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ARTICLE TITLE	ORAL GONADOTROPIN-RELEASING HORMONE ANTAGONISTS IN THE MANAGEMENT OF ENDOMETRIOSIS-ASSOCIATED PAIN: A COMPREHENSIVE REVIEW OF CLINICAL EFFICACY, SAFETY AND SOCIOECONOMIC IMPACT
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ORAL GONADOTROPIN-RELEASING HORMONE ANTAGONISTS IN THE MANAGEMENT OF ENDOMETRIOSIS-ASSOCIATED PAIN: A COMPREHENSIVE REVIEW OF CLINICAL EFFICACY, SAFETY AND SOCIOECONOMIC IMPACT

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ABSTRACT

Endometriosis is a chronic, estrogen-dependent inflammatory disorder that affects approximately 10% of women of reproductive age, resulting in chronic pelvic pain and infertility. The principal clinical challenge is the management of endometriosis-associated pain (EAP), which substantially impairs quality of life and professional productivity. Conventional pharmacological treatments frequently provide inadequate relief or are constrained by significant adverse effects. Elagolix, relugolix, and linzagolix represent a newly developed class of oral non-peptide GnRH antagonists that have recently expanded the therapeutic landscape. Recent studies underscore the essential role of hormonal add-back therapy (ABT) in facilitating long-term management by preserving bone mineral density while suppressing pain. This review synthesizes current clinical data from major trials (ELARIS, SPIRIT, and SELECT) to evaluate the efficacy of these agents and examines their socio-technological impact, specifically how they reduce the socioeconomic burden of the disease and enhance patient autonomy and quality of life.

KEYWORDS

Endometriosis, GnRH Antagonists, Elagolix, Relugolix, Linzagolix, Pelvic Pain

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1. Introduction

Endometriosis is a condition where tissue similar to the endometrium grows outside of its proper place, usually within the pelvic area: in the pelvic peritoneum and ovaries (Zito et al., 2023). These lesions undergo the menstrual cycle, causing chronic inflammation, fibrosis, adhesions, and severe pain symptoms, including dysmenorrhea, non-menstrual pelvic pain (NMPP), and dyspareunia (Giudice et al., 2022). Beyond the clinical symptoms, endometriosis imposes a substantial socioeconomic burden, affecting women during their most productive years (Leyland et al., 2024).

Pharmacological management is often the first-line approach, typically involving nonsteroidal anti-inflammatory drugs (NSAIDs), combined oral contraceptives (COCs), or progestins (Simani et al., 2024). However, many patients experience progestin resistance or intolerable side effects, leading to the need for second-line options like GnRH agonists (Zito et al., 2023). While effective, GnRH agonists cause an initial "flare effect" and profound hypoestrogenism, which limits their use due to rapid bone mineral density loss and severe vasomotor symptoms (Taylor et al., 2017). Oral non-peptide GnRH antagonists have been developed to overcome these limitations by providing quick, reversible, and dose-dependent suppression of estrogen without the initial flare, offering a more tailored technological approach to patient care (Becker et al., 2022; Giudice et al., 2022).

2. Methodology

To ensure a comprehensive and rigorous synthesis of current evidence, a systematic search strategy was employed across major biomedical and technological databases, including PubMed/MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL).

The search utilized a combination of Medical Subject Headings (MeSH) terms and relevant keywords: "GnRH antagonists," "endometriosis-associated pain," "elagolix," "relugolix," "linzagolix," and "add-back therapy". Initial screening was performed based on titles and abstracts to identify Phase 3 randomized controlled trials (RCTs), long-term extension studies, and high-impact systematic reviews. Studies were

included if they reported on female patients with surgically confirmed endometriosis, evaluated the efficacy and safety of oral GnRH antagonists, and provided data on quality of life (QoL) or socioeconomic impacts.

Priority was given to the SPIRIT (relugolix), ELARIS (elagolix), and SELECT (linzagolix) trial programs as they represent the current technological frontier in pharmacological management.

To close the gap between clinical data and social science implications, secondary searches centered on "work productivity," "socioeconomic burden of endometriosis," and "patient-reported outcomes" were carried out in accordance with the journal's scope.

3. Results

Mechanism of Action

Oral GnRH antagonists provide a competitive blockade of GnRH receptors within the pituitary gland (Zito et al., 2023). In comparison to traditional agonists, they do not induce an initial surge of gonadotropins, which worsens pelvic pain. They provide an instant suppression of LH and FSH release, resulting in a swift reduction of ovarian estrogen levels (Taylor et al., 2017). This controllable suppression enables clinicians to maintain the 'therapeutic window' where estrogen levels remain between 20 to 50 pg/mL (Simani et al., 2024) which is sufficient to preserve bone mineral density while simultaneously inducing the regression of endometriotic implants (Donnez et al., 2023) Furthermore, the potential antagonism of overexpressed GnRH II receptors within the endometriotic implants suggests a localized anti-proliferative effect, independent of systemic hormonal levels (Zito et al., 2023).

As discussed above, traditional GnRH agonists require several weeks to achieve suppression of the hypothalamic–pituitary–ovarian (HPO) axis. In contrast, oral GnRH antagonists competitively and rapidly displace endogenous GnRH from pituitary receptors, resulting in immediate suppression of gonadotropin release. This targeted receptor blockade prevents the initial stimulatory surge known as the flare effect, which can transiently worsen pelvic pain. Additionally, dose-dependent titration enables maintenance of estradiol levels within a therapeutic window—low enough to promote atrophy of ectopic lesions while high enough to reduce the systemic consequences of profound hypoestrogenism, such as accelerated bone resorption (Zito et al., 2023; Taylor et al., 2017).

Clinical Efficacy of Major Oral GnRH Antagonists

a) Elagolix

Elagolix was the first oral GnRH antagonist approved by the FDA for endometriosis-associated pain. Its efficacy was established in the ELARIS I and ELARIS II phase 3 trials, which demonstrated significant, dose-dependent reductions in dysmenorrhea and NMPP over 6 months (Taylor et al., 2017). Higher doses (200 mg twice daily) showed superior pain relief compared to lower doses (150 mg once daily), though both were more effective than placebos (Taylor et al., 2017; Osuga et al., 2023). Long-term extension studies (ELARIS III, ELARIS IV) confirmed that these benefits are sustained for up to 12 months, with continued reductions in rescue analgesic and opioid use (Osuga et al., 2023).

b) Relugolix

Relugolix is typically administered as a combination therapy (Relugolix CT), containing 40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethisterone acetate in a single tablet. The SPIRIT 1 and SPIRIT 2 trials demonstrated that Relugolix CT significantly reduced dysmenorrhea in approximately 75% of participants, compared to roughly 27-30% in the placebo groups (Giudice et al., 2022). The SPIRIT open-label extension study further demonstrated that efficacy is maintained for up to 2 years, with 84.8% of patients reporting a clinically meaningful reduction in dysmenorrhea (Donnez et al., 2023). The data also confirmed that bone mineral density (BMD) remains stable through the 104-week period due to the integrated add-back therapy (Donnez et al., 2023; Giudice et al., 2022). Moreover, Relugolix CT significantly improved daily function and reduced opioid dependence among treated patients (Giudice et al., 2022).

c) Linzagolix

Linzagolix is an emerging oral GnRH antagonist that has demonstrated significant clinical efficacy in the management of endometriosis (Becker et al., 2022). The EDELWEISS and subsequent Phase 3 SELECT trial programs indicated that doses of 75 mg (without ABT) and 200 mg (with ABT) significantly reduced endometriosis-associated pain and improved health-related quality of life (Becker et al., 2022; Simani et al., 2024). A key finding from these trials was the minimal impact on bone mineral density (BMD) when using the 200 mg dose combined with add-back therapy or the lower 75 mg dose alone (Becker et al., 2022). These trials highlighted the unique potential for personalized dosing, showcasing a "tailored" medical technology

approach that allows clinicians to adjust treatment based on the severity of symptoms and individual patient contraindications to hormonal therapy (Becker et al., 2022; Zito et al., 2023).

Pharmacokinetic and Pharmacodynamic Profiling

The clinical utility of oral GnRH antagonists is fundamentally rooted in their distinct pharmacokinetic profiles, which allow for a level of precision not possible with injectable formulations.

The three primary antagonists exhibit significant differences in absorption and metabolism:

Elagolix is characterized by rapid absorption with a time to maximum concentration *Tmax* of approximately 1 hour (Taylor et al., 2017). However, its relatively short half-life of 4–6 hours necessitates twice-daily (BID) dosing to maintain the deep hormonal suppression required for severe cases, particularly at the 200 mg dose level (Osuga et al., 2023).

Relugolix exhibits a significantly longer half-life of approximately 25 hours, which supports a convenient once-daily (QD) dosing regimen, thereby improving patient adherence (Giudice et al., 2022). While its absolute bioavailability is relatively low (~12%), steady-state concentrations are reliably achieved, providing stable suppression of the HPO axis (Zito et al., 2023).

Linzagolix, with a half-life of approximately 15 hours, provides a metabolic middle ground, effectively maintaining estradiol levels within the target "threshold" of 20–60 pg/mL throughout a 24-hour cycle (Becker et al., 2022).

The Estrogen Threshold Hypothesis

A defining technological advantage of oral antagonists is the ability to achieve "partial suppression." This is based on the estrogen threshold hypothesis, which posits that endometriotic implants are more sensitive to low estrogen levels than bone tissues or the central nervous system (Simani et al., 2024). By titrating the dose, clinicians can maintain estradiol levels that are high enough to protect bone mineral density (BMD) and mitigate vasomotor symptoms, yet low enough to induce the atrophy of ectopic endometrial tissue (Donnez et al., 2023; Zito et al., 2023).

Metabolic Precision and Pharmacological Interference

As delineated by Taylor et al. (2022), the pharmacological innovation of oral GnRH antagonists introduces specific metabolic considerations. Unlike injectable agonists, small-molecule antagonists such as elagolix and relugolix are subject to extensive hepatic metabolism, which increases the risk of concomitant medication interplay.

Cytochrome P450 Integration: Elagolix acts as a weak-to-moderate inducer of CYP3A4, necessitating clinical vigilance regarding potential pharmacological interference, particularly with co-administered statins or anti-fungal agents (Taylor et al., 2022).

Transporter Mechanisms: Relugolix serves as a substrate for the P-glycoprotein (P-gp) transporter. Consequently, its bioavailability may be modulated by reciprocal xenobiotic effects when administered alongside P-gp inhibitors (Zito et al., 2023).

Detailed Analysis of Adverse Effects and Clinical Tolerability

The clinical adoption of oral GnRH antagonists is heavily dependent on their safety profile, particularly as these medications are intended for long-term chronic management. The hypoestrogenic state required to treat endometriosis symptoms inherently carries a risk of side effects that mirror the physiological changes of menopause.

a) Vasomotor Symptoms and Thermoregulation

Vasomotor symptoms, primarily hot flushes and night sweats, are the most frequently reported adverse events in clinical trials evaluating oral GnRH antagonists, including the ELARIS, SPIRIT, and SELECT programs (Simani et al., 2024). In the ELARIS I and II trials, the incidence of hot flushes was dose-dependent: 24% in the 150 mg once-daily group and 46% in the 200 mg twice-daily group, compared with 9% in the placebo group (Taylor et al., 2017).

The introduction of integrated add-back therapy (ABT) has reduced the severity and frequency of vasomotor symptoms. In the SPIRIT trials, co-administration of estradiol and norethisterone acetate was associated with a lower incidence of hot flushes compared with high-dose antagonist monotherapy, contributing to improved tolerability and lower discontinuation rates (Giudice et al., 2022).

b) Bone Mineral Density (BMD) and Long-term Skeletal Safety

Reduction in bone mineral density (BMD) is the most clinically significant long-term safety concern associated with GnRH antagonist therapy. Estradiol plays a central role in inhibiting osteoclast-mediated bone resorption; therefore, sustained suppression of estradiol may result in decreased BMD. Data from Taylor et al. (2017) demonstrated a dose-dependent decline in lumbar spine BMD after 6 months of elagolix treatment.

Long-term data from the SPIRIT program showed that when relugolix was administered in combination with add-back therapy (ABT), the mean percentage change in BMD from baseline at week 104 was −0.7% (Donnez et al., 2023). These findings indicate that combination therapy with ABT substantially mitigates bone loss during extended treatment and may reduce the risk of treatment-associated osteoporosis (Donnez et al., 2023; Zito et al., 2023). The addition of 1 mg estradiol and 0.5 mg norethisterone acetate (NETA) serves not only as a safety measure but also as an effective strategy to preserve skeletal integrity. As shown by Donnez et al. (2023), this combination prevents RANKL-mediated activation of osteoclasts that typically follows estrogen depletion. By stabilizing the bone microenvironment, ABT allows for an extension of the treatment window from a few months (typical for GnRH agonists) to several years, providing a clinically meaningful option for women requiring long-term management of endometriosis-associated pain.

c) Neuropsychiatric and Metabolic Considerations

The potential effects of GnRH antagonists on mood and metabolic parameters have also been evaluated. A small proportion of patients report symptoms such as anxiety, depressive mood, or mood fluctuations. The reported incidence is generally low (approximately 3–6%), but these effects may influence treatment tolerability in susceptible individuals (Osuga et al., 2023).

Suppression of estrogen levels may be associated with mild increases in low-density lipoprotein (LDL) cholesterol. In the ELARIS trials, these changes were observed but were not considered clinically significant for most patients (Taylor et al., 2017).

A common pharmacodynamic effect of GnRH antagonist therapy is the induction of amenorrhea or marked reduction in menstrual bleeding. In the SELECT and SPIRIT trials, 70–80% of women experienced cessation or substantial reduction of menstrual bleeding, which was associated with improvements in patient-reported quality-of-life measures (Becker et al., 2022; Donnez et al., 2023).

Discontinuation Rates and Treatment Adherence

Treatment tolerability is commonly assessed through discontinuation rates due to adverse events. In the SPIRIT 1 and 2 trials, discontinuation rates attributable to adverse events were low (less than 5% in the relugolix combination therapy group) and comparable to placebo (Giudice et al., 2022).

These findings indicate that the use of integrated add-back therapy improves overall tolerability and supports sustained treatment adherence during long-term management.

Patient-Reported Outcomes (PROs) and the De-medicalization of Care

The clinical utility of these technologies is being validated through Patient-Reported Outcomes (PROs), which also allow a more holistic approach to pain management. As per Lensen et al. (2024), the patients using oral antagonists showed a statistically significant improvement in the Work Productivity and Activity Impairment (WPAI) metrics.

Importantly, transitioning to an oral form of therapy addresses the psychological burden of invasive administration often linked with injectable agonists. Vercellini et al. (2023) indicate that patients perceive the daily oral tablets as constituting a de-medicalizing treatment, which helps in inculcating a feeling of normalcy in patients, reducing their "sick role" identification, usually experienced by women suffering from pain. This change patient perception constitutes an important social innovation, significantly supporting better therapy compliance in patients (Lensen et al., 2024; Vercellini et al., 2023).

Socioeconomic Impact and the Paradigm of Innovative Social Care

The introduction of oral GnRH antagonists represents a significant technological intervention in a landscape historically defined by high economic costs and social invisibility. Endometriosis is not merely a biological pathology; it is a social disease that disrupts the educational, professional, and personal trajectories of women (Nnoaham et al., 2011).

The Economic Burden: Direct and Indirect Costs

The global economic impact of endometriosis is staggering. In a landmark multi-country study, Nnoaham et al. (2011) demonstrated that the total cost of the disease is driven largely by productivity loss rather than direct medical expenses.

Direct costs include frequent hospitalizations, repeated laparoscopic surgeries, and long-term pharmacological management.

The quantification of indirect costs reveals a significant erosion of human capital, with women suffering from moderate-to-severe endometriosis-related distress losing approximately 10.8 hours of occupational productivity on a weekly basis (Nnoaham et al., 2011). Technological breakthroughs, specifically the commercialization of relugolix and elagolix, mitigate these fiscal losses by facilitating consistent, long-term analgesic control, thereby decreasing the clinical necessity for repetitive surgical interventions. By pivoting

the management paradigm from inpatient surgical theaters to outpatient oral regimens, these therapeutic agents effectively lower the "threshold of accessibility" to high-quality care and alleviate the aggregate strain on public health infrastructures.

The Diagnostic Delay and Cumulative Economic Attrition

A critical systemic factor identified in recent humanistic burden studies is the pervasive diagnostic delay, which averages between 7 and 11 years globally (As-Sanie et al., 2024). From a socioeconomic perspective, this delay represents a cumulative loss of human capital. During this protracted period of clinical uncertainty, patients frequently undergo sub-optimal first-line interventions, leading to a vicious cycle of medical marginalization and symptom exacerbation.

The introduction of non-invasive, oral GnRH antagonists offers a transformative solution to this systemic failure. By providing a clear, pharmacological diagnostic-therapeutic pathway, these agents reduce the reliance on "wait-and-see" approaches. Furthermore, As-Sanie et al. (2024) emphasize that the indirect costs of endometriosis are exacerbated by the unpredictable nature of flare-ups; the stability provided by oral antagonist therapy allows for improved long-term life planning and significantly mitigates the illness-related anxiety that hinders professional advancement.

Workplace Productivity

A critical focus of recent social science research is "presenteeism" - working while in significant pain, which results in reduced efficiency and increased errors. Leyland et al. (2024) highlighted that oral GnRH antagonists significantly improve workplace metrics. In the SPIRIT and ELARIS programs, participants reported a measurable decrease in days missed from work due to pelvic pain (Giudice et al., 2022; Taylor et al., 2017).

For many women, the predictability of a once-daily oral tablet (like Relugolix CT) allows for better career planning and participation in the labor market, which is essential for narrowing the gender pay gap in chronic disease management (Leyland et al., 2024).

Patient Autonomy and the Technological Empowerment

The social value of a technology is often determined by the level of autonomy it grants the user. Traditional injectable GnRH agonists require clinical visits and “lock" the patient into a state of hypoestrogenism for months at a time.

Oral antagonists can be discontinued at any time, with ovarian function returning within days (Zito et al., 2023). This provides a psychological safety net for patients, allowing them to manage their treatment in alignment with their social and reproductive goals.

In the SPIRIT trials, significant gains were observed in all domains of the Endometriosis Health Profile (EHP-30), particularly in social support and emotional well-being (Giudice et al., 2022). This suggests that effective pain management via innovative technology restores a patient’s ability to engage in social activities, reducing the isolation often caused by chronic pain.

Gender Equity and Health Policy

From a policy perspective, the adoption of oral GnRH antagonists is an investment in women's health as a pillar of social stability. By providing an effective, non-invasive alternative to surgery, these technologies empower women to maintain their social roles and economic independence. The shift toward personalized or tailored dosing, as seen with linzagolix, further enhances this by ensuring that treatment is not a "one-size-fits-all" solution but a responsive technological tool (Becker et al., 2022)

Digital Health and Future Technological Horizons

The future of endometriosis management lies at the intersection of pharmacology and digital health technologies. Current research is focusing on the identification of predictive biomarkers (e.g., microRNAs or specific inflammatory cytokines) that could determine a patient’s response to a specific GnRH antagonist before treatment begins (Zito et al., 2023). Moreover, the integration of mHealth (mobile health) applications for real-time symptom monitoring represents a significant advancement in patient care. These tools enable a precision medicine approach, allowing dose adjustments of agents like linzagolix to be made based on digitized patient-reported outcomes (PROs), thereby maximizing patient autonomy and reducing the frequency of hospital visits (Simani et al., 2024).

4. Discussion

The pharmacological transition from injectable GnRH agonists to oral GnRH antagonists represents more than a simple change in the route of administration; it signifies a paradigm shift toward personalized clinical management. The findings from the ELARIS, SPIRIT, and SELECT programs collectively suggest that the primary challenge of endometriosis—balancing the mitigation of the nociceptive burden with the preservation of skeletal integrity—has been addressed through the technological innovation of integrated add-back modalities (Taylor et al., 2017; Giudice et al., 2022; Becker et al., 2022).

A critical point of discussion is the therapeutic trajectory of the patient. Historically, the "flare effect" associated with agonists often led to a transient exacerbation of algic symptoms, potentially discouraging treatment adherence during the initial phase. In contrast, the immediate competitive blockade provided by agents like relugolix and elagolix ensures a rapid attenuation of symptoms, which is a vital factor in maintaining patient psychological resilience and trust in the medical intervention (Zito et al., 2023; Vercellini et al., 2023).

Moreover, the socioeconomic implications discussed in this review underscore the necessity of viewing endometriosis through a biopsychosocial lens. The reduction in occupational presenteeism and the stabilization of professional functionality reported by Leyland et al. (2024) suggest that the "cost-of-illness" can be significantly lowered through pharmacological precision. However, a remaining barrier is the pervasive diagnostic delay (As-Sanie et al., 2024). Future social policy must focus on integrating these innovative oral therapies earlier in the clinical pathway to prevent the cumulative loss of human capital associated with years of unmanaged pelvic distress.

5. Conclusions

The development of oral GnRH antagonists - elagolix, relugolix, and linzagolix marks a definitive era of innovation in gynaecological endocrinology. This review has synthesized evidence demonstrating that these pharmacological agents provide a highly effective, reversible, and dose-dependent suppression of the HPO axis, effectively bypassing the limitations of traditional therapies.

The integration of add-back therapy has successfully neutralized the risk of iatrogenic bone resorption, allowing for extended therapeutic windows and sustained relief from chronic clinical manifestations of endometriosis (Donnez et al., 2023).

By facilitating patient-centered autonomy and reducing the need for invasive surgical procedures, oral antagonists empower women to maintain their social capital and professional stability (Simani et al., 2024; Leyland et al., 2024).

The future of endometriosis care lies in tailored pharmacological interventions. The ability to titrate estrogen levels to the "estrogen threshold" allows for a nuanced approach that prioritizes both efficacy and long-term safety.

In conclusion, oral GnRH antagonists represent a synthesis of advanced pharmacology and social necessity. As these technologies become more accessible, they hold the potential to redefine the lived experience of millions of women, transforming endometriosis from a debilitating silent epidemic into a manageable chronic condition, thereby fostering greater biopsychosocial equity in global healthcare systems.

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