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ORAL GNRH ANTAGONISTS IN THE TREATMENT OF ENDOMETRIOSIS: EFFICACY, SAFETY, AND IMPACT ON QUALITY OF LIFE

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NARRATIVE LITERATURE REVIEW

ABSTRACT

Endometriosis is a chronic, inflammatory, estrogen-dependent gynecological disease characterized by the presence of endometrial-like tissue outside the uterine cavity and is frequently associated with chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility, leading to substantial impairment in quality of life. Although traditional hormonal therapies are widely used for symptom control, they are often limited by adverse effects, incomplete clinical response, and reduced long-term adherence. In this context, oral gonadotropin-releasing hormone (GnRH) antagonists have emerged as a promising therapeutic alternative, as they provide rapid, reversible, and dose-dependent hormonal suppression with the potential for individualized treatment. This narrative literature review aims to analyze the efficacy, safety, and impact on quality of life of oral GnRH antagonists in the treatment of endometriosis. The literature was examined using the PICo strategy, including studies published between 2017 and 2025. The evidence indicates that oral GnRH antagonists are effective in reducing endometriosis-associated pain, present a favorable safety profile when appropriately dosed, and contribute to meaningful improvements in patients' quality of life. Despite these benefits, concerns remain regarding long-term safety, bone health, and accessibility, underscoring the need for continued research.

Keywords: Endometriosis; GnRH antagonists; Hormonal therapy; Quality of life

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1 INTRODUCTION

Endometriosis is a chronic, inflammatory, estrogen-dependent condition affecting women of reproductive age and represents a major public health concern. In addition to its heterogeneous clinical presentation, commonly including dysmenorrhea, chronic pelvic pain, dyspareunia, and infertility, the disease is associated with persistent functional and psychosocial impairments that substantially affect daily life and overall well-being. Recent global estimates reinforce the magnitude of the problem, indicating a prevalence of approximately 10% among women worldwide (WORLD HEALTH ORGANIZATION, 2025).

Clinical management of endometriosis is primarily focused on symptom control and improvement of quality of life, relying largely on hormonal therapies such as combined oral contraceptives, progestins, and GnRH agonists, as well as surgical approaches when indicated. However, a significant proportion of patients experience therapeutic failure, intolerance, or symptom recurrence after treatment discontinuation, posing challenges in the management of this chronic condition. Contemporary reviews highlight limitations related to tolerability, hypoestrogenic adverse effects, and the need for more individualized treatment strategies, particularly for patients with moderate to severe pain (DONNEZ; DOLMANS, 2021; FERNANDEZ *et al*., 2023).

In recent years, oral GnRH antagonists have been introduced as an innovative option with relevant pharmacodynamic advantages, including direct blockade of the GnRH receptor, rapid suppression of gonadotropin secretion, absence of the initial flare effect, and the possibility of dose modulation (BARRETTA *et al*., 2024). Clinical trials and international guidelines have acknowledged their role in reducing endometriosis-associated pain, often positioning them as second-line options due to considerations regarding adverse effects and monitoring requirements (BECKER *et al*., 2024). Accordingly, this narrative review aims to analyze the efficacy, safety, and impact on quality of life of oral GnRH antagonists in the treatment of endometriosis.

2 METHOD

This study is a narrative literature review, a methodological approach well suited for integrating and critically discussing heterogeneous evidence on efficacy, safety, and patient-centered outcomes in chronic conditions. Narrative reviews allow the synthesis of randomized clinical trials, observational studies, guidelines, and relevant reviews, supporting an applied understanding of care, particularly in contexts characterized by variability in dosing regimens, comparators, and quality-of-life assessment tools.

The review was guided by the PICo strategy: Population (P)- women of reproductive age diagnosed with endometriosis; Interest (I)- use of oral GnRH antagonists, including monotherapy and regimens with add-back therapy when applicable; and Context (Co)- clinical management of endometriosis with a focus on efficacy (pain reduction), safety (hypoestrogenic effects and bone health), and quality of life (validated instruments and functional outcomes).

Based on this framework, the following guiding question was formulated: What is the efficacy, safety profile, and impact on quality of life of oral GnRH antagonists in the treatment of endometriosis?

The literature search prioritized evidence published between 2017 and 2025 in databases including PubMed, Scopus, Web of Science, and SciELO, combining controlled descriptors and free-text terms (e.g., endometriosis; GnRH antagonist; elagolix; relugolix; linzagolix; pelvic pain; quality of life). Articles in English, Portuguese, and Spanish were considered, including randomized controlled trials, observational studies, reviews, and clinical guidelines. Editorials, opinion pieces, duplicates, and studies not directly addressing the clinical use of oral GnRH antagonists were excluded. Following critical appraisal, the selected studies were organized into thematic axes for narrative synthesis.

3 RESULTS

The analyzed literature consistently demonstrates that oral GnRH antagonists significantly reduce endometriosis-associated pain, particularly dysmenorrhea and non-menstrual pelvic pain. Landmark trials with elagolix showed clinically meaningful improvements in pain outcomes compared with placebo, with responses observed

over months of treatment, albeit accompanied by estrogen suppression–related effects (TAYLOR *et al*., 2017). Similarly, randomized trials evaluating relugolix combination therapy reported higher response rates for pain reduction compared with placebo, supporting its role as an effective option in selected cases (GIUDICE *et al*., 2022).

Regarding safety, findings indicate a dose-dependent profile, with increased hypoestrogenic symptoms and effects on bone mineral density associated with greater estradiol suppression. The 2022 ESHRE guideline recognizes emerging evidence for elagolix, relugolix, and linzagolix and generally recommends GnRH antagonists as second-line options, given the need to balance symptomatic benefit with adverse effects (MILLER *et al*., 2024; BECKER *et al*., 2024). Longer-term follow-up data on relugolix combination therapy suggest sustained pain improvement and functional benefits for up to two years, with stabilization of bone mineral density after a modest initial decline, highlighting the role of add-back therapy in mitigating bone loss (BECKER *et al*., 2024).

In terms of quality of life, studies focusing on patient-reported outcomes demonstrate significant improvements across functional and well-being domains in parallel with pain reduction. Analyses of relugolix combination therapy show gains in functioning and quality-of-life measures using disease-specific instruments, reinforcing the importance of incorporating patient-centered outcomes into therapeutic evaluation (AS-SANIE *et al*., 2024). Recent trials of linzagolix also reported pain reduction and quality-of-life improvements, alongside dose-dependent decreases in bone mineral density, emphasizing the need for individualized dosing and monitoring (DONNEZ *et al*., 2024).

Table 1. Summary of evidence on oral GnRH antagonists in the treatment of endometriosis

Thematic axis / Therapeutic modality	Main findings (efficacy, safety, QoL)	Key evidence (author, year)
Pain reduction with oral GnRH antagonists	Oral GnRH antagonists significantly reduce endometriosis-associated pain, particularly dysmenorrhea and non-menstrual pelvic pain, with clinically meaningful responses observed during treatment.	Taylor *et al*., 2017; Giudice *et al*., 2022
Dose-dependent safety profile	Safety outcomes are dose-dependent, with greater estradiol suppression associated with increased	Becker *et al*., 2024; Miller *et al*., 2024

	hypoestrogenic symptoms and reductions in bone mineral density, requiring individualized dosing strategies.	
Role of add-back therapy	Add-back therapy mitigates hypoestrogenic effects and supports sustained symptom control, contributing to stabilization of bone mineral density during longer treatment courses.	Becker *et al*., 2024; Carballo García *et al*., 2025
Long-term efficacy and tolerability	Long-term follow-up studies demonstrate sustained pain relief and functional improvement for up to two years, with acceptable tolerability when therapy is appropriately monitored.	Becker *et al*., 2024
Quality of life improvements (QoL)	Significant improvements in quality of life and functional outcomes accompany pain reduction, as assessed by patient-reported outcome measures, reinforcing the relevance of patient-centered endpoints.	As-Sanie *et al*., 2024; Xie *et al*., 2025
Comparative evidence among oral antagonists	Elagolix, relugolix, and linzagolix show efficacy in pain reduction, with differences in safety profiles and bone density effects that highlight the importance of individualized treatment selection.	Donnez *et al*., 2024; Donnez, Dolmans, 2021
Guideline positioning and clinical role	International guidelines position oral GnRH antagonists mainly as second-line therapies, emphasizing careful patient selection, dose modulation, and monitoring of long-term safety outcomes.	Becker *et al*., 2024; Kalaitzopoulos et al., 2021
Access, cost, and health system considerations	Cost-effectiveness, eligibility criteria, and access influence real-world applicability, underscoring the need to align clinical benefits with health policy frameworks.	NICE, 2025

4. DISCUSSION

The evidence synthesized in this narrative review indicates that oral GnRH antagonists represent a relevant advancement in the pharmacological management of endometriosis by combining effective pain relief with pharmacological characteristics that allow rapid onset and predictable hormonal suppression. At the same time, contemporary discussions emphasize that their incorporation into clinical practice requires careful patient selection, dose adjustment, and monitoring of hypoestrogenic effects, particularly in longer treatment courses (BECKER *et al*., 2024; KALAITZOPOULOS *et al*., 2021). The discussion is organized into two analytical categories.

4.1 Clinical efficacy and safety profile of oral GnRH antagonists

Clinical efficacy in pain control is a robust and consistent finding, particularly for dysmenorrhea and non-menstrual pelvic pain. Trials with elagolix demonstrated

superior pain outcomes compared with placebo, supporting its therapeutic effect (TAYLOR *et al*., 2017). Likewise, relugolix combination therapy showed clinically meaningful response rates in randomized trials, sustaining its use in patients with moderate to severe symptoms requiring durable control (GIUDICE *et al*., 2022).

From a safety perspective, dose dependency is a central consideration: greater estradiol suppression is associated with higher rates of vasomotor symptoms, mood changes, and risk of bone mineral density loss. Consequently, international guidelines generally position oral GnRH antagonists as second-line options and emphasize individualized dosing and treatment duration based on risk–benefit assessment (BECKER *et al*., 2024). Trials with linzagolix further illustrate this gradient, demonstrating pain and quality-of-life improvements accompanied by dose-dependent bone density reductions (DONNEZ *et al*., 2024).

For longer-term management, add-back therapy has been explored to balance efficacy and safety. Two-year follow-up data with relugolix combination therapy suggest sustained clinical benefit with relative stabilization of bone mineral density after an initial small decline, supporting the rationale for combined regimens in selected patients (CARBALLO GARCÍA *et al*., 2025; XIE *et al*., 2025). Nonetheless, ongoing clinical surveillance, individualized fracture risk assessment, and clearer definitions of optimal treatment duration remain essential.

4.2 Impact on quality of life and implications for endometriosis management

Endometriosis exerts a broad impact on quality of life, encompassing physical limitations, emotional distress, and social and occupational impairment. Consequently, therapeutic success should not be assessed solely through hormonal or pain metrics but should also consider patient-reported outcomes. Recent studies demonstrate that relugolix combination therapy is associated with significant improvements in functioning and quality of life, including domains related to pain interference and daily activities (AS-SANIE *et al*., 2024). These findings underscore the clinical relevance of incorporating validated quality-of-life instruments into routine follow-up.

The oral route of administration and the ability to modulate dosage enhance convenience and adherence, particularly in a chronic condition requiring long-term management. Reviews emphasize that oral GnRH antagonists may represent an

important alternative to GnRH agonists, offering rapid action and greater flexibility over time, especially when combined with strategies to minimize hypoestrogenic effects (FERNANDEZ *et al*., 2023; KALAITZOPOULOS *et al*., 2021).

From a health system perspective, cost and access are critical determinants of population-level benefit. Technology appraisals, such as the NICE recommendation for relugolix–estradiol–norethisterone, highlight that effectiveness must be interpreted alongside eligibility criteria and cost-effectiveness considerations (NICE, 2025). These aspects illustrate that, beyond clinical efficacy, policy and access frameworks play a decisive role in translating therapeutic advances into real-world benefit.

5 CONCLUSION

Oral GnRH antagonists constitute a relevant innovation in the treatment of endometriosis by providing effective pain control, rapid onset of action, and pharmacological properties that allow predictable and adjustable hormonal suppression. Evidence from clinical trials supports improvements in dysmenorrhea and non-menstrual pelvic pain across different agents and regimens, including combined therapies when indicated.

Beyond clinical efficacy, available data indicate meaningful improvements in quality of life and functional outcomes, reinforcing the importance of patient-centered endpoints in endometriosis care. These findings support the role of oral GnRH antagonists as part of an individualized, woman-centered therapeutic approach.

Nevertheless, challenges remain regarding long-term safety, bone health, optimal treatment duration, and equitable access. Continued research, careful clinical judgment, and individualized risk–benefit assessment are essential to ensure the safe and effective incorporation of these agents into endometriosis management.

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