in fibroid volume were modest (ranging from 1% to 25% after 24 weeks, not different from placebo when add-back therapy was used), and clinical benefit was primarily driven by improvements in bleeding and related symptoms [40]. The PRIMROSE trials therefore reinforce the concept that GnRH antagonists function predominantly as symptom-modifying therapies, rather than disease-eradicating interventions [40].

Although no head-to-head trials have directly compared elagolix, relugolix, and linzagolix, several consistent class effects emerge. All agents showed robust efficacy in reducing fibroid-associated HMB in phase III trials, with responder rates exceeding 70% in the relugolix program and in higher-dose linzagolix plus add-back regimens, and with elagolix plus add-back also demonstrating clear superiority over placebo [39,40,53]. Add-back therapy was crucial in supporting longer-term treatment by attenuating hypoestrogenic adverse effects, particularly vasomotor symptoms and BMD loss. In addition, clinically meaningful improvements in anemia and QoL were observed across programs [39,40,53,55].

Differences between agents are primarily related to pharmacokinetics, dosing convenience, and flexibility of add-back strategies rather than fundamental differences in efficacy [11]. Relugolix offers the advantage of a once-daily fixed combination, while elagolix and linzagolix allow greater flexibility in dose titration and add-back customization. Linzagolix, in particular, provides a spectrum of suppression levels (100 mg for partial suppression, 200 mg for full suppression), which may be advantageous in selected clinical scenarios, particularly for women who cannot or do not wish to take concomitant hormonal add-back therapy [40].

A critical insight emerging from clinical trials is that the benefits of oral GnRH antagonists are predominantly functional rather than structural. Although reductions in fibroid or uterine volume may occur, particularly with higher levels of ovarian suppression and in the absence of add-back therapy, the main therapeutic benefit is the control of HMB and related symptoms. When used with add-back therapy, fibroid volume reduction ranges between 1% and 25% after 24 weeks, which is not significantly different from placebo. In contrast, GnRH agonists (used without add-back therapy) may substantially reduce uterine volume, but at the cost of greater hypoestrogenic effects [59].

This distinction has important implications for clinical expectations and patient counseling. From a practical perspective, GnRH antagonists are best viewed as symptom-controlling agents that effectively reduce HMB, improve anemia, and enhance health-related QoL, rather than as therapies aimed at eradicating fibroids. Accordingly, their place in care is best conceptualized within a broader treatment strategy that may involve prolonged medical therapy, intermittent courses, or combination with procedural and surgical interventions. In line with this approach, American Congress of Obstetricians and Gynecologists (ACOG) recommends that oral GnRH antagonists with hormonal add-back therapy may be considered for the treatment of abnormal uterine bleeding related to leiomyomas for up to 2 years [38].

## 5. Clinical evidence of GnRH antagonists in adenomyosis

In contrast to uterine fibroids, the clinical evidence supporting oral GnRH antagonists in adenomyosis remains limited and substantially less mature. To date, no phase III regulatory program comparable to ELARIS, LIBERTY, or PRIMROSE has positioned these agents as an established standard of care for adenomyosis [18,60–62]. Instead, the available literature consists mainly of pilot studies, case reports, small observational series, and narrative reviews, with most published data focused on linzagolix [16,17,63] and a smaller number of reports involving relugolix [64,65]. This difference in evidence strength should be considered when translating fibroid data to adenomyosis.

Despite the limited dataset, the available studies suggest a relatively consistent therapeutic signal across three domains: reduction in uterine or adenomyotic lesion volume, improvement in pain symptoms (particularly dysmenorrhea) and better control of abnormal uterine bleeding [17,63,65]. This pattern is biologically coherent with the endocrine and inflammatory pathophysiology of adenomyosis [5]. In contrast to uterine fibroids, where bleeding control is often the dominant measurable endpoint, adenomyosis requires a broader assessment of treatment response, including pelvic pain, uterine tenderness, bulk-related symptoms, and imaging-defined changes in diffuse or focal myometrial disease. Early reports therefore support the concept that GnRH antagonists may provide both symptomatic benefit and, in some patients, measurable structural improvement [5,17,63].

Among oral GnRH antagonists, linzagolix currently has the most specific published clinical evidence in adenomyosis. Initial data came from a case report describing marked regression of severe diffuse adenomyosis, with uterine volume decreasing from 875 $cm^3$ to 290 $cm^3$ on MRI and substantial symptomatic and QoL improvement in a woman previously showing an inadequate response to ulipristal acetate [5].

Although anecdotal by nature, this report was important because it provided early proof of concept that oral GnRH antagonism could influence adenomyotic disease activity beyond simple menstrual suppression [16].

This was followed by a pilot study that specifically evaluated linzagolix for symptomatic uterine adenomyosis [17,63]. In that study, a once-daily regimen of 200 mg for 12 weeks followed by 100 mg for another 12 weeks was associated with a 55% decrease in adenomyotic uterine volume at 12 weeks and a 32% reduction at 24 weeks, along with improvement in overall pelvic pain, dysmenorrhea, non-menstrual pelvic pain, dyspareunia, dyschezia, and QoL. The step-down design is noteworthy because it reflects one of the central theoretical advantages of this drug class in adenomyosis: an initial phase of stronger ovarian suppression to rapidly control pain and bleeding, followed by a lower-maintenance dose intended to preserve benefit while reducing the burden of hypoestrogenism. While the study was small ($n = 8$) and uncontrolled, it remains one of the most informative prospective datasets currently available for oral GnRH antagonists in adenomyosis. Subsequent analysis of volume evolution during and after linzagolix treatment provided an additional clinically relevant insight: adenomyotic uterine volume appears to decrease during treatment but may increase again after discontinuation [63]. From a practical perspective, this has major implications for patient counseling because symptom recurrence after cessation should be anticipated and discussed when defining treatment goals.

The evidence for relugolix in adenomyosis is more limited than that for linzagolix, but growing clinical interest is increasing. Published data include a retrospective study showing a rapid reduction in adenomyosis coexisting with leiomyomas, with uterine volume decreasing by 43% in the adenomyosis group versus 27% in women with fibroids alone, while adenomyotic lesions within the adenomyosis group decreased by 61% [65]. More recently, a post hoc subgroup analysis of the LIBERTY 1 and LIBERTY 2 trials showed that, among women with uterine fibroids and concomitant ultrasound-diagnosed adenomyosis ($n = 111$; 18.2% of the pooled study population), relugolix combination therapy achieved a treatment response rate of 83.8%, compared with 27.6% with placebo. In the same subgroup, 64.9% of women achieved amenorrhea, and uterine volume decreased by 22.2% [64]. These reports are encouraging, particularly because relugolix offers the practical advantage of once-daily oral dosing and, in fixed-combination formulations, the possibility of standardized add-back therapy [64,65].

The relugolix experience is also relevant because adenomyosis frequently coexists with endometriosis or fibroids, and this overlap may expand the potential clinical niche for GnRH antagonists [64]. In real-world practice, many patients do not present with 'pure' adenomyosis, but rather with mixed estrogen-dependent pelvic disease. In such settings, a therapy that simultaneously reduces bleeding, dysmenorrhea, and endometriosis-related pain may be particularly attractive, even if adenomyosis-specific randomized evidence is still lacking.

In contrast with fibroids, where elagolix has been rigorously evaluated in large randomized trials, direct adenomyosis-specific evidence for elagolix is sparse. Current discussion of elagolix in adenomyosis is therefore driven more by pharmacologic rationale and extrapolation from endometriosis and fibroid data than by dedicated clinical trials. This is an important distinction, because it highlights a recurring issue in the adenomyosis field: promising mechanisms often outpace formal evidence generation. Reviews of conservative adenomyosis management and broader appraisals of oral GnRH antagonists acknowledge this potential, but they also emphasize that the supporting clinical data remain limited. Accordingly, elagolix cannot presently be positioned as an evidence-based standard for adenomyosis, although it remains a scientifically plausible candidate for future investigation [5,60,62].

A critical issue in interpreting adenomyosis studies is the heterogeneity of reported endpoints. Bleeding reduction is important, but in adenomyosis, the most clinically meaningful outcome may often be pain relief, especially improvement in dysmenorrhea. Available reports suggest that both pain and bleeding can improve under GnRH antagonist therapy, with volume reduction representing a supportive but not necessarily essential correlate of clinical response [17,63,65]. This is important because adenomyosis is not simply a mass lesion; it is also a disorder of uterine inflammation, myometrial dysfunction, and altered contractility. As a result, symptom improvement may occur even when imaging changes are modest or difficult to quantify. This pattern parallels the broader concept already observed in fibroids that endocrine suppression modifies disease activity more than it eradicates lesions, but in adenomyosis the disconnect between symptom relief and anatomy may be even more pronounced.

The major limitation of the adenomyosis literature lies not in the absence of therapeutic activity, but in the lack of robust, adequately powered comparative evidence. Most studies published to date are limited by small sample size, short duration of follow-up, non-randomized design, and the inclusion of highly selected populations. Interpretation is further complicated by diagnostic heterogeneity, since adenomyosis may present as diffuse or focal disease, occur in isolation or in association with fibroids and/or endometriosis, and be diagnosed by ultrasound or MRI using non-equivalent criteria. As a result, cross-study comparisons are challenging and the generalizability of available data remains limited. In addition, several key long-term issues remain incompletely characterized, including symptom recurrence after treatment discontinuation, effects on bone health, implications for fertility-oriented care, and the place of GnRH antagonists relative to established progestin-based strategies [18,61].

Taken together, the available evidence suggests that oral GnRH antagonists are promising agents for symptomatic adenomyosis, particularly in women with severe dysmenorrhea, HMB, enlarged uterus, or coexisting endometriosis who wish to avoid or postpone surgery [17,18,63,65]. The most convincing current signal comes from linzagolix pilot data, supported by early reports with relugolix and by a strong mechanistic rationale for the drug class as a whole. At the same time, the literature does not yet support viewing GnRH antagonists as established standard therapy for adenomyosis in the same way that they are increasingly regarded for fibroid-associated HMB. Their current place is best understood as selective and individualized: a potentially valuable option in expert practice, but one that still requires formal validation through

prospective controlled trials with standardized diagnostic criteria, patient-centered symptom endpoints, and long-term safety assessment [18,60,62,63,65].

## 6. Safety, tolerability, and risk–benefit profile of GnRH antagonists

The clinical utility of oral GnRH antagonists in uterine fibroids and adenomyosis is fundamentally determined by the balance between effective endocrine suppression and the prevention of hypoestrogenic complications. While these agents offer clear advantages over GnRH agonists in terms of rapid onset of action, oral administration, and dose-dependent modulation of ovarian function, their safety profile remains intrinsically linked to the degree and duration of estradiol suppression. The introduction of add-back therapy has significantly improved tolerability and expanded the potential for longer-term use; however, important considerations regarding bone health, metabolic effects, and individualized risk stratification persist [39,40,53].

The most common adverse events associated with GnRH antagonist therapy are related to reduced circulating estrogen levels and include vasomotor symptoms such as hot flushes and night sweats, as well as headache, fatigue, mood changes, and decreased libido. These effects are generally dose-dependent and more pronounced in regimens achieving near-complete ovarian suppression [39,40,53].

Compared with GnRH agonists, the severity of hypoestrogenic symptoms is generally reduced, reflecting the ability of antagonists to maintain partial estrogen levels, particularly when used in conjunction with add-back therapy. Clinical trials in uterine fibroids consistently show that the incidence of hot flushes is lower in patients receiving combination regimens with low-dose estrogen and progestin than in those treated with GnRH antagonist monotherapy. In randomized trials, hot flushes were reported in a relatively small proportion of patients receiving add-back combination regimens, whereas substantially higher rates were observed in monotherapy groups, supporting the role of add-back therapy in improving tolerability and enabling longer-term use. From a clinical perspective, this improved tolerability is a key factor supporting patient adherence and acceptance, particularly in the context of chronic or repeated treatment courses [38–40,53].

Among safety considerations, the impact of GnRH antagonists on BMD is one of the most clinically relevant constraints on prolonged treatment. Because estrogen is essential for skeletal homeostasis, particularly through inhibition of osteoclast-mediated bone resorption, sustained hypoestrogenism is associated with accelerated bone turnover and progressive BMD loss [66].

Clinical trials have consistently demonstrated that GnRH antagonist monotherapy is associated with measurable reductions in BMD over relatively short treatment durations [39,67]. However, the concomitant use of add-back therapy markedly attenuates this effect. In the landmark LIBERTY phase 3 trials of relugolix combination therapy, BMD was similar to placebo in the combination therapy group but decreased significantly with relugolix monotherapy [39]. A recent meta-analysis found that BMD decrease with GnRH antagonists plus add-back therapy ranged from 0% to 2%, compared with significantly greater reductions with monotherapy [67]. These findings support the concept that maintaining circulating estradiol above a critical threshold (approximately 20–50 pg/mL) is sufficient to preserve skeletal health while retaining therapeutic efficacy.

Despite these reassuring early data, several uncertainties remain. Long-term outcomes with oral GnRH antagonists in adenomyosis have not yet been adequately characterized, and the cumulative impact of repeated treatment courses on bone health requires further investigation. In clinical practice, careful patient selection, baseline risk assessment, and, when appropriate, monitoring of BMD should be considered, particularly in women with additional risk factors for osteoporosis.

Add-back therapy, most commonly consisting of low-dose estradiol (1 mg) plus norethindrone acetate (0.5 mg), is a fundamental component of current GnRH antagonist regimens. Its principal objective is to reduce the systemic consequences of hypoestrogenism, particularly vasomotor symptoms and BMD loss, without compromising therapeutic activity on uterine targets [13].

The success of this approach is based on the differential sensitivity of target tissues to estrogen levels, often referred to as the 'estrogen threshold hypothesis.' While bone and the central nervous system are highly sensitive to reductions in circulating estrogen, the endometrium and hormonally responsive uterine lesions appear to require higher levels of estrogen stimulation to sustain pathological activity. This differential allows the establishment of a therapeutic window in which symptoms can be controlled without inducing clinically significant hypoestrogenism [13].

Importantly, clinical trials have shown that the addition of low-dose hormonal therapy does not substantially compromise efficacy in controlling HMB or other fibroid-related symptoms [39,40].

The safety profile of GnRH antagonists must also be interpreted in the context of the hormonal components used in add-back therapy. Low-dose estrogen–progestin combinations carry a theoretical risk of thromboembolic events, although the absolute risk in clinical trials has been low and comparable to that observed with other low-dose hormonal therapies. It is important to note that most cardiovascular data on GnRH antagonists derive from studies in men with prostate cancer receiving androgen deprivation therapy [68–70]. In this population, GnRH agonists have been associated with increased cardiovascular risk, including myocardial infarction, stroke, and metabolic syndrome, while some evidence suggests GnRH antagonists may have a more favorable cardiovascular profile [69–72]. However, the applicability of these findings to premenopausal women receiving GnRH antagonists with add-back therapy for benign gynecologic conditions remains uncertain [68].

Cardiometabolic effects, including potential changes in lipid profiles, body weight, and insulin sensitivity, have not emerged as major concerns in clinical studies of GnRH antagonists for fibroids to date, but available data remain relatively limited. In clinical practice, individual risk factors (such as age, smoking status, obesity, and personal or family history of thromboembolism) should be considered when selecting patients for treatment and when choosing specific regimens.

Endometrial safety is ensured by the progestin component of add-back therapy, which counteracts estrogen's proliferative effects on the endometrium. Clinical trials have not demonstrated an increased risk of endometrial hyperplasia or neoplasia with combination GnRH antagonist regimens over the durations studied [13,39]. Bleeding patterns during treatment may vary, with many patients experiencing significant reductions in menstrual blood loss or amenorrhea. Amenorrhea rates in clinical trials ranged from 34% to 81% at 24 weeks of follow-up. In some cases, irregular or breakthrough bleeding may occur, particularly during the initial phases of treatment or with partial suppression regimens. These patterns are generally manageable and tend to stabilize over time [39,40].

A notable advantage of GnRH antagonists is the rapid reversibility of their pharmacodynamic effects. Upon discontinuation, gonadotropin secretion and ovarian steroid production typically recover quickly, leading to the resumption of ovulatory cycles. This feature is particularly relevant in women desiring future fertility and distinguishes antagonists from longer-acting depot therapies [11,43,44].

However, reversibility of endocrine suppression is also associated with symptom recurrence. Clinical studies, particularly randomized withdrawal trials, have shown that HMB and other fibroid-related symptoms may return within weeks after treatment cessation, reinforcing the concept that GnRH antagonists function primarily as suppressive rather than curative therapies and underscoring the need for long-term management strategies in chronic disease [56,57].

Overall, GnRH antagonists have redefined the medical management of hormone-dependent uterine disease by offering effective symptom control with a more flexible and potentially better tolerated suppressive strategy. Their optimal role, however, remains inherently individualized and depends on a careful balance between efficacy, safety, treatment goals, and long-term management needs.

## 7. Current role of GnRH antagonist in the treatment of benign uterine disorders

Oral GnRH antagonists represent an important addition to the therapeutic options for benign uterine disorders, particularly uterine fibroids and, to a lesser extent, adenomyosis. Rather than replacing existing therapies, they function as integrative tools.

Oral GnRH antagonists with add-back therapy are among the most effective medical options for fibroid-related HMB, with phase III trials consistently showing substantial reductions in menstrual blood loss and high amenorrhea rates [11,53]. The American College of Obstetricians and Gynecologists states that oral GnRH antagonists with hormonal add-back therapy can be considered for the treatment of abnormal uterine bleeding associated with leiomyomas for up to 24 months [38]. The American College of Radiology includes oral GnRH antagonists among second-line medical management options for uterine fibroids [73].

Unlike the LNG-IUS, which may be less effective in the presence of cavity-distorting fibroids and is associated with higher expulsion rates in women with fibroids (approximately 11% vs 0%–3% in women without fibroids), GnRH antagonists act independently of uterine cavity anatomy [74]. Compared with GnRH agonists, antagonists offer a more rapid onset of action without an initial flare effect, oral administration, and the potential for longer-term use when combined with add-back therapy [11,43,44].

Potential candidates include women with moderate-to-severe HMB or dysmenorrhea who wish to avoid or defer surgery, have contraindications to or failure of first-line hormonal therapies, require rapid bleeding control because of anemia, or need preoperative optimization. They may also be considered in selected perimenopausal women as a bridge to menopause, if bone and thromboembolic risk factors are assessed [8,11,59].

Evidence for GnRH antagonists in adenomyosis is more limited. They should be considered second-line or individualized therapy rather than standard first-line treatment [16]. First-line management typically includes progestins (particularly dienogest) and the LNG-IUS [10,18].

Pilot studies suggest that linzagolix may reduce uterine volume by approximately 32%–55% and improve pain, dysmenorrhea, and QoL in women with adenomyosis [17,63]. GnRH antagonists may be particularly valuable in women with severe symptoms, enlarged uteri, or coexisting fibroids or endometriosis who have failed first-line therapies [5]. Their use remains largely off-label and expert-driven, requiring individualized decision-making.

GnRH antagonists are currently the only available oral agents that directly and rapidly suppress ovarian steroid production in a reversible manner. Combined oral contraceptives and progestins are widely available but generally provide more limited control of fibroid-associated HMB. The LNG-IUS is highly effective for HMB, but its efficacy may be reduced in the presence of large or cavity-distorting fibroids [74]. GnRH agonists are effective but are limited by hypoestrogenic adverse effects, flare-up phenomena, and parenteral administration [59]. When combined with add-back therapy, GnRH antagonists offer comparable efficacy to GnRH agonists with improved tolerability and oral administration.

GnRH antagonists can also be used in the preoperative setting to improve hemoglobin levels and, in some cases, reduce uterine volume, thereby potentially facilitating less invasive surgical approaches. In addition, they may help postpone surgery in perimenopausal women or provide intermittent symptom control in selected patients, although the optimal treatment regimens remain to be clearly defined.

Oral administration and rapid onset enhance clinical usability. Fixed-dose combination regimens, approved in the United States for up to 24 months, simplify treatment and may support adherence [11,39].

The role of oral GnRH antagonists in women wishing to conceive or undergoing assisted reproductive technology (ART) requires specific consideration. At present, these agents should not be regarded as fertility-enhancing treatments per se, because no randomized trials have evaluated relugolix, elagolix, or linzagolix as pretreatment before IVF or frozen embryo transfer in women with fibroids or adenomyosis. In women with fertility-impairing fibroids, particularly submucosal, cavity-distorting, or large intramural lesions, myomectomy

remains the preferred strategy when anatomical correction is expected to improve reproductive outcomes [75]. GnRH antagonists may nevertheless have a potential role as short-term bridging therapy before surgery or ART, especially to control HMB, improve anemia, and temporarily reduce uterine or fibroid volume. Their rapid onset, absence of flare effect, oral administration, and reversibility may be advantageous compared with depot GnRH agonists when timing of ART is important [11].

In adenomyosis, most ART-related evidence concerns prolonged pretreatment with GnRH agonists rather than oral GnRH antagonists. Several retrospective studies and meta-analyses suggest that GnRH agonist downregulation before embryo transfer may improve implantation or clinical pregnancy rates, particularly in women with diffuse adenomyosis, although the effect on live birth remains inconsistent and the quality of evidence is limited [76–78]. Oral GnRH antagonists are biologically plausible alternatives because they may reduce uterine volume, bleeding, pain, and adenomyosis-related inflammatory activity; however, fertility outcomes after antagonist pretreatment have not yet been reported [16,17,64].

Therefore, in patients planning ART, oral GnRH antagonists should currently be considered investigational for reproductive optimization, although they may be useful for symptom control while awaiting treatment, for preoperative optimization, or potentially as a future alternative to GnRH agonist downregulation once dedicated fertility studies become available. Because these agents do not provide reliable contraception and symptoms may recur rapidly after discontinuation, their use in women seeking pregnancy requires careful counseling regarding timing, avoidance of conception during treatment, and the limited evidence on reproductive outcomes [79].

Economic considerations are increasingly relevant when positioning oral GnRH antagonists within treatment algorithms for benign uterine disorders. However, published cost-effectiveness data specifically evaluating these agents for fibroid-associated symptoms remain limited, particularly in European healthcare systems. In general, GnRH antagonist combination therapy involves a recurring pharmaceutical cost, whereas surgery and interventional radiology procedures are associated with higher upfront but usually non-continuous costs. In the United States, annual wholesale costs for relugolix or elagolix combination therapy have been estimated at approximately 12,000– 15,000 US dollars, broadly overlapping with the episode-of-care costs reported for major fibroid procedures in claims-based analyses [80]. In Europe, direct comparisons are more difficult because drug prices and reimbursement vary substantially across countries and are often shaped by health technology assessment and national price negotiations [81]. In the UK FEMME trial, myomectomy was more cost-effective than uterine artery embolization over a 2-year horizon, highlighting that procedural costs must be interpreted together with QoL outcomes and reintervention risk [82,83]. Therefore, GnRH antagonists may be economically attractive as short-term bridging therapy, preoperative optimization, or treatment for women approaching menopause, whereas cumulative costs may become less favorable when therapy is continued for several years, especially in younger patients. Economic value should therefore be assessed in relation to treatment duration, avoidance or postponement of surgery, fertility and uterus preservation, symptom recurrence after discontinuation, and patient preferences.

Overall, the combination of high efficacy, manageable safety with add-back therapy, and patient-friendly administration supports the integration of GnRH antagonists into contemporary treatment algorithms for benign uterine disorders [8,11].

## 8. Conclusion

Oral GnRH antagonists have expanded the medical management of hormone-dependent benign uterine disorders by providing effective, reversible ovarian suppression with improved tolerability when combined with add-back therapy. Their efficacy is well established for fibroid-associated HMB, whereas their role in adenomyosis remains promising but requires dedicated controlled studies, particularly to define long-term safety, optimal duration, reproductive implications, and positioning within individualized uterus-preserving strategies.

## 9. Expert opinion

The introduction of oral GnRH antagonists has marked one of the most relevant pharmacological advances in the management of benign uterine disorders over the past decade. Their development has redefined the therapeutic paradigm, moving from short-term endocrine suppression toward a model of chronic and modulated disease control, particularly for uterine fibroids and, to a lesser extent, adenomyosis.

For many years, medical treatment was polarized between partial hormonal modulation on one side and profound hypoestrogenism on the other. Oral GnRH antagonists have introduced an intermediate and more flexible strategy based on dose-dependent endocrine modulation. This allows ovarian suppression to be aligned with therapeutic goals rather than pursued indiscriminately. From our perspective, this is the real conceptual breakthrough: the recognition that the optimal therapeutic target is not maximal estrogen suppression, but a controlled hormonal environment capable of reducing disease activity while preserving tolerability and long-term usability. In this respect, the success of add-back therapy provides strong clinical confirmation that effective symptom control can be achieved without complete estrogen deprivation.

In uterine fibroids, the position of GnRH antagonists is now relatively well defined. Phase III data across compounds support their use as high-efficacy agents for HMB control, with rapid onset and clinically meaningful improvements in anemia and QoL. RCTs demonstrated amenorrhea rates of 34–81% at 24 weeks, with significant improvements in QoL and symptom severity scores [8,9,39,40,53].

In adenomyosis, by contrast, the role of GnRH antagonists remains exploratory. The available evidence, although limited, suggests that these agents may improve abnormal uterine bleeding, pain, and uterine volume, with pilot data showing

uterine volume reductions of approximately 32% at 24 weeks [16,17]. However, the absence of large, randomized trials represents a major limitation. At present, GnRH antagonists should be considered second-line or expert-driven options rather than standard first-line therapy.

The overall risk–benefit profile of GnRH antagonists appears favorable, particularly when they are combined with add-back therapy, which reduces hypoestrogenic adverse effects to levels approaching those observed with placebo. Nevertheless, BMD remains a key concern [39,40]. In the PRIMROSE trials, dose-dependent decreases in lumbar spine BMD of up to approximately 4% at 24 weeks were observed with full-suppression regimens, whereas this decline was attenuated to around 0%–2% with add-back therapy [40]. Although part of this BMD loss may be reversible after treatment discontinuation, incomplete recovery has been reported after prolonged exposure, especially in the absence of add-back therapy. The need for continuous or repeated treatment also highlights the importance of shared decision-making, as some patients may prioritize noninvasive symptom control, whereas others may prefer definitive surgical management [8,11].

Future priorities include a better definition of long-term safety, particularly with respect to bone health over multiple years of use, as well as comparative effectiveness studies against established alternatives, including the levonorgestrel-releasing intrauterine system and surgical approaches [8,57,74]. In adenomyosis, adequately powered randomized trials using standardized diagnostic criteria and clinically meaningful outcome measures are still needed [60–62]. GnRH antagonists have already redefined the medical management of uterine fibroids and hold considerable promise for adenomyosis. Rather than replacing existing treatments, they should be considered versatile components of a broader and individualized therapeutic strategy, allowing management to be tailored according to disease characteristics, patient preferences, and long-term goals. As further evidence becomes available, their role will likely continue to expand, with the potential to reshape the management of benign uterine disease in the years ahead [8,11,18].

A further area of clinical interest is the potential role of oral GnRH antagonists in patients with overlapping estrogen-dependent gynecologic disorders. Endometriosis frequently coexists with adenomyosis and may also be present in women with fibroids, contributing to complex symptom phenotypes in which HMB, dysmenorrhea, non-menstrual pelvic pain, infertility, and bulk-related symptoms overlap. The efficacy of oral GnRH antagonists in endometriosis-associated pain, particularly with elagolix and relugolix combination therapy, supports the broader concept that titratable suppression of ovarian steroidogenesis may be useful across multiple hormone-dependent gynecologic conditions [14]. This may be particularly relevant in patients with coexisting adenomyosis and endometriosis, in whom both uterine bleeding and pain are clinically relevant treatment targets. Nevertheless, the evidence should not be extrapolated uncritically. In fibroids, the main therapeutic endpoint is usually control of heavy menstrual bleeding; in adenomyosis, both bleeding and pain are central; whereas in endometriosis, pain control and prevention of symptom recurrence are dominant objectives. Therefore, oral GnRH antagonists may become valuable systemic options in selected women with overlapping disease phenotypes, especially when surgery is undesirable, fertility preservation is a priority, or treatment is intended as a bridge to ART or menopause. However, dedicated studies are needed to define optimal dosing, duration, add-back strategies, and long-term outcomes in these mixed phenotypes.

Over the next five years, the role of oral GnRH antagonists in benign uterine disease is likely to expand from short-term symptom control toward more structured, individualized management strategies. In uterine fibroids, these agents are expected to consolidate their position as effective medical options for moderate-to-severe HMB, particularly in women wishing to avoid or defer surgery, those requiring preoperative optimization, or patients approaching menopause. Real-world data will be essential to define optimal treatment duration, the feasibility of repeated or intermittent courses, and the impact of cost and reimbursement policies on clinical uptake [8,11].

In adenomyosis, evidence generation remains the main priority. Dedicated randomized trials using standardized ultrasound and MRI phenotyping are needed to clarify the effects of GnRH antagonists on bleeding, pain, uterine volume, QoL, and long-term outcomes. These agents may emerge as accepted second-line options for symptomatic adenomyosis, especially in women with severe symptoms or inadequate response to progestin-based therapies [18,60,62].

Future research should also refine dose-modulation and add-back strategies to optimize the balance between efficacy and long-term safety, particularly with regard to BMD and cardiometabolic outcomes [13,40]. Finally, GnRH antagonists are likely to be increasingly evaluated within multimodal and personalized treatment pathways, including sequential or combined use with progestins, intrauterine systems, minimally invasive procedures, or in patients with overlapping fibroids, adenomyosis, and endometriosis. The identification of clinical, imaging, or molecular predictors of response may allow more targeted use, improve outcomes while minimizing unnecessary exposure.

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## Declaration of interest

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## Author contributions

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**Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.**


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