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Review Article

Advancing the pharmacotherapy of endometriosis: a clinical review of newer molecular agents and therapeutic guidelines

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ABSTRACT

Endometriosis is a chronic, estrogen-responsive inflammatory disease in which long-term medical treatment is central to controlling pain and reducing the need for repeated surgery. Conventional hormonal therapies remain effective but may be limited by hypoestrogenic adverse effects, bone mineral density loss, vasomotor symptoms, or androgenic effects. This clinical review summarizes the pharmacological rationale, dosing approaches, clinical evidence, safety considerations, and current therapeutic positioning of newer agents, with particular emphasis on dienogest and the oral gonadotropin-releasing hormone (GnRH) receptor antagonists elagolix, relugolix, and linzagolix. Investigational non-hormonal approaches, including prolactin-receptor antagonism, precision peptide therapy, receptor modulators, metabolic therapies, and antiangiogenic strategies, are also discussed. The newer agents provide greater flexibility in the degree and duration of ovarian suppression and, in selected regimens, permit add-back therapy to improve tolerability and skeletal safety. Treatment selection should nevertheless be individualized according to pain severity, prior treatment response, bone health, contraindications, reproductive plans, and the regulatory status of the agent in the relevant jurisdiction.

Keywords: Endometriosis, Dienogest, GnRH antagonists, Elagolix, Relugolix, Linzagolix, Pharmacotherapy, Endometriosis-associated pain

INTRODUCTION

Endometriosis is characterized by the presence of endometrial-like tissue outside the uterine cavity and is associated with chronic pelvic pain, dysmenorrhea, deep dyspareunia, and impaired fertility. Lesions are biologically active and are associated with inflammation, neuroangiogenesis, fibrosis and estrogen-dependent proliferation.

Contemporary management emphasizes symptom control, preservation of quality of life, and avoidance of repeated procedures when effective medical therapy can provide sustained benefit. International guidance supports the use of medical treatment according to symptoms and patient preferences and does not require diagnostic laparoscopy before treatment in every patient with clinically suspected disease.[1]

Medical therapy is appropriate for patients with clinically suspected or confirmed endometriosis-associated pain, for postoperative suppression when pregnancy is not immediately desired, and for patients in whom surgery is inappropriate, carries substantial morbidity, or is unlikely to provide durable symptom control. Treatment should be individualized according to disease phenotype, symptom severity, previous response, adverse-effect profile, bone health, cardiovascular and thromboembolic risk, and reproductive plans.[1]

Traditional options include progestins, combined hormonal contraceptives, non-steroidal anti-inflammatory drugs and GnRH agonists. GnRH agonists can provide effective ovarian suppression but induce an initial gonadotropin flare and, with prolonged treatment, clinically relevant hypoestrogenic adverse effects and bone mineral density loss. Androgenic agents such as danazol are limited by an unfavorable adverse-effect profile and have largely disappeared from contemporary routine practice.[1,2]

These limitations have driven the development of agents that provide more selective or titratable suppression of estrogenic stimulation. Oral GnRH antagonists act directly at the pituitary receptor and therefore avoid the initial flare associated with GnRH agonists. Their dose-dependent pharmacology also permits different degrees of estrogen suppression, while selected fixed-dose combinations incorporate add-back therapy to improve tolerability and skeletal safety.[2]

NEWER MOLECULAR AGENTS

Dienogest

Dienogest is an oral progestin with selective progesterone-receptor activity and limited androgenic, glucocorticoid, and mineralocorticoid effects. Its therapeutic action in endometriosis is mediated by suppression of endometrial-like tissue proliferation and modulation of local inflammatory and estrogen-dependent pathways. A commonly used regimen is 2 mg orally once daily. In a randomized multicentre trial, dienogest provided pelvic pain relief comparable to leuprolide while producing fewer hypoestrogenic symptoms, supporting its role as a longer-term medical option.[3]

The principal practical advantages of dienogest are oral administration, continuous use, and an adverse-effect profile that is generally more suitable for prolonged therapy than that of profound ovarian suppression. Irregular uterine bleeding is common, particularly during the early months of treatment, and counselling regarding bleeding patterns can improve adherence. The available evidence supports its use as a maintenance option for endometriosis-associated pain and as postoperative suppressive therapy when pregnancy is not immediately planned.[1,3]

Oral GnRH receptor antagonists

Unlike GnRH agonists, oral GnRH antagonists competitively inhibit pituitary GnRH receptors and produce rapid, dose-dependent reductions in gonadotropin secretion without an initial flare. This pharmacological characteristic permits a more predictable onset of ovarian suppression and allows treatment intensity to be tailored to symptom severity and the patient's tolerance of hypoestrogenic effects.[2]

Elagolix

Elagolix is an orally active, non-peptide GnRH receptor antagonist that produces dose-dependent suppression of ovarian estradiol production. Phase III Elaris trials demonstrated clinically meaningful reductions in endometriosis-associated pain. The commonly studied regimens are 150 mg once daily for moderate pain and 200 mg twice daily for more severe pain or deep dyspareunia. The higher dose produces greater estrogen suppression and consequently carries greater restrictions related to duration and bone health.[4,5]

Treatment selection should therefore include assessment of baseline bone health and individual risk factors for bone loss. Vasomotor symptoms, headache, and changes in bone mineral density are recognized class-related adverse effects. Elagolix is most appropriately considered when symptom severity warrants greater ovarian suppression and first-line options are inadequate or not tolerated.[4,5]

Relugolix combination therapy

Relugolix is a potent oral GnRH receptor antagonist. For endometriosis-associated pain, the fixed-dose combination of relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg provides ovarian suppression together with low-dose hormonal add-back therapy. The SPIRIT 1 and SPIRIT 2 phase III trials demonstrated reductions in dysmenorrhea and non-menstrual pelvic pain, with the combination designed to mitigate the hypoestrogenic effects of GnRH antagonism and support bone health during extended treatment.[6]

The fixed-dose formulation simplifies administration and may be particularly useful for patients requiring sustained suppression. However, the estrogen-containing add-back component requires assessment of contraindications to estrogen and of cardiovascular and thromboembolic risk.[6]

Linzagolix

Linzagolix is an oral GnRH receptor antagonist evaluated in the EDELWEISS phase III development program. Its clinical value lies in the availability of different dosing strategies that permit adjustment of the degree of estrogen suppression. In the EDELWEISS 1 and EDELWEISS 3 studies, linzagolix reduced endometriosis-associated pain compared with placebo. Regimens have included 75 mg once daily without add-back therapy and higher-dose treatment, including 200 mg once daily, with add-back therapy when longer treatment is required.[7,8]

As with other GnRH antagonists, the choice of dose should consider symptom severity, duration of treatment, baseline skeletal risk, and the need for add-back therapy. The drug remains subject to regulatory and jurisdiction-specific prescribing considerations, which should be checked before clinical use.[7,8]

Investigational non-hormonal and pathogenetic therapies

Several emerging strategies aim to treat endometriosis by targeting disease biology rather than suppressing ovarian function. These approaches remain investigational and should not be presented as established alternatives to approved hormonal therapy.

HMI-115 is a fully humanized monoclonal antibody directed against the prolactin receptor. The rationale for this approach is based on evidence implicating prolactin signalling in endometriotic lesion biology and pain pathways. Early clinical development has evaluated subcutaneous administration, but its efficacy, optimal dosing, long-term safety, and ultimate clinical position require further evidence before routine use can be recommended.[9]

ENDO-205 is described as a non-hormonal precision peptide designed to act within the pathological microenvironment of endometriotic tissue. The available information identifies it as an investigational program rather than an established treatment, and its clinical efficacy and safety remain to be determined in ongoing development.[10]

Receptor modulators and other experimental approaches

Selective estrogen receptor modulators have been investigated because tissue-selective estrogen antagonism could theoretically inhibit estrogen-dependent activity in endometriotic lesions while maintaining estrogenic effects in bone. Bazedoxifene combined with conjugated estrogens has been explored in this context, although evidence remains insufficient to establish such therapy as routine endometriosis treatment.[11,12]

Selective progesterone receptor modulators have also been studied because progesterone resistance is an important feature of endometriotic lesions. Agents such as mifepristone and ulipristal acetate have demonstrated biological and symptomatic effects in clinical studies, but concerns regarding endometrial effects and the absence of a sufficiently established long-term therapeutic framework limit their routine use.[13]

Metformin has been investigated as a non-hormonal adjunct because of proposed effects on insulin signalling, aromatase expression, cellular proliferation, and inflammatory pathways. Current evidence is heterogeneous and includes substantial preclinical data; therefore, metformin should not be regarded as a standard pharmacological treatment for endometriosis-associated pain.[14]

Non-hormonal anti-inflammatory approaches, including selective cyclooxygenase-2 inhibition, may have a role in symptomatic pain control, but these agents remain adjunctive rather than disease-modifying therapies. Cabergoline has also been investigated as an antiangiogenic strategy, while broader antiangiogenic approaches have been explored experimentally. These strategies require careful consideration of adverse effects and currently do not replace established hormonal suppression.[15,16]

COMPARATIVE CLINICAL POSITIONING

The following comparison summarizes the principal characteristics of selected conventional and newer pharmacological options. Doses are those described in the reviewed literature and should not be interpreted as universally applicable prescribing instructions; duration limits, contraindications, monitoring requirements, and regulatory approvals vary by agent and jurisdiction.

Table 1: Comparative clinical positioning.

Agents	Typical regimen described	Principal pharmacological effect	Important limitations	Clinical position
Danazol	200–800 mg/day	Suppresses hypothalamic-pituitary-ovarian activity and produces an androgen-dominant state	Weight gain, acne, hirsutism, adverse lipid effects and voice changes	Largely obsolete in contemporary practice
Leuprolide acetate	3.75 mg IM monthly or 11.25 mg every 3 months	GnRH agonist with pituitary downregulation after an initial flare	Hot flushes, hypoestrogenic symptoms and bone loss	Shorter-term or selected use, often with add-back
Dienogest	2 mg orally once daily	Progestogenic suppression of endometriotic tissue activity	Irregular bleeding and other progestin-related effects	Established long-term option
Elagolix	150 mg once daily or 200 mg twice daily in studied regimens	Immediate, dose-dependent GnRH receptor antagonism	Vasomotor symptoms and bone loss, particularly at higher exposure	Option for moderate-to-severe pain with duration/monitoring constraints

Continued.

Agents	Typical regimen described	Principal pharmacological effect	Important limitations	Clinical position
Relugolix combination	Relugolix 40 mg + estradiol 1 mg + norethindrone acetate 0.5 mg once daily	GnRH antagonism with hormonal add-back	Estrogen-related contraindications and adverse effects	Long-term option for appropriately selected patients
Linzagolix	75 mg once daily without add-back; higher-dose regimens with add-back in clinical development	Dose-dependent GnRH receptor antagonism	Hypoestrogenic effects and regimen-specific duration limits	Flexible investigational/approved-use option depending on jurisdiction

PATIENT SELECTION AND PRACTICAL TREATMENT CONSIDERATIONS

For a patient requiring long-term maintenance treatment, particularly after surgery or when surgery is undesirable, a progestin such as dienogest is a reasonable established option when there are no contraindications. Patients should be counselled about expected bleeding changes and should be reviewed for treatment response and tolerability.[1,3]

For moderate-to-severe pain that persists despite first-line hormonal treatment, an oral GnRH antagonist may be considered. Elagolix provides dose-dependent suppression without a flare effect, whereas relugolix combination therapy incorporates add-back therapy in the same tablet. Linzagolix provides additional flexibility in the degree of ovarian suppression in settings where the regimen is approved and available. Selection should be based on symptom severity, bone health, treatment duration, need for add-back therapy, and contraindications.[4-8]

Before initiating a GnRH antagonist, clinicians should review reproductive plans because these agents are not contraceptive substitutes and are not appropriate during pregnancy. Baseline skeletal risk, hepatic function where relevant, cardiovascular and thromboembolic risk, concomitant medications, and the anticipated duration of treatment should be considered. Monitoring should be individualized rather than based on a single universal protocol.[4-8]

Patients with deep infiltrating disease, persistent severe pain, organ involvement, infertility concerns, or symptoms refractory to medical treatment may require multidisciplinary assessment. Pharmacological suppression can reduce symptoms but does not eliminate the need for individualized surgical or fertility planning when clinically indicated.[1]

DISCUSSION

The pharmacological management of endometriosis has moved from relatively non-selective endocrine suppression toward therapies that provide more predictable and adjustable control of estrogen-dependent disease activity. The principal clinical advance is not simply the introduction of new molecules, but the ability to match the intensity and duration of ovarian suppression to the patient's symptoms and risk profile. Dienogest provides an established continuous progestin-based strategy, while oral GnRH antagonists provide rapid suppression without the flare associated with GnRH agonists.[1-5]

Dienogest has particular relevance for long-term maintenance because randomized evidence demonstrates pain efficacy comparable to leuprolide with fewer hypoestrogenic symptoms. This balance between efficacy and tolerability makes it a useful option when prolonged suppression is required. Nevertheless, treatment response and bleeding tolerability vary between individuals, and therapy should be reviewed periodically.[3]

GnRH antagonists broaden the therapeutic range for patients with moderate-to-severe symptoms. Elagolix demonstrates the value of dose-dependent suppression, allowing a lower-intensity regimen for selected patients and a higher-intensity regimen for severe symptoms, at the cost of greater hypoestrogenic exposure and stricter duration limitations.[4,5] Relugolix combination therapy illustrates a different strategy in which ovarian suppression is paired with low-dose add-back therapy from the outset, aiming to preserve efficacy while reducing the consequences of estrogen deficiency.[6] Linzagolix similarly explores flexible suppression according to clinical need and skeletal risk.[7,8]

The evidence base for emerging non-hormonal therapies is considerably less mature. HMI-115 and ENDO-205 are scientifically attractive because they seek to modify lesion biology without conventional ovarian suppression, but they remain investigational. Similarly, receptor modulators, metformin, and antiangiogenic approaches should be distinguished from established therapies because available evidence does not yet support their routine use for endometriosis-associated pain.[9-16]

An important clinical principle is that pharmacological efficacy must be considered alongside the patient's reproductive goals and long-term safety. Endometriosis is a chronic disease, and recurrence of symptoms after discontinuation is common when treatment is suppressive rather than curative. Consequently, the most appropriate regimen is the one that provides adequate symptom control

with an adverse-effect burden acceptable to the patient and a duration that is compatible with her reproductive and skeletal health goals.[1,2]

In the Indian clinical setting, access, regulatory approval, cost, availability of add-back formulations, and local prescribing guidance are additional determinants of treatment choice. International trial evidence can inform practice, but treatment recommendations should be aligned with the current approval status and national guidance applicable to the individual patient.

CONCLUSION

The pharmacological management of endometriosis is increasingly focused on durable symptom control with a more individualized balance between efficacy and systemic safety. Dienogest represents an established long-term progestin option, while oral GnRH antagonists such as elagolix, relugolix combination therapy, and linzagolix provide rapid and adjustable suppression for patients with moderate-to-severe disease. The use of add-back therapy can improve the feasibility of longer treatment in appropriately selected patients. Investigational non-hormonal and pathogenetic therapies are expanding the therapeutic pipeline, but they require further clinical validation before they can be incorporated into routine practice. Ultimately, treatment should be individualized according to pain severity, previous response, adverse-effect risk, bone health, reproductive plans, comorbidities, patient preference, and the regulatory status of the selected therapy.

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