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+15878858911
editorial-office@sciformat.ca

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ORAL GnRH RECEPTOR ANTAGONISTS IN THE TREATMENT OF ENDOMETRIOSIS: CURRENT EVIDENCE AND FUTURE THERAPEUTIC PERSPECTIVES

Karolina Grodkowska-Szukala (Corresponding Author, Email: karolinagrodowska@gmail.com)
Municipal Hospital in Zabrze, Zabrze, Poland
ORCID ID: 0009-0000-6179-7242

Vanessa Gąsiorowska
Our Lady of Perpetual Help Hospital in Wołomin, Wołomin, Poland
ORCID ID: 0009-0008-2420-627X

Ewa Jachimczak
University Hospital in Krakow, Krakow, Poland
ORCID ID: 0009-0009-6899-3460

Paulina Jaruga
Regional Specialized Hospital No. 4, Bytom, Poland
ORCID ID: 0009-0009-3178-3785

Natalia Smyczyńska
SZPZLO Warsaw Praga-Północ, Warsaw, Poland
ORCID ID: 0009-0008-8213-3531

Mateusz Michalak
Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0002-5495-4670

Julia Paczyna
WSS 4 Bytom, Bytom, Poland
ORCID ID: 0009-0006-5485-7167

Ewa Wojtanowska
Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0007-4813-9473

Julia Kozicka
Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0003-8138-6231

Marcin Mazur
Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0008-2408-2107

ABSTRACT

Endometriosis is a chronic, estrogen-dependent systemic disease that significantly impairs women's quality of life and remains a major therapeutic challenge due to frequent symptom recurrence and the limitations of currently available treatments. This review aimed to summarize current evidence regarding the efficacy, safety, and clinical role of oral gonadotropin-releasing hormone (GnRH) antagonists in the management of endometriosis-associated pain. A literature search was conducted using the PubMed and Cochrane Library databases with the terms “endometriosis,” “GnRH antagonists,” “elagolix,” “relugolix,” and “linzagolix.” Relevant prospective and retrospective studies, systematic reviews, meta-analyses, and landmark publications providing essential background on the pathophysiology of endometriosis and the mechanism of action of GnRH antagonists were included. Current evidence indicates that oral GnRH antagonists provide rapid, reversible, and dose-dependent suppression of ovarian estrogen production without the initial flare effect observed with GnRH agonists. Clinical trials have demonstrated significant reductions in dysmenorrhea, non-menstrual pelvic pain, and dyspareunia, accompanied by improvements in health-related quality of life and reductions in analgesic use. The availability of different dosing strategies and add-back therapy enables individualized treatment while minimizing hypoestrogenic adverse effects, including bone mineral density loss. Despite their favorable efficacy and safety profile, treatment remains limited by high costs, the need for long-term monitoring, and the lack of direct comparisons with standard hormonal therapies. Oral GnRH antagonists represent an important advancement in the pharmacological management of endometriosis and offer a promising option for long-term individualized treatment, particularly in women with persistent symptoms or resistance to conventional hormonal therapy.

KEYWORDS

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

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Introduction

The exact prevalence of endometriosis is unknown, but estimates range from 2% to 10% in the general female population and up to 50% in women with infertility [1–3]. Defining endometriosis solely as a localized gynecological pathology resulting from the ectopic implantation of endometrial cells following retrograde menstruation is currently considered insufficient. The classical pathogenetic model does not fully reflect the complexity of this disease entity, which is characterized by significant clinical polymorphism, heterogeneity of pelvic lesions, and the occurrence of extrapelvic lesions. According to the current paradigm, endometriosis is a systemic disease. Studies indicate its ability to modulate metabolic pathways in the liver and adipose tissue and to induce a generalized inflammatory response. Furthermore, the disease has been shown to affect the central nervous system; secondary changes in gene expression in the brain correlate with the development of affective disorders and the phenomenon of central pain sensitization. This proves that the pathophysiological consequences of endometriosis extend well beyond the reproductive system [4]. Given the limited efficacy, high recurrence rates, and unacceptable safety profile of conventional methods, current therapeutic options for the long-term control of pain symptoms remain highly insufficient. This urgent, unmet clinical need prompts researchers to radically reformulate treatment strategies based on the latest pathophysiological discoveries [5]. Further research is still urgently needed to provide greater clarity on the most appropriate therapeutic options, as endometriosis significantly reduces women's quality of life [6] and generates a substantial socio-economic

burden, primarily associated with a drastic decline in patients' work productivity [7]. Pharmacotherapy of endometriosis is currently a key component of clinical management, finding application in both first-line treatment and postoperative prophylaxis. In this context, hypothalamic gonadotropin-releasing hormone (GnRH) antagonists are of particular importance. These compounds inhibit the hypothalamic-pituitary-gonadal axis, leading to pharmacological hypoestrogenism. The induced ovarian suppression effectively inhibits the progression of existing lesions, and in postoperative regimens, significantly reduces the disease recurrence rate [8]. This review summarizes the latest reports on the role of oral GnRH antagonists as an important therapeutic option, focusing on their impact on pain reduction and the long-term improvement of patients' quality of life and social functioning.

Materials and Methods

The PubMed and Cochrane Library databases were searched using the terms "endometriosis", "GnRH antagonists", "relugolix", "elagolix", and "linzagolix". Prospective and retrospective studies, systematic reviews, meta-analyses, and landmark publications relevant to the pathogenesis of endometriosis, the mechanism of action of GnRH antagonists, and their clinical application were included to provide a comprehensive overview of the topic.

Pathogenesis of Endometriosis

The pathogenesis of endometriosis is complex and multifactorial, involving interrelated genetic, hormonal, immunological, and inflammatory mechanisms in its development. Despite its benign histopathological nature, endometriosis exhibits several biological features typical of neoplastic processes, including the capacity for proliferation, tissue invasion, and the formation of foci in locations distant from their primary site of origin. The disease is widely recognized as estrogen-dependent, and increased estrogenic activity along with progesterone resistance are among the key endocrinological disorders associated with its pathogenesis. Despite the significant role of steroid hormones, the exact mechanisms through which disturbances in estrogen and progesterone signaling affect the initiation and progression of endometriosis remain a subject of intense research [4, 8, 9]. The occurrence of symptomatic endometriosis in postmenopausal women, in whom elevated estrogen concentrations are not observed, further indicates the potential involvement of mechanisms independent of classical estrogen stimulation [10]. The most widely accepted concept explaining the origin of endometriosis was the retrograde menstruation theory, proposed by Sampson. According to its premises, during menstruation, fragments of desquamated endometrial tissue can migrate through the fallopian tubes into the peritoneal cavity, where they implant, survive, and further proliferate. However, the mechanism of retrograde menstruation itself does not seem sufficient to explain the development of endometriosis, as this phenomenon occurs in a significant proportion of women, while the disease develops in only a subset of them. Consequently, it is currently accepted that the formation and progression of endometriotic lesions are conditioned by the interaction of multiple additional factors, including disturbances in the hormonal response, immune system dysregulation, chronic inflammation, the increased invasive capacity of endometrial cells, and intensified angiogenic processes [4, 8]. Significant importance in explaining the mechanisms of endometriotic lesion formation is also attributed to the theories of lymphatic and hematogenous dissemination. According to these concepts, endometrial cells can enter lymphatic or blood vessels and subsequently travel to distant locations, which may explain the occurrence of endometriotic foci outside the minor pelvis [11]. Another proposed mechanism is the involvement of stem cells. According to this hypothesis, undifferentiated cells present in the peritoneum, ovarian surface epithelial cells, and mesenchymal stem cells derived from the endometrium may differentiate towards an endometrial phenotype. This process may be related, among other factors, to the influence of menstrual blood retrograding into the peritoneal cavity and the persistent environment of chronic inflammation [4, 8, 12]. Contemporary pathogenetic models of endometriosis thus point to its multifactorial etiology, wherein the interplay of hormonal disturbances, immune response dysregulation, and chronic inflammation promotes the implantation, survival, and progression of ectopic endometrial foci. Processes of cellular proliferation, tissue invasion, and angiogenesis may also play a crucial role in the persistence of pathological lesions. The complexity of the described mechanisms indicates that none of the existing theories fully explains all aspects of the development of endometriosis, and its pathogenesis is most likely the result of the interaction of multiple interrelated biological processes. Further research into their interdependencies may contribute to a better understanding of the disease mechanisms and the identification of new diagnostic and therapeutic targets [4, 8].

Quality of Life in Patients with Endometriosis

Endometriosis is a chronic inflammatory disease whose consequences extend beyond pain symptoms and fertility disorders. The condition affects multiple aspects of women's functioning, encompassing the physical, psychological, social, and occupational spheres, leading to a significant deterioration in the quality of life. Additionally, the disease is associated with a substantial economic burden for both patients and healthcare systems, resulting from the costs of diagnosis and treatment, as well as the loss of work productivity [13–15]. One of the most important problems associated with endometriosis remains its delayed diagnosis. Diagnosing the disease is difficult due to the lack of specific biomarkers and its nonspecific clinical presentation. Although imaging studies are a vital component of the diagnostic process, their diagnostic value depends on the location and stage of the lesions, and a normal result does not exclude the presence of the disease. An additional challenge is the absence of pathognomonic symptoms, as the complaints reported by patients can also occur in the course of other gynecological and gastroenterological conditions [16]. Consequently, the time from the onset of the first symptoms to establishing the correct diagnosis often spans many years, which favors disease progression, the chronification of pain syndromes, and the deterioration of patients' quality of life [17]. The clinical presentation of endometriosis is characterized by significant heterogeneity. In some women, the disease is asymptomatic, while in others, chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, dyschezia, and fertility problems predominate. The variation in clinical manifestations and diagnostic difficulties also contribute to discrepancies regarding the estimated prevalence of endometriosis in the population and complicate the assessment of the true disease burden [16, 18, 19]. The chronic nature of the disease and persistent pain symptoms exert a significant impact on women's daily functioning. Reduced physical activity, absenteeism from work, decreased occupational performance, and difficulties in maintaining interpersonal relationships lead to deteriorated social functioning. Simultaneously, chronic pain, uncertainty related to the course of the disease, and fertility issues increase the risk of anxiety and depressive disorders [16]. The impact of the disease on sexual life also remains a significant aspect. Dyspareunia and chronic pelvic pain can lead to reduced sexual activity, lower sexual satisfaction, and deteriorated partner relationships. Consequently, endometriosis affects not only physical health but also the mental and emotional well-being of patients and their social functioning [20–22]. Since endometriosis most commonly affects women of reproductive age—i.e., during the period of greatest professional and social activity—its consequences also have an economic dimension. The disease is associated with an increased number of days of incapacity for work, decreased productivity, and high direct and indirect costs, representing a significant burden for both patients and healthcare systems [13–15]. It should be emphasized that although the symptoms of endometriosis are not always reflected in imaging results or physical examination, their impact on the daily functioning and quality of life of patients is substantial. For this reason, modern therapeutic management should focus not only on pain reduction and inhibiting disease progression but also on improving the quality of life and restoring the fullest possible functioning of women affected by endometriosis.

Mechanism of Action of GnRH Analogues in Modulating the Hypothalamic-Pituitary-Gonadal Axis

The significant impact of endometriosis on patients' quality of life underscores the need to develop effective and safe long-term treatment methods. In recent years, oral GnRH receptor antagonists have attracted particular interest, representing a promising alternative to previously used hormonal therapies. The discovery of the biochemical structure of gonadotropin-releasing hormone (GnRH) in 1971 [23] paved the way for the use of its synthetic derivatives in the treatment of hormone-dependent diseases. The efficacy of this group of pharmaceuticals stems from direct interference with the physiological hypothalamic-pituitary-gonadal (HPG) axis. Under normal conditions, the hypothalamus releases endogenous GnRH in a pulsatile manner, which stimulates specific receptors in the anterior pituitary gland to secrete gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones are essential for stimulating peripheral steroid production in the ovaries. The use of synthetic GnRH analogues aims to purposefully disrupt this pulsatile stimulation. This results in the inhibition of LH and FSH secretion, which in turn leads to a systemic decrease in estrogen concentrations [24, 25]. Despite a shared clinical goal, GnRH analogues are divided into two main categories—agonists and antagonists—which differ significantly in their pharmacodynamic profiles. The mechanism of action of traditional GnRH agonists involves rapid binding to pituitary receptors, which initially

triggers a surge in the release of gonadotropins and a secondary, transient increase in estrogen levels (a phenomenon known as the flare-up effect). Only after prolonged exposure (at least 7 days) does the down-regulation of receptors occur, blocking the HPG axis [26]. Therefore, their introduction is more complex and is associated with an initial exacerbation of pain. In response to these limitations, a new generation of drugs has been introduced into clinical practice—oral, non-peptide GnRH antagonists (e.g., elagolix, relugolix, linzagolix, and opigolix). Their specific, non-peptide biochemical structure prevents protein hydrolysis in the gastrointestinal tract, allowing injections to be replaced by convenient oral administration [27, 28]. The mechanism of action of oral antagonists is multifaceted. First, these drugs competitively and immediately block pituitary GnRH type I (GnRH I) receptors. Unlike agonists, they induce rapid suppression of LH and FSH secretion, completely bypassing the undesirable "flare" effect. Furthermore, they are characterized by a unique ability to modulate ovarian steroid secretion in a strictly dose-dependent manner—lower doses allow for partial suppression of the axis, while higher doses lead to near-complete suppression [29, 30]. Second, recent studies highlight the importance of the GnRH type II (GnRH II) isoform, which is strongly expressed in peripheral tissues, including placental cells, the ovarian granulosa layer, and the endometrium itself [31]. In the pathogenesis of endometriosis, the physiological, inhibitory action of endogenous GnRH II is disrupted, which promotes increased proliferation of ectopic endometrial cells. Oral GnRH antagonists effectively block GnRH II receptors as well, indicating that their therapeutic efficacy stems not only from a systemic reduction in estrogen levels but also from a direct, local antiproliferative effect within the pathological foci [26, 32]. This is confirmed by molecular studies demonstrating that GnRH analogues directly affect endometrial cells, rendering them more susceptible to apoptosis and inhibiting angiogenesis. This mechanism is associated with increased expression of pro-apoptotic factors (including Bax and FasL proteins) alongside a reduction in the level of the anti-apoptotic Bcl-2 protein [33]. Moreover, because elevated levels of vascular endothelial growth factor (VEGF) are observed in patients with endometriosis [34, 35], it is worth mentioning studies showing that targeting the GnRH system reduces the secretion of both interleukin 1-beta (IL-1 β) and the aforementioned VEGF in ectopic endometrial cells [36]. Although pharmacologically induced hypoestrogenism is highly effective in treating pain, GnRH antagonists are associated with bothersome complications (vasomotor symptoms, headaches, vaginal dryness) and a progressive decline in bone mineral density (BMD) [37]. To minimize these negative consequences, "add-back therapy" (ABT) has become the standard during long-term treatment with agonists [38]. This involves the controlled administration of sex hormones to maintain estradiol within a so-called therapeutic window—at a level sufficient to prevent osteopenia but not stimulating to endometriosis [37]. In this regard, oral antagonists offer a significant advantage. Because their action is dose-dependent, lower doses of the drug (e.g., elagolix or linzagolix) maintain estradiol concentrations within a safe therapeutic window, which in many cases allows for effective treatment without the need for ABT. However, in clinical protocols requiring maximum suppression of pain foci using higher doses (e.g., relugolix), the concurrent use of add-back therapy is fully justified, highly effective, and prevents bone loss [26, 39]. In conclusion, oral GnRH antagonists—due to their rapid reversibility of action, precise control of ovarian suppression, and elimination of the flare effect—are currently among the most promising, modern tools in the pharmacotherapy of endometriosis.

Elagolix

Elagolix is the first oral GnRH receptor antagonist approved by the US Food and Drug Administration (FDA) for the treatment of endometriosis-associated pain. As an oral GnRH receptor antagonist, it enables precise, reversible, and dose-dependent modulation of the hypothalamic-pituitary-gonadal axis [40]. Key evidence for the efficacy and safety of this molecule was provided by a multicenter Phase III research program comprising two double-blind, twin studies: ELARIS EM-I and ELARIS EM-II. These studies included a total of nearly 1,700 patients with moderate to severe endometriosis-associated pain. Two dosing regimens were evaluated: a lower dose (150 mg once daily) aimed at achieving partial estrogen suppression, and a higher dose (200 mg twice daily) leading to nearly complete suppression [41]. The results of the ELARIS trials clearly confirmed the high clinical efficacy of elagolix, consistent with earlier observations from Phase II studies [42]. In both pivotal trials, after 3 months of therapy, patients receiving active treatment demonstrated a statistically and clinically significant reduction in dysmenorrhea, non-menstrual pelvic pain (NMPP), and dyspareunia compared to the placebo group. A significant reduction in the need for rescue analgesics and an overall improvement in the patients' quality of life were also demonstrated. Although detailed statistical comparisons between the two doses of elagolix were not performed, women in the higher-dose group reported greater pain

reduction and more pronounced hypoestrogenic side effects than those in the lower-dose group, suggesting the possibility of individualizing these two doses to balance efficacy and hypoestrogenic effects [41]. Extension studies have shown that the achieved clinical improvement is maintained for at least 12 months of treatment [43]. Estradiol suppression with elagolix is observed within hours of the first dose and is dose-dependent, with partial suppression (median estradiol concentration ~42 pg/mL) at a daily dose of 150 mg, and maximum estradiol suppression (estradiol concentration approaching the lower limit of quantification [~12 pg/mL]) at doses of 200 mg twice daily or higher. The availability of two dosing options allows for individualized treatment based on baseline clinical factors and response to therapy. Elagolix is well tolerated, and its hypoestrogenic effects are less pronounced compared to GnRH agonists [40].

Relugolix

Relugolix is another non-peptide GnRH receptor antagonist. It was originally approved in Japan in 2019 for the treatment of symptoms associated with uterine fibroids, following a study by Osuga et al. that compared its efficacy with leuporelin injections [44]. A breakthrough in the treatment of endometriosis occurred in 2022, when the FDA approved a fixed-dose tablet taken once daily. This tablet contains 40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethisterone acetate, and is intended for the treatment of moderate to severe endometriosis-associated pain in premenopausal women, with a treatment duration of up to 24 months. What distinguishes this relugolix treatment regimen is an innovative approach to optimizing the safety profile through the standard use of integrated add-back therapy [26]. The foundation for these doses was laid by Japanese Phase II trials conducted in 101 clinical centers. Initially, a 12-week study evaluated the dose-response relationship in premenopausal women. Participants were randomly assigned to receive daily oral relugolix at doses of 10, 20, or 40 mg, placebo, or a monthly injection of 3.75 mg leuporelin acetate (a GnRH agonist). Oral relugolix reduced endometriosis-associated pain in a dose-dependent manner and was generally well tolerated [45]. A subsequent study extended the observation period to 24 weeks to assess long-term safety and efficacy. This study confirmed that relugolix (particularly at the 40 mg dose) demonstrated similar pain reduction and a comparable benefit-risk profile to leuporelin injection therapy. As expected with GnRH antagonist monotherapy, a dose-dependent loss of bone mineral density (BMD) was observed due to the induced hypoestrogenic state [46]. Conclusive evidence of the efficacy and safety of the integrated add-back regimen was provided by the landmark, global Phase III trials: SPIRIT 1 and SPIRIT 2 [47]. These studies showed that relugolix combination therapy significantly alleviated dysmenorrhea and non-menstrual pain in women with endometriosis compared with placebo. Importantly, from the perspective of long-term treatment, the addition of the add-back component effectively minimized the loss of bone mineral density (BMD) and reduced the incidence of hot flashes to levels comparable with placebo. This oral, integrated, single-tablet therapy has the potential to address an unmet clinical need in the chronic management of endometriosis, reducing the requirement for opioids or repeated surgical interventions [26, 47].

Linzagolix

Linzagolix is an oral, non-peptide GnRH receptor antagonist which, like elagolix and relugolix, acts by blocking receptors in the pituitary gland, resulting in a dose-dependent decrease in gonadotropin and estradiol production [26]. It is characterized by high bioavailability, a lack of food interactions, and a half-life of approximately 15-18 hours. These parameters allow for convenient once-daily dosing as a single tablet without concerns about significant fluctuations in the active substance concentration. Furthermore, the lack of interaction with the CYP3A4 enzymatic pathway minimizes the risk of polypharmacy, which is a significant advantage in the long-term treatment of diseases [48]. Its efficacy and safety were initially evaluated in the 24-week, randomized, pivotal EDELWEISS 3 trial [49]. Patients who completed this study were subsequently invited to participate in the prospective EDELWEISS 6 extension study, which evaluated the long-term (12-month) effects of treatment and a 6-month follow-up period after drug discontinuation. This study evaluated two main once-daily dosing regimens: a higher dose of 200 mg administered with add-back therapy (1 mg estradiol and 0.5 mg norethisterone acetate) and a lower dose of 75 mg administered as monotherapy [50]. The results of the EDELWEISS 6 study unequivocally confirmed the high long-term efficacy of both regimens. At the 12th month of therapy, the proportion of patients who reported a clinically meaningful reduction in dysmenorrhea with stable or decreased analgesic use was 91.0% in the 200 mg plus add-back group and 55.9% in the 75 mg monotherapy group. A similar trend was observed for non-menstrual pelvic pain (NMPP), with

response rates of 67.6% and 59.5%, respectively [50]. Linzagolix at both doses also induced a consistent decrease in mean daily scores for dyschezia, dyspareunia, and overall pelvic pain. This translated into a significant reduction in the need for analgesics—at month 12, over 95% of participants in both groups were not taking opioids, and patients reported substantial improvement across all dimensions of quality of life as measured by the EHP-30 questionnaire [50]. In the EDELWEISS 6 study, the loss of bone mineral density (BMD) was effectively minimized in both treatment regimens. The mean percentage change at the lumbar spine (L1-L4) from baseline to month 12 was -1.10% for both the 75 mg dose and the 200 mg + ABT regimen. Adverse events were rare, and hot flushes occurred in less than 1% of patients. In addition, it was demonstrated that some clinical improvement is maintained for several months after complete cessation of treatment [50]. From a clinical perspective, the 200 mg regimen with add-back therapy is an effective alternative in cases where traditional estrogen-progestin or progestin therapy is ineffective. Conversely, the 75 mg monotherapy without add-back therapy offers a documented, long-term treatment option for women in whom concurrent hormonal therapy is contraindicated [50].

Discussion

The introduction of oral, non-peptide GnRH antagonists expands the possibilities of endometriosis pharmacotherapy, characterized by a different pharmacokinetic profile compared to classical agonists. These drugs are distinguished by high oral bioavailability, the absence of an initial gonadotropin surge (flare-up), and a relatively short half-life. This latter property ensures rapid reversal of hormonal suppression and restoration of hypothalamic-pituitary-ovarian axis function following drug discontinuation [8, 26]. Furthermore, the dose-dependent degree of estradiol inhibition allows for dose titration to achieve partial hormonal suppression [26]. The use of this drug class, however, is associated with documented clinical and metabolic limitations. Clinical studies have shown that elagolix therapy induces adverse changes in the lipid profile, including a statistically significant increase in total cholesterol, LDL, HDL, and triglyceride levels, which requires close monitoring [8]. Fertility control also remains a significant challenge. In contrast to traditional hormonal contraceptive methods, GnRH antagonists in regimens combined with add-back therapy do not consistently inhibit ovulation in all patients. In the SPIRIT 1 and SPIRIT 2 trials, a total of six pregnancies were reported among women using relugolix combination therapy, which necessitates the use of additional barrier contraceptive methods [51]. Moreover, Wang et al. emphasize the need to assess the risk of malignant transformation with the long-term use of GnRH antagonists, which is associated with the persistent, slow proliferation of residual endometriotic foci [26]. The primary factor limiting the widespread use of oral GnRH antagonists is economic barriers. The costs of pharmacotherapy in this group are many times higher than those of commonly used first-line drugs. Compared to traditional progestin therapy, the use of newer drugs is associated with significantly lower cost-effectiveness, which currently constitutes one of the main challenges in providing patients with broader access to this modern treatment [8, 51]. Methodologically, Othman et al. point out a significant gap in pre-registration studies. Phase III programs to date (including studies on relugolix) have relied on comparing the drug with placebo or injectable GnRH agonists. There is a lack of randomized head-to-head trials in the literature with an active comparator in the form of standard oral contraceptive pills or progestins, which prevents an objective verification of their superiority over the most inexpensive and most frequently used conservative treatment [51]. Furthermore, when evaluating the broader implications of endometriosis management, it is crucial to address the profound challenges associated with the patients' reduced quality of life [16]. As previously highlighted, the chronic nature of endometriosis—marked by debilitating pelvic pain, emotional distress, and substantial limitations in both daily and professional spheres—often results in severe psychological fatigue [16, 19]. This complex burden can negatively impact therapeutic compliance and overall treatment outcomes. Therefore, the introduction of modern pharmacotherapy, such as oral GnRH antagonists, should not be viewed in isolation. While these agents demonstrate high efficacy in alleviating the physical symptoms of the disease, achieving optimal long-term outcomes requires a multidisciplinary approach. Integrating advanced pharmacological treatments with targeted psychological support, physical rehabilitation, and individualized patient education is essential [6, 16]. Addressing the multifaceted psychosocial dimensions of endometriosis not only maximizes the clinical benefits of medical interventions but also facilitates the comprehensive restoration of the patients' social and occupational functioning [14, 19].

Conclusions

Oral GnRH antagonists represent an innovative and effective alternative for the long-term, conservative treatment of endometriosis-associated pain, particularly in patients resistant to standard hormonal therapy. Recent studies confirm their high efficacy in reducing pelvic pain, dysmenorrhea, and dyspareunia, while offering a convenient oral route of administration and eliminating the problem of the initial flare effect. However, their use requires an individualized clinical approach taking into account the adverse impact on the lipid profile, high therapy costs, and the need to monitor patients for bone mineral density—while simultaneously considering the implementation of add-back therapy. Ultimately, the overarching goal of modern endometriosis management extends beyond mere symptom control; it must encompass the holistic rehabilitation of the patient. The successful integration of these novel therapies depends on a careful balance between maximizing clinical benefits and minimizing adverse effects, thereby ensuring that patients can regain control over their physical, emotional, and professional lives.

REFERENCES

1. Eskenazi, B., & Warner, M. L. (1997). Epidemiology of endometriosis. *Obstetrics and gynecology clinics of North America*, 24(2), 235–258. [https://doi.org/10.1016/s0889-8545\(05\)70302-8](https://doi.org/10.1016/s0889-8545(05)70302-8)
2. Meuleman, C., Vandenabeele, B., Fieuws, S., Spiessens, C., Timmerman, D., & D’Hooghe, T. (2009). High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. *Fertility and Sterility*, 92(1), 68–74. <https://doi.org/10.1016/j.fertnstert.2008.04.056>
3. Zondervan, K. T., Becker, C. M., & Missmer, S. A. (2020). Endometriosis. *The New England Journal of Medicine*, 382(13), 1244–1256. <https://doi.org/10.1056/NEJMr1810764>
4. Taylor, H. S., Kotlyar, A. M., & Flores, V. A. (2021). Endometriosis is a chronic systemic disease: Clinical challenges and novel innovations. *The Lancet*, 397(10276), 839–852. [https://doi.org/10.1016/S0140-6736\(21\)00389-5](https://doi.org/10.1016/S0140-6736(21)00389-5)
5. Saunders, P. T. K., & Horne, A. W. (2021). Endometriosis: Etiology, pathobiology, and therapeutic prospects. *Cell*, 184(11), 2807–2824. <https://doi.org/10.1016/j.cell.2021.04.041>
6. Baczek, G., Mietus, M., Klimanek, J., Tataj-Puzyna, U., Sienkiewicz, Z., Dykowska, G., Duda-Zalewska, A., & Teliga-Czajkowska, J. (2024). The impact of endometriosis on the quality of women's life. *Ginekologia polska*, 95(5), 356–364. <https://doi.org/10.5603/gpl.93995>
7. Tewhaiti-Smith, J., Gannott, M., Semprini, A., et al. (2025). The cost of endometriosis and chronic pelvic pain burden in New Zealand (Aotearoa): Results from a nationwide survey. *Women*, 5(4), Article 47. <https://doi.org/10.3390/women5040047>
8. Rzewuska, A. M., Żybowska, M., Sajkiewicz, I., Spiechowicz, I., Żak, K., Abramiuk, M., Kułak, K., & Tarkowski, R. (2023). Gonadotropin-Releasing Hormone Antagonists-A New Hope in Endometriosis Treatment?. *Journal of clinical medicine*, 12(3), 1008. <https://doi.org/10.3390/jcm12031008>
9. Velasco, I., Rueda, J., & Acién, P. (2006). Aromatase expression in endometriotic tissues and cell cultures of patients with endometriosis. *Molecular Human Reproduction*, 12(6), 377–381. <https://doi.org/10.1093/molehr/gal041>
10. de Almeida Asencio, F., Ribeiro, H. A., Ayrosa Ribeiro, P., Malzoni, M., Adamyan, L., Ussia, A., Gomel, V., Martin, D. C., & Koninckx, P. R. (2019). Symptomatic endometriosis developing several years after menopause in the absence of increased circulating estrogen concentrations: a systematic review and seven case reports. *Gynecological Surgery*, 16(1). <https://doi.org/10.1186/s10397-019-1056-x>
11. Jerman, L. F., & Hey-Cunningham, A. J. (2015). The role of the lymphatic system in endometriosis: A comprehensive review of the literature. *Biology of Reproduction*, 92(3), Article 64. <https://doi.org/10.1095/biolreprod.114.124313>

12. Gargett, C. E., Schwab, K. E., & Deane, J. A. (2016). Endometrial stem/progenitor cells: The first 10 years. *Human Reproduction Update*, 22(2), 137–163. <https://doi.org/10.1093/humupd/dmv051>
13. Soliman, A. M., Yang, H., Du, E. X., Kelley, C., & Winkel, C. (2016). The direct and indirect costs associated with endometriosis: A systematic literature review. *Human Reproduction*, 31(4), 712–722. <https://doi.org/10.1093/humrep/dev335>
14. Mundo-López, A., Ocón-Hernández, O., Lozano-Lozano, M., San-Sebastián, A., Fernández-Lao, C., Galiano-Castillo, N., Cantarero-Villanueva, I., Arroyo-Morales, M., & Artacho-Cordón, F. (2021). Impact of symptom burden on work performance status in Spanish women diagnosed with endometriosis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 261, 92–97. <https://doi.org/10.1016/j.ejogrb.2021.04.008>
15. Darbà, J., & Marsà, A. (2022). Economic implications of endometriosis: A review. *Pharmacoeconomics*, 40(12), 1143–1158. <https://doi.org/10.1007/s40273-022-01211-0>
16. Maulenkul, T., Kuandyk, A., Makhadiyeva, D., Dautova, A., Terzic, M., Oshibayeva, A., Moldaliyev, I., Ayazbekov, A., Maimakov, T., Saruarov, Y., Foster, F., & Sarria-Santamera, A. (2024). Understanding the impact of endometriosis on women's life: an integrative review of systematic reviews. *BMC Women's Health*, 24(1). <https://doi.org/10.1186/s12905-024-03369-5>
17. Ballard, K., Lowton, K., & Wright, J. (2006). What's the delay? A qualitative study of women's experiences of reaching a diagnosis of endometriosis. *Fertility and Sterility*, 86(5), 1296–1301. <https://doi.org/10.1016/j.fertnstert.2006.04.054>
18. Sarria-Santamera, A., Orazumbekova, B., Terzic, M., Issanov, A., Chaowen, C., & Asúnsolo-del-Barco, A. (2020). Systematic Review and Meta-Analysis of Incidence and Prevalence of Endometriosis. *Healthcare*, 9(1), 29. <https://doi.org/10.3390/healthcare9010029>
19. Nnoaham, K. E., Hummelshoj, L., Webster, P., d'Hooghe, T., de Cicco Nardone, F., de Cicco Nardone, C., Jenkinson, C., Kennedy, S. H., & Zondervan, K. T. (2011). Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertility and Sterility*, 96(2), 366-373.e8. <https://doi.org/10.1016/j.fertnstert.2011.05.090>
20. Buster, J. E. (2013). Managing female sexual dysfunction. *Fertility and Sterility*, 100(4), 905–915. <https://doi.org/10.1016/j.fertnstert.2013.08.026>
21. Montanari, G., Di Donato, N., Benfenati, A., Giovanardi, G., Zannoni, L., Vicenzi, C., Solfrini, S., Mignemi, G., Villa, G., Mabrouk, M., Schioppa, C., Venturoli, S., & Seracchioli, R. (2013). Women with Deep Infiltrating Endometriosis: Sexual Satisfaction, Desire, Orgasm, and Pelvic Problem Interference with Sex. *The Journal of Sexual Medicine*, 10(6), 1559–1566. <https://doi.org/10.1111/jsm.12133>
22. Jia, S., Leng, J., Sun, P., & Lang, J. (2013). Prevalence and Associated Factors of Female Sexual Dysfunction in Women With Endometriosis. *Obstetrics & Gynecology*, 121(3), 601–606. <https://doi.org/10.1097/aog.0b013e3182835777>
23. Matsuo, H., Baba, Y., Nair, R. M. G., Arimura, A., & Schally, A. V. (1971). Structure of the porcine LH- and FSH-releasing hormone. I. The proposed amino acid sequence. *Biochemical and Biophysical Research Communications*, 43(6), 1334–1339. [https://doi.org/10.1016/S0006-291X\(71\)80019-0](https://doi.org/10.1016/S0006-291X(71)80019-0)
24. Ortmann, O., Weiss, J., & Diedrich, K. (2002). Gonadotrophin-releasing hormone (GnRH) and GnRH agonists: Mechanisms of action. *Reproductive BioMedicine Online*, 5, 1–7. [https://doi.org/10.1016/S1472-6483\(11\)60210-1](https://doi.org/10.1016/S1472-6483(11)60210-1)
25. Tsutsumi, R., & Webster, N. J. G. (2009). GnRH pulsatility, the pituitary response and reproductive dysfunction. *Endocrine Journal*, 56(6), 729–737. <https://doi.org/10.1507/endocrj.K09E-185>
26. Wang, J. Y., Zhang, Y., & Ding, J. (2025). Oral gonadotropin-releasing hormone antagonists in the treatment of endometriosis: Advances in research. *Journal of Clinical Medicine Research*, 17(6), 299–308. <https://doi.org/10.14740/jocmr6236>
27. Donnez, J., & Dolmans, M. M. (2021). Endometriosis and medical therapy: From progestogens to progesterone resistance to GnRH antagonists: A review. *Journal of Clinical Medicine*, 10(5), Article 1085. <https://doi.org/10.3390/jcm10051085>

28. Clemenza, S., Sorbi, F., Noci, I., Capezzuoli, T., Turrini, I., Carriero, C., Buffi, N., Fambrini, M., & Petraglia, F. (2018). From pathogenesis to clinical practice: Emerging medical treatments for endometriosis. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 51, 92–101. <https://doi.org/10.1016/j.bpobgyn.2018.01.021>
29. Donnez, J., Taylor, R. N., & Taylor, H. S. (2017). Partial suppression of estradiol: A new strategy in endometriosis management? *Fertility and Sterility*, 107(3), 568–570. <https://doi.org/10.1016/j.fertnstert.2017.01.013>
30. Ali, M., Raslan, M., Ciebiera, M., Zaręba, K., & Al-Hendy, A. (2021). Current approaches to overcome the side effects of GnRH analogs in the treatment of patients with uterine fibroids. *Expert Opinion on Drug Safety*, 21(4), 477–486. <https://doi.org/10.1080/14740338.2022.1989409>
31. Neill, J. D. (2002). Minireview: GnRH and GnRH receptor genes in the human genome. *Endocrinology*, 143(3), 737–743. <https://doi.org/10.1210/endo.143.3.8705>
32. Gründker, C., Günthert, A. R., Millar, R. P., & Emons, G. (2002). Expression of gonadotropin-releasing hormone II (GnRH-II) receptor in human endometrial and ovarian cancer cells and effects of GnRH-II on tumor cell proliferation. *The Journal of Clinical Endocrinology & Metabolism*, 87(3), 1427–1430. <https://doi.org/10.1210/jcem.87.3.8437>
33. Kim, K. Y., Choi, K. C., Auersperg, N., & Leung, P. C. K. (2006). Mechanism of gonadotropin-releasing hormone (GnRH)-I and -II-induced cell growth inhibition in ovarian cancer cells: Role of the GnRH-I receptor and protein kinase C pathway. *Endocrine-Related Cancer*, 13(1), 211–220. <https://doi.org/10.1677/ERC.1.01033>
34. Donnez, J., Smoes, P., Gillerot, S., Casanas-Roux, F., & Nisolle, M. (1998). Vascular endothelial growth factor (VEGF) in endometriosis. *Human Reproduction*, 13(6), 1686–1690. <https://doi.org/10.1093/humrep/13.6.1686>
35. McLaren, J. (2000). Vascular endothelial growth factor and endometriotic angiogenesis. *Human Reproduction Update*, 6(1), 45–55. <https://doi.org/10.1093/humupd/6.1.45>
36. Meresman, G. F. (2003). Effect of GnRH analogues on apoptosis and release of interleukin-1 and vascular endothelial growth factor in endometrial cell cultures from patients with endometriosis. *Human Reproduction*, 18(9), 1767–1771. <https://doi.org/10.1093/humrep/deg356>
37. Gargiulo, A., & Hornstein, M. (1997). The role of GnRH agonists plus add-back therapy in the treatment of endometriosis. *Seminars in Reproductive Medicine*, 15(3), 273–284. <https://doi.org/10.1055/s-2008-1068757>
38. Wang, Y. Q., Zhang, S. F., Chen, X., et al. (2009). Effects and safety of gonadotrophin-releasing hormone agonist combined with estradiol patch and oral medroxyprogesterone acetate on endometriosis. *Zhonghua Fu Chan Ke Za Zhi*, 44(7), 504–508.
39. Donnez, J., & Dolmans, M. M. (2021). GnRH antagonists with or without add-back therapy: A new alternative in the management of endometriosis? *International Journal of Molecular Sciences*, 22(21), Article 11342. <https://doi.org/10.3390/ijms222111342>
40. Leyland, N., Estes, S. J., Lessey, B. A., Advincula, A. P., & Taylor, H. S. (2021). A clinician's guide to the treatment of endometriosis with elagolix. *Journal of Women's Health*, 30(4), 569–578. <https://doi.org/10.1089/jwh.2019.8096>
41. Taylor, H. S., Giudice, L. C., Lessey, B. A., Abrao, M. S., Kotarski, J., Archer, D. F., Diamond, M. P., Surrey, E., Johnson, N. P., Watts, N. B., Gallagher, J. C., Simon, J. A., Carr, B. R., Dmowski, W. P., Leyland, N., Rowan, J. P., Duan, W. R., Ng, J., Schwefel, B., ... Chwalisz, K. (2017). Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *New England Journal of Medicine*, 377(1), 28–40. <https://doi.org/10.1056/nejmoa1700089>
42. Diamond, M. P., Carr, B., Dmowski, W. P., Koltun, W., O'Brien, C., Jiang, P., Burke, J., Jimenez, R., Garner, E., & Chwalisz, K. (2014). Elagolix Treatment for Endometriosis-Associated Pain: Results from a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study. *Reproductive Sciences*, 21(3), 363–371. <https://doi.org/10.1177/1933719113497292>
43. Surrey, E., Taylor, H. S., Giudice, L., Lessey, B. A., Abrao, M. S., Archer, D. F., Diamond, M. P., Johnson, N. P., Watts, N. B., Gallagher, J. C., Simon, J. A., Carr, B. R., Dmowski, W. P., Leyland, N., Singh, S. S., Rechberger, T., Agarwal, S. K., Duan, W. R., Schwefel, B., ... Chwalisz, K. (2018). Long-Term Outcomes of Elagolix in Women With Endometriosis. *Obstetrics & Gynecology*, 132(1), 147–160. <https://doi.org/10.1097/aog.0000000000002675>

44. Osuga, Y., Enya, K., Kudou, K., Tanimoto, M., & Hoshiai, H. (2019). Oral gonadotropin-releasing hormone antagonist relugolix compared with leuprorelin injections for uterine leiomyomas. *Obstetrics & Gynecology*, 133(3), 423–433. <https://doi.org/10.1097/AOG.00000000000003141>
45. Osuga, Y., Seki, Y., Tanimoto, M., Kusumoto, T., Kudou, K., & Terakawa, N. (2021). Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain in a dose-response manner: A randomized, double-blind, placebo-controlled study. *Fertility and Sterility*, 115(2), 397–405. <https://doi.org/10.1016/j.fertnstert.2020.07.055>
46. Osuga, Y., Seki, Y., Tanimoto, M., Kusumoto, T., Kudou, K., & Terakawa, N. (2021). Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, in women with endometriosis-associated pain: Phase 2 safety and efficacy 24-week results. *BMC Women's Health*, 21(1). <https://doi.org/10.1186/s12905-021-01393-3>
47. Giudice, L. C., As-Sanie, S., Arjona Ferreira, J. C., et al. (2022). Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: Two replicate phase 3, randomised, double-blind, studies (SPIRIT 1 and 2). *The Lancet*, 399(10343), 2267–2279. [https://doi.org/10.1016/S0140-6736\(22\)00622-5](https://doi.org/10.1016/S0140-6736(22)00622-5)
48. Paszkowski, T. (2025). Linzagolix—New perspectives in the pharmacotherapeutic management of uterine fibroids and endometriosis. *Prz Menopauzalny*, 24(2), 126–130. <https://doi.org/10.5114/pm.2025.152947>
49. Donnez, J., Taylor, H. S., Taylor, R. N., Akin, M. D., Tatarchuk, T. F., Wilk, K., Gotteland, J.-P., Lecomte, V., & Bestel, E. (2020). Treatment of endometriosis-associated pain with linzagolix, an oral gonadotropin-releasing hormone–antagonist: a randomized clinical trial. *Fertility and Sterility*, 114(1), 44–55. <https://doi.org/10.1016/j.fertnstert.2020.02.114>
50. Donnez, J., Becker, C. M., Petraglia, F., Horne, A. W., Becker, S., Renner, S. P., Carmona Herrera, F., Taylor, H. S., Paszkowski, M., Bestel, E., Hori, S., & Dolmans, M.-M. (2026). Linzagolix, with and without add-back therapy, in women with endometriosis-associated pain: results from EDELWEISS 6, a double-blind randomized extension and withdrawal study. *Human Reproduction Open*, 2026(2). <https://doi.org/10.1093/hropen/hoag030>
51. Othman, E., Al-Hendy, A., Mostafa, R., Lambalk, C., & Mijatovic, V. (2024). Oral GnRH antagonists in combination with estradiol and norethindrone acetate for pain relief associated with endometriosis: A review of evidence of a novel class of hormonal agents. *International Journal of Women's Health*, 16, 309–321. <https://doi.org/10.2147/IJWH.S442357>