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REVIEW

A review of phase II and III drugs for the treatment and management of endometriosis

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ABSTRACT

Introduction: Endometriosis is an estrogen-dependent disease that gives rise to pelvic pain and infertility. Although estroprogestins and progestins currently stand as the first-line treatments for this condition, demonstrating efficacy in two-thirds of patients, a significant portion of individuals experience only partial relief or symptom recurrence following the cessation of these therapies. The coexistence of superficial, deep endometriosis, and ovarian endometriomas, as three distinct phenotypes with unique pathogenetic and molecular characteristics, may elucidate the current heterogeneous biological response to available therapy.

Areas Covered: The objective of this review is to furnish the reader with a comprehensive summary pertaining to phase II-III hormonal treatments for endometriosis.

Expert Opinion: Ongoing research endeavors are directed toward the development of novel hormonal options for this benign yet debilitating disease. Among them, oral GnRH antagonists emerge as a noteworthy option, furnishing rapid therapeutic onset without an initial flare-up; these drugs facilitate partial or complete estrogen suppression, and promote prompt ovarian function recovery upon discontinuation, effectively surmounting the limitations associated with previously employed GnRH agonists. Limited evidence supports the use of selective estrogen and progesterone receptor modulators. Consequently, further extensive clinical research is imperative to garner a more profound understanding of innovative targets for novel hormonal options.

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Endometriosis; hormonal treatments; gonadotropin-releasing hormone antagonists; SERM; SPRM; progestins; medical therapy; aromatase inhibitors

1. Introduction

Endometriosis is a chronic, estrogen-dependent disorder characterized by the ectopic presence of endometriotic glands and stroma beyond the confines of the uterine cavity. Primarily affecting up to 10–18% of women in their reproductive years, this benign yet debilitating condition can also be diagnosed in postmenopausal women [1,2].

The exact etiology of endometriosis remains uncertain, with a complex interplay of factors contributing to the development of this benign chronic disease; multiple abnormalities of the immune system, genetic factors, and environmental influences are believed to influence women's susceptibility to endometriosis [3]. While endometriosis can be asymptomatic, it most commonly presents with distressing pain symptoms and/or infertility, significantly impacting affected women's quality of life (QoL) [4]. Presently, there is a growing awareness that peritoneal nodules, ovarian endometriomas, or nodules of deep endometriosis represent three distinct phenotypes of endometriosis, each with unique clinical, pathogenetic, and molecular characteristics. In this complex scenario, these phenotypes of endometriosis often coexist in the same patient, leading to an intricate pathogenic overlapping [5]. Overall, the diverse anatomical sites affected by endometriosis contribute to the wide range of symptoms experienced by individuals, necessitating comprehensive evaluation and tailored management strategies [6–8].

The primary objective of surgical intervention for endometriosis is to restore normal anatomy by effectively removing endometriotic lesions and conducting thorough pelvic adhesiolysis. However, surgical procedures, especially in cases of deep endometriosis, present significant challenges for gynecologists [9]. This complexity is further compounded by the potential occurrence of rare, yet notable, complications involving the urological, intestinal, neurological, and vascular systems [10]. Furthermore, there is a potential recurrence risk of pain despite the efforts of conservative surgery for

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Article highlights

- Standard first-line treatments for pain related to endometriosis involve the use of low-dose combined estro-progestins and progestins, which prove effective in approximately two-thirds of affected women.
- The current second-line therapy for endometriosis is centered around GnRH agonists. However, due to their undesirable tolerability profile resulting from induced sustained hypoestrogenism, their use should be limited to a specific period and combined with an appropriate add-back therapy.
- In recent years, there has been a growing interest in the use of GnRH antagonists for endometriosis therapy, with the majority of phase II and III trials being organized.
- The primary benefits of oral GnRH antagonists encompass estrogen suppression dependent on the dosage, rapid restoration of hormone secretion once treatment concludes, and prevention of the flare-up effect.
- Nevertheless, data on their efficacy and safety remain limited. Additionally, they are associated with considerable costs, and at higher dosages, the induced hypoestrogenism may necessitate the use of add-back therapy, akin to the approach with GnRH agonists.
- Current limited and low-quality evidence supports the use of SERMs and SPRMs for endometriosis treatment.

endometriosis [11]. While surgical intervention is essential for specific severe cases (ureteral stenosis, bowel occlusion, or ovarian cysts with malignant features), the initial therapeutic approach for the majority of patients suffering from endometriosis-related pain is predominantly focused on medical management, which is mainly based on hormonal therapies [12]. The aim of long-term medical therapy for endometriosis is to alleviate pain symptoms for women who prefer to delay or avoid surgical intervention [13];

Furthermore, a recent emerging concept involves the implementation of a secondary prevention strategy through the timely initiation of pharmacological long-term menstrual suppression using hormonal therapies upon clinical suspicion or imaging evidence of diseases during the early postmenarchal years. This approach aims to alleviate symptoms, prevent lesion progression, and preserve future reproductive potential [14]. Lastly, it has been repeatedly demonstrated that lesion and symptom recurrence after surgery is substantially higher in women who undergo postoperative expectant management compared with those who use postoperative medical treatment [15]; therefore, medical therapy can be started after the surgical approach aiming to reduce the risk of disease recurrence [16]. The selection of the most appropriate therapy depends on factors such as pain severity, age, fertility goals, financial considerations, route of administration, and the impact of endometriosis on work productivity, sexual function, and overall QoL [17].

While endometriosis displays considerable heterogeneity in lesions, resulting in diverse biological responses to medical therapy [3], and considering the current limitations in the design of trials investigating this condition [18], numerous compounds have been explored for the treatment of endometriosis.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as a non-hormonal primary symptomatic therapy for managing pelvic pain and dysmenorrhea [19]; however, their efficacy lacks strong evidence, and no specific NSAID is proven superior for pain related to endometriosis [20]. Combined hormonal estro-progestins and progestins are considered first-line medical therapies for women affected, and they are frequently initiated empirically even in the absence of a confirmed surgical diagnosis [21]. Gonadotropin-releasing hormone (GnRH) agonists have been utilized as second-line medical options for treating endometriosis patients for the past 30 years; these drugs, nevertheless, are characterized by the onset of adverse events (AEs) associated with sustained estrogen deprivation [22]; consequently, it is suggested to establish a definitive diagnosis of endometriosis prior to commencing the use of such drugs to carefully assess the balance between benefits and risks within this drug class.

It is widely recognized that the development, maintenance, and progression of endometriosis are influenced by a multitude of aberrant mechanisms, such as dysregulated cell proliferation, compromised immune function, impaired apoptosis, enhanced invasive capacity, and abnormal angiogenesis [3]. Investigating these intricate pathways offers promising avenues for the development of novel therapeutic strategies (Table 1). Among emerging investigational drug classes for endometriosis therapy, most studies in recent years have focused on GnRH antagonists. This comprehensive review aims to provide a concise summary of recent advancements related to drugs under late clinical study (phase II and III) for the treatment and management of endometriosis.

2. Current hormonal options

2.1. First-line medical options: combined estro-progestins and progestins

The inhibition of ovulation is regarded as the most important mechanism underlying the contraceptive efficacy of combined estro-progestins and progestins; in fact, these drugs exert inhibitory effects on ovarian estradiol (E_2) secretion, ovulation, and progesterone production by having an anti-gonadotrophic activity. These compounds reduce menstrual flow and cause a decidualization of endometriotic implants, enhancing apoptosis and inhibiting cells proliferation [23]. Previous research has revealed that progestins possess additional direct anti-inflammatory properties on endometriotic implants [24,25].

The introduction of combined estro-progestins can be dated back approximately six decades with the approval of the first combined oral contraceptive (COC), which consisted of a combination of mestranol and norethynodrel [26]. The subsequent evolution of COCs has comprehended the predominant use of ethinylestradiol (EE), a synthetic estrogen molecule. Furthermore, there has been a progressive reduction in the dosage of EE (to 15 µg), followed by the recent introduction of estradiol (E_2), which is the natural estrogen produced by the human ovary (micronized E_2; E_2 valerate) [27]. Across the years, a plethora of progestins from distinct generations have been utilized aiming to tailor contraception to the individual needs of women [28]. Indeed, a notable progression in the development of combined estro-progestins has been the

Table 1. Current and investigational hormonal drugs of the treatment of endometriosis.

Drug class	Advantages	Disadvantages
Estroprogestins	• First-line therapy • Not expensive • Low rates of AEs • Multiple route of administration available	• Between one-fourth and one-third of patients treated do not respond to them
Progestins	• First-line therapy • Not expensive • Lower thrombotic risk • Low rates of AEs • Multiple route of administration available	• Only some progestins approved for contraception purpose (desogestrel, etonorgestrel-subdermal implant and levonorgestrel-intrauterine system) • Between one-fourth and one-third of patients treated do not respond to them
Gn-RH agonists	• Secondary-line therapy (efficacious in treating patients who did not respond to estroprogestins or progestins)	• Not oral administration (subcutaneous) • Expensive • High rate of AEs (estrogen-related)
Gn-RH antagonists	• Oral administration • No flare-up effect • Dosage flexibility	• Expensive • Recently approved (no long-term study)
Aromatase inhibitors	• Efficacy in women refractories to other traditional hormonal treatments (should be used only in scientific setting)	• Expensive • High rate of AEs (myalgia, osteoporosis etc.) • Few studies with limited design
SPRM	• Oral administration	• Limited data on humans • PAEC onset
SERM	• Efficacy on endometriosis symptoms (bazedoxifene)	• Limited data on humans • Endometrial hyperplasia onset

AE: adverse event; Gn-RH: Gonadotropin-Releasing Hormone; PAEC: progesterone receptor modulator associated endometrial changes; SERM: Selective estrogen receptor modulator; SPRM: Selective progesterone receptor modulator.

increasing feasibility of parenteral administration routes, such as intravaginal and transdermal approaches.

Numerous trials have investigated their effectiveness in this setting, comparing them to alternative medical therapies such as GnRH-agonists, progestins, and NSAIDs [29]. A recent systematic review has reported that the treatment of endometriosis with combined estro-progestins, whether administered cyclically or continuously, leads to clinically important and statistically significant reductions in pain when compared to baseline [30]. Combined estro-progestins have generally shown enhanced QoL in endometriosis treatment studies associated with improvements in treatment outcomes [3], but the data quality is often low due to methodological limitations [31]. COCs are currently the only medical therapy that has demonstrated a reduction in recurrence of ovarian endometriomas following surgical intervention [32,33]. Nonetheless, a marked disparity in recurrence rates was observed following surgery when comparing continuous and cyclic schedule COC administration. Specifically, lower recurrence rates were noted for dysmenorrhea, while no significant difference was observed for ovarian endometriomas [32]. Limited evidence exists for the use of vaginal rings and patches in treating pain associated with endometriosis. However, the available data suggest that their effectiveness is comparable to that of COCs [34,35].

The use of progestins is recommended for the management of endometriosis-associated pain in women [36]. These drugs can be administered through various routes, including oral, subdermal, intramuscular (by depot formulations), or intrauterine systems (IUS). Dienogest (DNG) is approved for the treatment of endometriosis-related pain in many states, including the European Union, Japan, Australia, and others, whereas norethisterone acetate (NETA) and medroxyprogesterone acetate (MPA) are currently approved by the Food and Drug Administration (FDA) in the U.S.A. [37]. However, only a few formulations have received global approval as hormonal contraceptives, such as oral desogestrel (DSG, 75 µg per day) and etonogestrel implants, although, in some countries, MPA depot injections and levonorgestrel-containing IUS (LNG-IUS) are also approved in this setting [28,38].

Progestins have been reported to reduce pain in women with endometriosis suffering from concomitant migraine or rectovaginal endometriosis, with similar efficacy to COCs [34,39]. Some important studies have found that progestin implants and depot MPA can effectively reduce pain in endometriosis patients, offering a comparable safety profile and satisfaction level [40,41]. The LNG-IUS is widely used for endometriosis treatment, offering benefits like long-term therapy (up to 5 years), easy removal, cost-effectiveness, and minimal systemic effects. However, drawbacks include menstrual irregularities, weight gain, breast tenderness, depression, expulsion risk, intermittent ovulation inhibition, and uncertainty of prevention of the recurrence of endometriomas [37].

Oral dienogest, at the daily dose of 2 mg, is the progestin supported by the largest evidence originating from RCTs and cohort studies and is currently the reference progestogen monotherapy for endometriosis [14]. This drug demonstrated effectiveness in alleviating endometriosis-related symptoms and improving patients' QoL across various diagnostic modalities (clinical or surgical) [42,43].

A narrative review [42] has summarized data on dienogest efficacy for treating distinct endometriosis phenotypes: although the current literature lacks comparative randomized studies between dienogest and other progestins, this drug proved efficacy in patients with ovarian endometrioma, without adversely affecting ovarian reserve; additionally, dienogest

effectively reduced pain symptoms associated with deep endometriosis, including dysmenorrhea, dyspareunia, and dyschezia, thereby enhancing QoL, also in long-term regimens; its postoperative use has been also effective in the prevention of endometriosis symptom recurrence and endometrioma [42]. A prospective phase III trial (NCT05697471) is recruiting patients to compare the efficacy of dienogest and danazol, an isoxazole testosterone derivative, which is characterized by anti-gonadotropic, hypoestrogenic, and hyperandrogenic properties and has been traditionally employed in endometriosis [44]. All consecutive women, who have endometriosis, will be randomized to receive dienogest or danazol treatment, and will assess symptoms severity, receive CA125 examination, sonographic examination at baseline, 4 weeks and 16 weeks after treatment.

The subdermal implant-bioabsorbable gestrinone pellet represents an experimental delivery mode for this progestin. This method holds promise as it offers a controlled and sustained release of the progestin, potentially enhancing its therapeutic efficacy [45]. Another multicenter, prospective, randomized, double-blind, and placebo-controlled phase II study (NCT05570786) is enrolling subjects to evaluate its safety and tolerability in women with pelvic pain related to endometriosis. The exploratory aim is to compare the use of a gestrinone pellet with a placebo pellet in the results of participant satisfaction, change in pelvic pain intensity, use of rescue pain medication, QoL, sexual function, and work activity. One hundred patients will be randomized in a 1:1 ratio. Initially, all the patients will undergo insertion of an IUS as a contraceptive method. On the same day, after randomization, the subdermal implantation of the gestrinone (85 mg) or placebo pellet will be performed. The primary endpoint is a combination of serious AEs accumulated within 6 months of pellet insertion and collected through spontaneous reporting and/or clinical findings.

2.2. Gonadotropin releasing hormone agonists

GnRH agonists, including goserelin, leuprolide (LEU), nafarelin, buserelin, and triptorelin (TRP), are considered second-line therapies for endometriosis. These decapeptides differ from endogenous GnRH by the substitution of one or more amino acids. GnRH agonists act by suppressing ovarian estrogen production, leading to amenorrhea and regression of endometriotic lesions [46]. However, they can cause AEs like lipid profile changes, hot flashes, and bone mineral density (BMD) loss. To mitigate these effects, 'add-back' treatments, such as low-dose COCs or NETA, are recommended and should ideally be initiated within six months of starting GnRH agonist therapy [47].

A systematic review, conducted by Cochrane, critically assessed the utilization of GnRH-agonists at diverse dosages, regimens, and routes of administration [48]. This review, based on 41 randomizes controlled trials (RCTs; $n = 4935$ women), compared their efficacy for alleviating pain symptoms associated with endometriosis against other treatments, including danazol, LNG-IUS, and placebo. GnRH-agonists exhibited superior efficacy in alleviating pain symptoms compared to no treatment or placebo. While there was no statistically significant difference in the effectiveness of GnRH-agonists and danazol for dysmenorrhea, the overall resolution of symptoms favored GnRH-agonists over danazol. Additionally, no significant disparity in overall pain relief was found between GnRH-agonists and LNG-IUS.

Various trials have compared the efficacy of GnRH-agonists against no treatment or placebo. An RCT showed that a 6-month treatment with intranasal buserelin (1,200 µg/day) improved pain symptoms in infertile patients with endometriosis compared to expectant management [49]. Several RCTs investigated the efficacy of LEU and TRP compared to placebo [50–53]: a double-blind RCT involving 25 women with confirmed endometriosis found that monthly TRP (3.75 mg) was more effective in reducing pain symptoms than a placebo [50]. In another RCT with 52 participants, monthly intramuscular LEU (3.75 mg) significantly improved endometriosis-related dysmenorrhea and pelvic pain compared to a placebo [51]. A recent double-blind RCT with 120 women explored pain intensity and quality of life during GnRH-agonist therapy, finding that LEU (3.75 mg) is able to cause a temporary increase in pain severity compared to placebo during the stimulatory phase [53].

GnRH-agonists have been extensively studied in comparison to various hormonal treatments commonly used for managing endometriosis-associated pain. These comparative analyses have evaluated their efficacy and safety profiles relative to other available hormonal therapies, offering insights into their role in alleviating pain symptoms associated with endometriosis [54–56]. In one of these studies, goserelin showed slightly better results for deep dyspareunia and chronic pelvic pain after 6 months compared to a low-dose cyclic COC. Initially, dysmenorrhea seemed to improve significantly with COC, but both groups had similar pain recurrence by the end of the follow-up [54]. Another RCT evaluated a 12-month treatment with a COC versus a regimen of TRP for 4 months followed by COC for 8 months. Both groups experienced significant improvements in dysmenorrhea and non-menstrual pain at the 12-month follow-up, with no notable differences [55]. In another 11-month RCT, LEU with the addition of NETA (as add-back therapy) compared with continuous COC showed similar significant pain improvement, with no significant difference between the two groups [56].

Several studies compared GnRH-agonists with progestin. In a multicenter, double-blind randomized controlled, 24-week trial, DNG (2 mg twice daily) and buserelin (300 µg/day intranasal three times daily) demonstrated similar reductions in menstrual symptom severity and low abdominal pain [57]. Another RCT involving 252 women found that both DNG and LEU effectively reduced pelvic pain associated with endometriosis over 24 weeks [58]. Two multicenter RCTs compared depot MPA and LEU for 6 months in endometriosis patients; both treatments showed similar pain symptom reduction at the 12-month follow-up [59,60]. Three RCTs were conducted to assess the effectiveness of LNG-IUS in comparison to GnRH-agonists [61–63]; in the first involving 83 women, both LNG-IUS (20 µg/day) and LEU (3.75 mg every 3 months) significantly improved pain symptoms over 6 months, with no significant

difference between them; however, faster pain relief was observed in women with advanced stage disease compared to those with mild stage disease [61]. Another RCT with 83 patients found that both LNG-IUS (20 µg/day) and LEU (3.75 mg every month) significantly reduced pain severity after 6 months, with no difference between the two groups [62]. In a further RCT on 40 women with severe endometriosis, LNG-IUS (20 µg/day) and goserelin (3.6 mg every month) showed similar effectiveness in treating pelvic pain after 24 weeks [63]. To the best of our knowledge, there are currently no RCTs that directly compare GnRH-agonists with NETA for the treatment of endometriosis.

A 2010 Cochrane review of 27 studies found no significant difference between GnRH-agonists and danazol in treating endometriosis-related pain [48].

There have been studies examining the effectiveness of GnRH-agonists with different methods of administration. These studies evaluated the impact of varying routes of administration on the efficacy of GnRH-agonists for the treatment of endometriosis. Comparing intranasal and subcutaneous buserelin administration, no clear advantage for either route was found in relieving pain and symptoms [64–66]. Additionally, a study compared intranasal nafarelin to intramuscular LEU, finding no significant difference in pain relief [67]. Three trials testing various doses of GnRH-agonists (400–800 nafarelin daily; 300-600-900 buserelin daily) showed similar improvements in pain, regardless of the specific regimen used [68–70].

3. Investigational pharmacological therapies

3.1. Aromatase inhibitors

Studies from the 1990s found the presence of aromatase P450, an enzyme converting hormones into estrone and E_2, in the eutopic and ectopic endometrium of women with endometriosis. Otherwise, this enzyme seems to be absent in healthy women and peritoneal tissue without endometriosis [71]. Considering this biological setting, several clinical studies have explored the use of third-generation nonsteroidal AIs, such as letrozole (LTZ) and anastrozole (ANA), in treating endometriosis.

Ferrero *et al*. identified about ten studies involving roughly 200 patients globally suggesting that continuous LTZ and ANA administration effectively reduces pain intensity and improves the QoL for women with endometriosis [72]. Present-day data reveal that the utilization of AIs is restricted by a relevant rate of AEs, such as bone and joint pain, muscle discomfort, and fatigue [73,74]. Additionally, treatment-induced estrogen depletion can lead to elevated FSH levels, stimulating ovarian activity and the development of functional ovarian cysts [75]; as a result, it is advisable to combine AIs with contraceptives, progestins, or GnRH-agonists in order to suppress gonadotropins in reproductive-aged patients [76–80]. Currently, the ESHRE guidelines only recommend the administration of AIs in combination with COCs, progestogens, GnRH-agonists, or GnRH antagonists, in women with endometriosis-associated pain refractory to other medical or surgical treatment [36].

In prior trials, AIs have been subjected to effective evaluation as a therapeutic approach for ovarian endometriomas [39] and deep endometriosis localizations, such as bladder, ureter [6,7,75], bowel and rectovaginal septum [77,79]. These medications were demonstrated to not only alleviate pain symptoms [72,81] but also to effectively address concerns related to intestinal and urinary functions [75,79].

Within this drug class, LTZ has been the focus of extensive research. A prospective study involving 35 rectovaginal endometriosis patients explored its effectiveness; the combination of LTZ with NETA or TRP significantly reduced chronic pelvic pain and deep dyspareunia over 3 and 6 months, compared to baseline. Notably, LTZ and NETA achieved higher patient satisfaction (64.7%) than LTZ and TRP (22.2%). The addition of GnRH-a to the regimen led to a more pronounced reduction in endometriotic implant volume, particularly when progestin was included [80]. Furthermore, a successive prospective clinical trial involving 8 patients treated with LTZ and NETA for 12 months showed a reduction in the volume of rectovaginal nodules [82]. In a recent study involving 820 women, treatment with a combination of LTZ and COCs (DSG and EE) or COCs alone for 6 months reduced chronic endometriosis-associated pelvic pain and deep dyspareunia. The LTZ group showed a slightly, but statistically significantly, lower pain intensity compared to the COC-only group, introducing a conflicting viewpoint [83].

In addition, few studies have explored the effectiveness of LTZ and NETA for ovarian endometriomas. In a patient-preference trial, the combination of LTZ and NETA resulted in a significantly higher average reduction in OE volume compared to NETA alone; however, complete regression of ovarian endometriomas was not achieved in either group [39]. In another study involving five reproductive-age patients with recurrent ovarian endometriomas and chronic pelvic pain, a 6-month treatment regimen of LTZ, DSG, and EE following prior surgeries and unsuccessful therapies led to complete regression of ovarian endometriomas in two patients, with impressively no recurrence during a 2-year follow-up period [84].

An RCT compared two post-surgery treatment approaches for severe endometriosis. The study investigated the effectiveness of a combination therapy involving ANA (1 mg/day) and goserelin (3.6 mg monthly) versus goserelin alone (3.6 mg monthly) over a 6-month period. The combination therapy showed significant improvements in pain relief and a longer recurrence-free interval (over 24 months versus 17 months). Recurrences were less frequent in the combination group (7.5%) compared to the single therapy group (35%) during a 24-month follow-up [85]. Contrarily, in a separate RCT, a 2-month LTZ treatment post-surgery did not reduce the risk of disease recurrence compared to GnRH agonists or placebo [86]. In a 6-month prospective trial with 10 patients having rectovaginal endometriosis, ANA vaginal suppository treatment led to significant improvements in dysmenorrhea and QoL; the response of rectovaginal nodules varied, as six of them remained stable or decreased in volume, while three of them increased in size [87]. Recently, additional research investigated the combined use of ANA and LNG-IUS for treating endometriosis-related pelvic pain. The ANA group

experienced a significantly greater reduction in pain and a longer delay in pain recurrence compared to the LNG-IUS-only group. However, no other significant differences were observed between the two groups over the study period [88].

Currently, a randomized, double-blind, parallel-group, multicenter phase IIb clinical trial (NCT02203331) is in progress. This trial, comprising 319 enrolled patients, aims to evaluate the efficacy and safety of BAY98–7196, an intravaginal ring formulated with varying doses of ANA (300-600-1050 µg/d) and LNG. This investigation is designed to compare these innovative interventions against placebo and LEU, administered through a subcutaneous depot. The trial focuses on women grappling with symptomatic endometriosis and extends over a duration of 12 weeks. Another randomized parallel phase IV trial (NCT01769781) aims to evaluate the effectiveness of the combined approach involving ANA and LEU as compared to the usage of LEU, as monotherapy. The primary focus of this trial lies in preventing the recurrence of endometriosis.

Moreover, an ongoing randomized, double-blinded, placebo-controlled, phase II trial (NCT04002141) is actively enrolling participants. This study aims to assess the influence of ovarian hyperstimulation on symptoms associated with endometriosis and to evaluate the effects of LTZ utilization during ovarian hyperstimulation; the evaluation encompasses various aspects, including endometriosis-related symptoms, embryo, and egg quality and quantity, as well as pregnancy rates.

3.2. Gonadotropin-releasing hormone antagonists

GnRH antagonists act by competitively blocking the GnRH receptor, leading to an immediate suppression in LH and FSH production. As a result, the secretion of gonadal steroid hormones is effectively inhibited (Figure 1) [89].

In contrast to GnRH agonists, GnRH antagonists exhibit a distinct characteristic of not triggering the initial flare-up phase. Instead, they rapidly initiate the therapeutic effect without any delay [90]. The decrease in circulating estrogen levels, without complete suppression, leads to an improvement in pain symptoms associated with endometriosis. This approach also results in a reduction of estrogen-related AEs [12].

Furthermore, GnRH antagonists exhibit a dose-dependent estrogen suppression effect. When administered at lower doses, they induce partial suppression, while higher doses

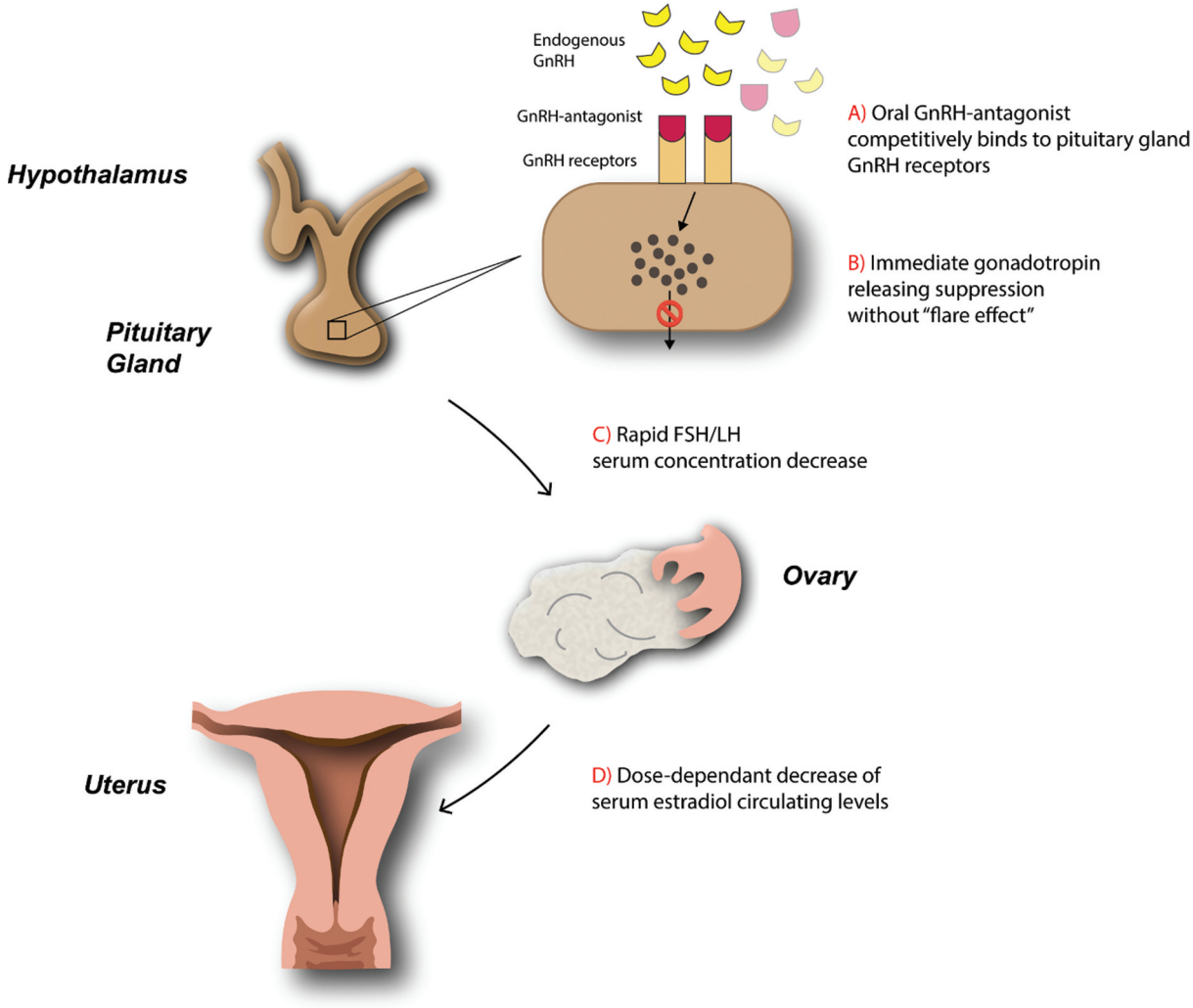

Figure 1. Mechanism of action of gonadotropin-releasing hormone (GnRH) antagonists.

result in nearly complete suppression of estrogen levels [91]. This customized suppression approach offers a significant advantage of GnRH antagonists with an optimal compromise between effectiveness, tolerance, and safety [92]. This strategy ensures the maintenance of adequate E_2 levels, preventing the emergence of typical adverse hypoestrogenic effects, such as decreased BMD and vasomotor menopausal symptoms [37,93]. Additional benefits of the majority of GnRH antagonists involve their capability for oral delivery, along with the swift reversibility and rapid restoration of ovarian function following the end of drug use [91]. Different trials investigated the use of GnRH antagonists (Table 2).

Elagolix (ELX) is an orally administered, non-peptide GnRH antagonist with a short duration of action, which has been approved by the FDA for the management of moderate to severe pain linked with endometriosis in 2018 [102].

In a phase II RCT involving 137 reproductive-age women with confirmed endometriosis and moderate to severe non-menstrual pelvic pain and dysmenorrhea, ELX at 150 mg daily was assessed for its efficacy [103]. The study incorporated an initial 8-week double-blind phase followed by a subsequent 16-week open-label period. Throughout the double-blind phase, ELX demonstrated a significant reduction in dysmenorrhea, non-menstrual pelvic pain, and dyspareunia scores in comparison to the placebo, with sustained improvements during the open-label phase. ELX exhibited additional positive effects on QoL, as assessed by the EHP-5 and PGIC questionnaires and led to a decrease in analgesic use. Notably, common AEs (including nausea, headache, and hot flushes) were reported, but no significant increase in bleeding was observed.

In a 24-week American phase II RCT involving 252 women with endometriosis-associated pain, the effects of ELX at two dosages (150 mg daily or 75 mg twice daily) and subcutaneous depot MPA on BMD were examined [104]. ELX significantly improved endometriosis-associated pain, with rapid relief of dysmenorrhea and sustained reduction in non-menstrual pelvic pain, persisting through week 48 after drug discontinuation. BMD changes were minimal and similar or lesser than baseline. Common AEs included headache, nausea, and nasopharyngitis, with low occurrences of mild to moderate hot flashes. Only one patient discontinued due to hot flashes (on the 75 mg twice daily regimen). Overall, ELX demonstrated effectiveness in pain relief and had minimal effects on BMD [104].

In a separate phase II investigation, the efficacy and safety of ELX in alleviating pain were assessed in 155 women diagnosed with endometriosis through laparoscopy [105]. Participants were randomized into three groups: placebo, ELX 150 mg, or ELX 250 mg once daily for 12 weeks. Placebo participants were later switched to ELX. While ELX showed more significant monthly pain reduction compared to placebo, the difference wasn't statistically significant. However, ELX significantly lowered monthly mean scores for dysmenorrhea and non-menstrual pelvic pain, especially notable at weeks 8 and 12. A higher proportion of ELX patients completed both treatment phases. AEs were more frequent in the ELX groups, including headache, nausea, and anxiety. Daily hot flushes were slightly more common in the ELX groups but mostly mild to moderate. ELX caused a minor decline in BMD [105].

A subsequent RCT conducted in Europe involved 174 women who were diagnosed with endometriosis through laparoscopy. These participants were divided into groups to receive ELX (either 150 mg or 250 mg once daily), LEU (administered intramuscularly at 3.75 mg per month), or a placebo for a duration of 12 weeks [106]. Participants initially received placebo, ELX 150 mg, or ELX 250 mg daily for 12 weeks. Then, placebo and LEU groups were re-randomized switching to ELX, while the ELX group continued the initial treatment. By week 4, both ELX doses groups showed significant pain reduction, with ELX 250 mg maintaining this effect at week 8. LEU also reduced pain significantly at weeks 4, 8, and 12. All groups reduced analgesic use from baseline and the most commonly side effects in ELX and LEU groups were headache and nausea [106].

In 2017, two double-blind, randomized, placebo-controlled, 6-month phase III trials (Elaris EM-I and Elaris EM-II) assessed the efficacy of ELX in managing endometriosis-associated pain [94]. These trials included 872 and 817 women with surgically confirmed moderate to severe endometriosis and pain. In Elaris EM-I, 46.4% of ELX 150 mg users, 75.8% of ELX 400 mg users, and 19.6% of placebo users achieved dysmenorrhea relief after three months. In Elaris EM-II, the corresponding figures were 43.4% and 72.4% (vs. 22.7% placebo users). Similar results were observed for non-menstrual pelvic pain. Responses for both pain types were sustained at six months. Higher ELX doses notably reduced dyspareunia after three months. Overall, ELX demonstrated significant and sustained pain relief compared to placebo, especially at higher doses. AEs were common, including hot flashes, headaches, and nausea, but the discontinuation rate due to side effects was relatively low [94].

The medium-term impacts of ELX treatment were assessed through two phase III extension trials (Elaris EM-III and Elaris EM-IV) [95]. In extension studies of ELX trials, 569 women continued treatment for an additional six months, followed by a 12-month post-treatment follow-up. About 48% of the initially enrolled participants completed this entire period, suggesting the possibility that participants with poorer outcomes, those who did not respond to or tolerate the treatment, might have been excluded [37,107]. During the follow-up, responder rates for dysmenorrhea were 52.1% and 50.8% for ELX 150 mg and 78.1% and 75.9% for ELX 400 mg, in EM-III and EM-IV, respectively. For non-menstrual pelvic pain, responder rates were 67.8% and 66.4% for ELX 150 mg and 69.1% and 67.2% for ELX 400 mg [95]. Vasomotor symptoms (hot flushes) were common AEs, with a dose-dependent pattern. The impact of ELX on BMD exhibited a correlation with the dosage, resulting in a more pronounced decrease in BMD among women receiving higher doses of the GnRH antagonist.

In the trials upon which the clinical investigation of ELX is based, 49 pregnancies occurred during treatment, underscoring the imperative of employing non-hormonal contraception concurrently to avert pregnancy [108]. A recently published

Table 2. Results of completed phase II and III trials investigating the use of GnRH antagonists in endometriosis.

Year of publication	NCT	Population	Study design	Number of patients enrolled	Study drugs	Treatment period	Follow-up period	Primary endpoints	Outcome
2017 [94]	NCT01620528 and NCT01931670	Premenopausal women between the ages of 18 and 49 years who had received a surgical diagnosis of endometriosis in the previous 10 years and who had moderate or severe endometriosis-associated pain	Double-blind, randomized, placebo-controlled, phase III studies	653 (74.9% of the initial participants) and 632 (77.4% of the initial participants) patients	Elagolix 150 mg/die (lower-dose group) vs. 400 mg/die (higher-dose group) vs. placebo	6 months	12 months	Percentage of women who exhibited a clinical response in terms of dysmenorrhea and NMPP after three months of treatment	• EM-I: dysmenorrhea improvement was observed in 46.4% of participants with elagolix 150 mg and 75.8% with elagolix 400 mg, compared to 19.6% in the placebo group • EM-I: NMPP reduction was observed in 50.4% with elagolix 150 mg and 54.5% with elagolix 400 mg, compared to 36.5% in the placebo group • EM-II: Corresponding percentages were 43.4% and 72.4% for dysmenorrhea; 49.8% and 57.8% for NMPP, compared to 22.7% and 36.5% in the placebo group • These responses in dysmenorrhea and NMPP were maintained at six months in both studies
2018 [95]	NCT01760954 and NCT02143713	Premenopausal women between the ages of 18 and 49 years who had received a surgical diagnosis of endometriosis in the previous 10 years and who had moderate or severe endometriosis-associated pain	Double-blind, randomized, phase III, extension studies	569 (59.7% of the initial participants) and 458 (48% of the initial participants) patients	Elagolix 150 mg/die (lower-dose group) vs. 400 mg/die (higher-dose group) vs. placebo	6 months	12 months	Medium-term effects of elagolix treatment	• EM-III: responder rates for dysmenorrhea were 52.1% with elagolix 150 mg and 78.1% with elagolix 400 mg. • EM-III: responder rates for non-menstrual pelvic pain were 67.8% with elagolix 150 mg and 69.1% with elagolix 400 mg • EM-IV: corresponding percentages were 50.8% with elagolix 150 mg and 75.9% with elagolix 400 mg for dysmenorrhea, and 66.4% with elagolix 150 mg and 67.2% with elagolix 400 mg for non-menstrual pelvic pain • At week 52, the mean percent change from baseline in lumbar spine BMD ranged from – 3.60% to – 3.91% for the high-dose group (200 mg twice daily)
2019 [96]	NCT01767090	Women aged 18–45 years with moderate-to-severe endometriosis-associated dysmenorrhea and non-menstrual pelvic pain, a surgically confirmed diagnosis of endometriosis, and a confirmed regular menstrual cycle of 24–35 days	Double-blind, randomized, parallel-group, placebo-controlled, multicenter, phase II study	540 participants	Opigolix (ASP1707) 3 mg ($n = 86$) or 5 mg ($n = 91$) or 10 mg ($n = 90$) or 15 mg ($n = 88$) vs placebo ($n = 88$) or LEU 3.75 mg/month ($n = 89$)	12 weeks	24 weeks	• Effectiveness of opigolix in reducing endometriosis-associated pelvic pain and the dose-response relationship • Safety, tolerability, pharmacokinetics, and the dose-response relationship of opigolix in decreasing serum E_2 levels	• Significant dose-dependent treatment effects were observed in decreasing numeric scores for overall pelvic pain, dysmenorrhea, and NMPP among opigolix doses after 12 weeks, and these effects were sustained through 24 weeks. • Serum E_2 levels and BMD decreased in a dose-dependent manner with opigolix over 24 weeks but to a lesser extent compared to LEU

(*Continued*)

Table 2. (Continued).

Year of publication	NCT	Population	Study design	Number of patients enrolled	Study drugs	Treatment period	Follow-up period	Primary endpoints	Outcome
2020 [97]	NCT02778399	Premenopausal women aged between 18 and 45 years, with a confirmed surgical diagnosis of endometriosis in the previous 10 years and currently experiencing moderate to severe EAP.	International, double-blind, randomized, parallel-group, placebo-controlled, dose-ranging study	328 participants	Linzagolix 50, 75, 100, 200 mg vs Placebo	24 weeks	24 weeks	Reduction in pain exceeding 30% after 12 weeks	• At week 12, significant percentages of women with a ≥ 30% reduction in overall pelvic pain compared to placebo: 34.5% placebo, 49.4% 50 mg, 61.5% 75 mg, 56.4% 100 mg, and 56.3% 200 mg. This reduction was statistically significant for all groups except the 50-mg group. • The percentages of women with a ≥ 30% reduction in dysmenorrhea and NMPP at week 12 and week 24 were significantly higher in all groups compared to placebo, except for the 50-mg group. • Observation of significant reduction in dyspareunia at 12 weeks in the 200 mg linzagolix group but not in the placebo, 50 mg, 75 mg, or 100 mg groups. • Mean percentage changes in lumbar spine BMD from baseline to the end of the treatment period: 0.14% for 50 mg, −0.80% for 75 mg (fixed-dose), −1.0% for 75 mg (titrated-dose), −1.37% for 100 mg, and − 2.60% for 200 mg.
2021 [98]	NCT01458301	Premenopausal women, ≥20 years of age, who had regular menstrual cycles (25–38 days), a diagnosis of endometriosis in the previous 5 years (confirmed by laparotomy, laparoscopy, or magnetic resonance imaging with detection of ovarian chocolate cysts), and dysmenorrhea and pelvic pain due to endometriosis, either one or both of which were at least moderate as determined by using the Biberoglu and Behrman scale	Multicentre, double-blind, randomized, placebo-controlled study	487 participants	Relugolix 10 mg (n = 103), 20 mg (n = 100), 40 mg (n = 103) vs. placebo (n = 97) or LEU 3.75 mg/month (n = 80)	12 weeks	4 weeks	Modifications in pelvic pain scores during the final month of treatment compared to baseline	• Pelvic pain VAS reduction: −3.8 (placebo), −6.2 (10 mg relugolix), −8.1 (20 mg relugolix), −10.4 (40 mg relugolix); −10.6 (LEU)
2021 [99]	NCT01452685	Premenopausal females who had completed treatment with the study drug in the preceding phase II study	Randomized, open-label, parallel-group extension, phase II study	397 participants	Relugolix 10 mg (n = 84), 20 mg (n = 78), 40 mg (n = 89) vs placebo (n = 77) or LEU 3.75 mg (n = 69)	12 weeks	4 weeks	Impact on BMD and safety	• Changes in BMD from baseline to week 24: −0.2% (placebo), −1.6% (10 mg relugolix), −2.6% (20 mg relugolix), −4.9% (40 mg relugolix), −4.4% (LEU)
2022 [100]	NCT03931915	Patients aged ≥20 years who had regular menstrual cycles (25–38 days) and diagnosed with at least 1 of the following: • endometriosis confirmed by laparotomy or laparoscopy within the past 5 years; • ovarian endometrioma within the previous year confirmed by magnetic resonance imaging or ultrasonography; • clinical endometriosis that included clinical signs of restricted uterine mobility, pelvic tenderness or induration of the Douglas cavity.	Multicenter, randomized, double-blind, double-dummy, active-controlled, phase III study	335 participants	Relugolix 40 mg vs. LEU 3.75 mg or LEU 1.88 mg	24 weeks	4 weeks	Change in maximum VAS score for endometriosis-associated pelvic pain from baseline to the end of treatment.	• The reduction in VAS scores for dysmenorrhea and NMPP was similar in both study groups, with scores of − 52.6 ± 1.3 in the relugolix group and − 57.5 ± 1.4 in the LEU group. • Improvement in EHP-30 and Work Productivity and AIQ scores was comparable in both groups. • Changes in BMD from baseline to the end of treatment were also comparable, with a decrease of − 4.80% in the relugolix group and − 4.84% in the LEU group.

(*Continued*)

Table 2. (Continued).

Year of publication	NCT	Population	Study design	Number of patients enrolled	Study drugs	Treatment period	Follow-up period	Primary endpoints	Outcome
2022 [101]	1)NCT03204318 and 2)NCT03204331	Premenopausal women between the ages of 18 and 49 years who had received a surgical diagnosis of endometriosis in the previous 10 years and who had moderate or severe endometriosis-associated pain	Replicate, randomized, double-blind, placebo-controlled, phase III study	SPIRIT I: 638 total participants, whose 212 receiving relugolix combination therapy (181 completed the intervention) vs. 213 receiving placebo (174 completed the intervention) vs. 213 receiving relugolix delayed combination therapy (182 completed the intervention) SPIRIT II 623 total participants, whose 208 receiving relugolix combination therapy (174 completed the intervention) vs. 208 receiving placebo (168 completed the intervention treatment) or 207 receiving relugolix delayed combination therapy (165 completed the intervention)	Relugolix combination therapy (relugolix 40 mg with E_2 1 mg and NETA 0.5 mg) or delayed relugolix combination therapy (relugolix 40 mg monotherapy followed by relugolix combination therapy) vs. placebo	24 weeks	4 weeks	The percentage of individuals who showed improvement in alleviating dysmenorrhea and NMPP at the conclusion of the treatment period.	• SPIRIT I: there was a significant treatment difference between the relugolix combination group and the placebo group for responders experiencing relief from dysmenorrhea (47.6%; $p < 0.0001$) and non-menstrual pelvic pain (18.9%; $p < 0.0001$). • SPIRIT II: relugolix combination group showed a notable treatment difference compared to the placebo group for responders in terms of dysmenorrhea (44.9%; $p < 0.0001$) and non-menstrual pelvic pain (23.4%; $p < 0.0001$) • The least squares mean percentage change in lumbar spine BMD was measured, and it was −0.70% versus 0.21% in SPIRIT I and −0.78% versus 0.02% in SPIRIT II for the relugolix combination therapy vs. placebo groups. In the delayed relugolix combination group, it was −2.0% in SPIRIT I and −1.9% in SPIRIT II • Reduction in opioid use was observed in patients who received treatment compared to those who received a placebo

BMD: bone mineral density; LEU: leuprolide; VAS: visual analogic scale; NMPP: non-menstrual pelvic pain; NETA: norethindrone acetate; E2: estradiol.

report has provided an update on the open-label safety findings of ELX at a daily dose of 400 mg, combined with add-back therapy, over a period of 24 months. The results indicate that this treatment regimen maintains a favorable safety profile, with minimal long-term effects on BMD [109].

An ongoing investigation (NCT03213457) aims to assess the long-term safety of ELX at a daily dose of 400 mg, in conjunction with add-back therapy. The primary objective of this phase III study is to evaluate the potential positive impacts of add-back therapy, involving the use of E_2 and NETA, when combined with ELX. The goal is to mitigate the AEs associated with hypoestrogenism, specifically addressing the concern of BMD loss. Another ongoing phase III clinical trial (NCT05648669) is currently enrolling participants. This multicenter study is designed as a double-blind, placebo-controlled, randomized trial. Its objective is to evaluate both the safety and effectiveness of ELX compared to a placebo in premenopausal women aged 18 to 49 who are experiencing moderate to severe endometriosis-associated pain. The participants will be randomly assigned in a 1:1 ratio to receive either ELX at a dose of 200 mg or a placebo. The study drug will be administered for a duration of up to six months. Finally, an American, multicenter, randomized, double-blinded, placebo-controlled, phase IIIb study (NCT04333576), started in 2020, is still currently enrolling participants. This study aims to evaluate the safety and efficacy of ELX in combination with COCs in premenopausal women with documented endometriosis and associated moderate to severe pain. Participants will receive oral ELX or placebo tablets in combination with COC or placebo capsules for 3 months. All the participants will receive ELX tablets in combination with COC tablets from the 4th to the 18th month of the trial. In summary, high-dose ELX effectively lowered E_2 levels and reduced endometriosis-associated pelvic pain but led to more hypoestrogenic side effects and greater BMD decline. Lower ELX doses had a limited impact and did not significantly reduce the need for rescue analgesics [37].

Recent phase II and III RCTs have shown promising results for two other oral GnRH antagonists, relugolix (TAK385) and linzagolix (OBE2109) [97–100].

Relugolix is an orally administered non-peptide GnRH-antagonist under investigation for managing symptoms related to endometriosis [12]. Recently, the results of a phase II, multicenter, randomized, double-blinded, placebo-controlled clinical trial have been released [98]. In this trial involving 487 women, three doses of relugolix (10 mg, 20 mg, and 40 mg) were compared to a placebo and subcutaneous LEU for treating endometriosis-associated pelvic pain. Over 12 weeks, the reduction in pelvic pain, as measured by VAS score, was greater with increasing relugolix doses (max −10.4 mm for 40 mg dose vs. −3.8 mm for the placebo). There was no consistent trend in dyspareunia improvement with relugolix. QoL, assessed by the EHP-30 score, improved in relugolix groups compared to the placebo. Hot flushes were dose-dependent, ranging from 8.7% for 10 mg to 52.4% for 40 mg relugolix, with higher doses causing more hot flushes than LEU (52.4% vs. 41.3%). BMD decline showed a dose-dependent pattern, with a − 2.1% decrease observed for 40 mg relugolix, a decline similar to that seen in individuals receiving LEU (−2.2%). In

summary, relugolix was superior to the placebo and equally effective as LEU at higher doses (40 mg) in treating endometriosis-associated pelvic pain.

A recent randomized phase III trial conducted in Japan compared the safety and effectiveness of 40 mg relugolix with LEU in a 24-week double-blind trial at multiple centers [100]. In this study involving 335 participants with endometriosis, both surgically and clinically diagnosed, the efficacy of relugolix was compared to LEU in relieving pelvic pain. The reduction in maximum VAS score for pelvic pain from baseline to the end of treatment was similar between the two groups: −52.6 for relugolix and − 57.5 for LEU. Both groups showed comparable improvements in dysmenorrhea and non-menstrual pelvic pain VAS scores, leading to reduced analgesic use. QoL (measured with EHP-30 score) and work productivity improved similarly in both groups, confirming relugolix's non-inferiority to LEU in terms of efficacy. AEs were slightly more common in the LEU group (90.9% vs. 79.5%), while changes in BMD were comparable between relugolix (−4.80%) and LEU (−4.84%). Notably, E_2 levels returned to normal within 4 weeks after discontinuing relugolix, while menstruation resumed earlier (median, 38 days) compared to LEU discontinuation (median, 68 days) [100].

During 2022, two phase III studies, conducted at multiple centers, employed a randomized, double-blind, placebo-controlled design to assess the effectiveness and safety of relugolix combination therapy (relugolix 40 mg with E_2 1 mg, and NETA 0.5 mg) for managing endometriosis-associated pain (SPIRIT 1 and SPIRIT 2) [101]. In this study, 1261 women with endometriosis were divided into three groups: placebo, relugolix combination therapy, or delayed relugolix combination therapy (relugolix alone for 12 weeks followed by relugolix combination therapy for 12 weeks). The primary goal was to assess responders based on relief from dysmenorrhea and non-menstrual pelvic pain. Dysmenorrhea responder rates were significantly higher in the relugolix combination therapy groups compared to placebo (75% vs. 27% in SPIRIT 1 and 75% vs. 30% in SPIRIT 2). For non-menstrual pelvic pain, responder rates were also higher in the relugolix combination therapy groups (59% vs. 40% in SPIRIT 1 and 66% vs. 43% in SPIRIT 2). BMD remained stable in patients receiving relugolix combination therapy. However, in the delayed relugolix combination therapy group, there was a significant decline in BMD during the initial 12 weeks (relugolix monotherapy), which stabilized during the transition to relugolix combination therapy [101].

An ongoing single-arm, open-label phase III study (NCT04756037; SERENE) is enrolling participants. The primary objective of this study is to evaluate the safety and contraceptive effectiveness of relugolix combination therapy, consisting of relugolix 40 mg, E_2 1 mg, and NETA 0.5 mg. The study focuses on women between the ages of 18 and 50 who have been diagnosed with uterine fibroids or endometriosis and are at risk of pregnancy.

Linzagolix is another orally administered non-peptide GnRH-antagonist under investigation for managing symptoms related to endometriosis. The EDELWEISS study (24-week trial) examined the effects of varying doses of linzagolix (50 mg, 75 mg, 100 mg, 200 mg) compared to a placebo in 328 patients suffering from endometriosis-related pain [97]. The primary goal was to achieve a ≥ 30% reduction in overall pelvic pain. At week 12, all linzagolix groups, except the 50 mg group, showed statistically significant improvements compared to the placebo. Similarly, reductions in dysmenorrhea and non-menstrual pelvic pain were significantly higher in all linzagolix groups compared to the placebo at both weeks 12 and 24. Linzagolix also improved dyspareunia at 12 weeks, particularly in the 200 mg group. The EHP-30 questionnaire revealed improvements in pain, powerlessness, emotional well-being, self-image, and social support in linzagolix-treated groups. Common side effects included headache and hot flashes, with more hot flashes in higher-dose groups (42.1% in the 200 mg group at week 12). BMD changes were assessed, with BMD reduction ranging from 0.14% to − 2.60% across doses. In the 200 mg group, over half the participants experienced BMD reduction exceeding 3% at week 24. A daily dose of 75 mg effectively reduced endometriosis-associated pain with minimal BMD changes, while higher doses (200 mg) required add-back therapy to counter significant BMD decrease during long-term use [97]. However, further long-term safety data, particularly regarding BMD, are necessary [37].

Opigolix (ASP1707), an oral GnRH antagonist, underwent a multicenter, double-blinded, randomized, placebo-controlled phase II trial (NCT01767090) evaluating its efficacy in endometriosis treatment [96]. Between 2012 and 2015, 540 women in Europe and Japan were recruited. Patients received treatment across six groups: opigolix at 3 mg (n = 86), 5 mg (n = 91), 10 mg (n = 90), and 15 mg (n = 88), LEU (n = 89), and placebo (n = 88). The study lasted 24 weeks, divided into two 12-week parts. The first part involved the placebo group, later randomized to opigolix doses in the second part. The primary aim was to gauge drug efficacy in reducing pelvic pain. After 12 weeks, various opigolix doses demonstrated significant reductions in numeric rating scale numeric scores for overall pelvic pain, dysmenorrhea, and non-menstrual pelvic pain, indicating pain relief. However, alleviating dyspareunia did not exhibit a dose-dependent pattern and did not significantly differ from placebo, regardless of opigolix dosage. Participants receiving opigolix or LEU experienced significant declines in BMD compared to baseline. Opigolix resulted in significantly less BMD loss compared to LEU, highlighting its potential advantage in terms of bone health. In summary, opigolix demonstrated effective reduction of endometriosis-related pelvic pain, including overall pelvic pain, dysmenorrhea, and non-menstrual pelvic pain, but did not show significant improvement in dyspareunia. Importantly, opigolix caused less BMD loss compared to LEU, making it a potentially better choice for patients concerned about bone health [96]. To the best of our knowledge, no phase III trials have been organized for studying opigolix in patients affected by endometriosis.

3.3. Selective estrogen and progesterone receptors modulators

Selective estrogen receptor modulators (SERMs) exhibit diverse actions in different estrogen-responsive tissues, functioning as estrogen receptor (ER) agonists in certain tissues

while acting as ER antagonists in others. SERMs exert an estrogen-antagonistic effect specifically on the endometrial tissue. This interaction effectively blocks the hormonal signaling pathway, leading to a decrease in estrogen activity. As a result, SERMs have the potential to alleviate endometriosis-associated pain, offering a possible therapeutic benefit in managing the condition [110,111].

Raloxifene (RLX) is a non-steroidal compound commonly used in clinical practice for the treatment of osteoporosis. This medication exhibits favorable estrogenic effects on BMD, which helps improve bone health. Importantly, RLX does not stimulate the growth of endometrial or breast tissue, making it a safer option in these regards. Furthermore, in animal models of endometriosis, RLX has demonstrated significant regression of endometriotic implants, indicating its potential therapeutic value in treating this condition [112,113]. An RCT was conducted to evaluate the effectiveness of RLX at a daily dosage of 180 mg, administered over a period of 6 months. The study aimed to compare the outcomes of RLX treatment with those of a placebo in women who were undergoing laparoscopic excision of all visible endometriotic lesions [114]. This specific study was terminated early due to unexpected findings: in fact, the patients who received RLX experienced more pain and required a second surgery significantly earlier compared to those who received the placebo. In contrast to rodents, RLX may not reliably prevent ovulation in humans, potentially allowing ovarian estrogen production to persist or rise, worsening symptoms for some patients [115].

Bazedoxifene (BZA) is another SERM utilized for the treatment of osteoporosis in postmenopausal women who are at an elevated risk of fractures. This medication appears to possess the ability to counteract estrogen-induced stimulation of the uterine endometrium while still maintaining estrogenic effects on bone and the central nervous system. In other words, BZA can act as an antagonist to estrogenic stimulation in the uterus while preserving beneficial estrogenic effects in the skeletal system and the central nervous system. This makes it a potentially valuable option for managing osteoporosis without posing the risk of excessive uterine stimulation [12]. Pre-clinical studies have provided evidence that BZA can induce regression of endometriotic lesions [116]. This effect is achieved through multiple mechanisms, including the inhibition of proliferation in stromal endometriotic cells. Additionally, BZA has been observed to reduce the recruitment of stem cells within the endometriotic implants [117]. In a small case series involving patients with stage III endometriosis, a combination of BZA and conjugated estrogens was administered for over 6 months. This therapy effectively resolved pelvic pain and improved symptoms without observed AEs on the reproductive tract [118]. In another small case series involving patients diagnosed with endometriosis, the combination of BZA and conjugated estrogens with LEU demonstrated promising results in improving pain symptoms; the use of this combined approach led to a significant reduction in pain symptoms experienced by these patients [119]. Additionally, it has been observed that the addition of estrogen to BZA does not stimulate endometrial growth or hyperplasia and the presence of estrogen does not compromise the effectiveness of SERM [120]. An ongoing single-blind placebo control randomized crossover study is enrolling participants to determine the effects of BZA and conjugated estrogens and simvastatin interventions on endothelial dysfunction in women with endometriosis (NCT05059626).

SR-16234 (TAS-108) is an additional investigational SERM exhibiting antagonistic effects on ERα and partial agonistic effects on Erβ [121,122]. In contrast to other SERMs, SR-16234 appears to have a more pronounced antagonistic effect on ER-α, a trait that might explain its potential efficacy in addressing endometriosis. In an open-label, single-arm clinical trial, this medication (administered at a dosage of 40 mg once daily for 12 weeks) was assessed in a cohort of 10 women with endometriosis and adenomyosis. The trial revealed that SR-16234 successfully reduced the severity of pelvic pain and dysmenorrhea [123].

Selective progesterone receptor modulators (SPRMs) are a class of compounds that interact with the PR, exhibiting both agonist and antagonist properties with distinct functions depending on the specific cell in which they are expressed [124]. One of the first SPRM, mifepristone demonstrates a higher binding affinity to the human PR when compared to progesterone (100% vs. 43%) and its metabolites from endometrial and myometrial samples; other SPRMs [125,126]. Other SPRMs include asoprisnil and ulipristal, with the latter being extensively utilized in the treatment of uterine fibroids [127].

In general, SPRMs can prevent ovulation without impacting the secretion of E_2. As a result, the levels of circulating E_2 are maintained within the normal range [120]. In addition, these drugs have been found to inhibit the growth and proliferation of the endometrium, effectively suppressing endometrial bleeding and reducing the production of prostaglandins by the endometrial tissue [120]. An area of uncertainty regarding SPRMs lies in their prolonged inhibitory effect on endometrial progesterone activity, leading to excessive estrogen exposure [128]. The administration of SPRMs has been linked to distinct structural alterations in the endometrium, such as cystic dilation of glands, distorted epithelium, apoptosis, and reduced mitotic activity in both glands and stroma [129]. These particular alterations in the endometrium are commonly referred to as progesterone receptor modulator-associated endometrial changes (PAEC) [130]. Therefore, the potential rationale for utilizing SPRMs in the treatment of endometriosis appeared reasonable; however, it is important to note that currently SPRMs are not commonly used in clinical practice for this purpose [37,73]. A phase IIb randomized, double-blind clinical study (NCT03573336; VILLENDO trial) was designed to explore two different doses of vilaprisan, another SPRM, compared to a placebo in women with endometriosis. However, all clinical studies involving vilaprisan were suspended due to the identification of drug toxicity signals discovered during long-term animal tests conducted concurrently with the final stage clinical trials for endometriosis and uterine fibroids [131].

3.4. Inhibitors of steroid sulfatase and hydroxysteroid dehydrogenase type 1

Endometriotic lesions exhibit aberrant expression of steroid sulfatase (STS), responsible for hydrolyzing estrogen sulfates and converting inactive precursors like estradiol sulfate and

estrone sulfate into metabolically active estrogens [132]. The initial identification of an STS inhibitor, Estrone-3-O-sulfamate [133], was followed by the synthesis of several others. STX64 effectively inhibited STS activity in endometriotic tissue, although it remains untested in animals [134]. Estradiol-3-O-sulfamate (E2MATE or PGL2001) emerges as a promising option for endometriosis treatment. In a double-blind, phase I randomized controlled study on healthy reproductive-age women, E2MATE reduced STS activity by 91%, reaching 96% when combined with NETA [133]. A multicenter, randomized, phase II study has investigated the use of E2MATE combined with NETA for treating endometriosis-associated pain in patients with clinical signs of the disease. Despite the completion of the trial, no results have been published as of now (NCT01631981)

The conversion of estrone to E_2 by 17β-HSD1 represents another potential therapeutic target [132]. The unbalanced activity of 17β-HSD1 and its counterpart, 17β-HSD2, is suggested to contribute to elevated E_2 levels within endometriotic lesions. Numerous inhibitors of 17β-HSD-1, successfully employed in preclinical studies and animal models of breast, endometrial cancer, and endometriosis, have been developed [135]. Other authors demonstrated that an HSD17B1 inhibitor decreased E_2 production by more than 85% in samples from women with endometriosis [136]. A randomized, double-blind, placebo-controlled phase I trial is currently investigating the safety, tolerability, and pharmacokinetics of a new HSD17B1 inhibitor, FOR-6219, in healthy postmenopausal women (NCT03709420) [103]. To the best of our knowledge, no late clinical trials have been yet organized for FOR-6219 in endometriosis.

4. Conclusion

Presently, scientific inquiry is concentrated on identifying novel effective medications for treating endometriosis in patients, particularly those who do not respond to traditional first-line treatments. Late-stage clinical trials on GnRH-antagonists, among the drugs being assessed, have shown the most hopeful results. Emerging innovative hormonal therapies for endometriosis have been discovered. However, the bulk of these new compounds have only been tested in laboratory studies or preliminary clinical trials, and their application in treating women is not yet viable. Consequently, additional clinical investigation is needed to gain a clearer understanding of their efficacy and safety in humans.

5. Expert opinion

The development, maintenance, and progression of endometriosis involve various altered mechanisms, such as abnormal cell proliferation, immune dysfunction, impaired apoptosis, increased invasive potential, and angiogenesis. The expanding understanding of the pathogenesis of this disease has opened avenues for the exploration of novel therapeutic agents [3].

In the long-term treatment of endometriosis-related pain, several significant challenges are often encountered. First, there is the recurrence of symptoms after discontinuing treatment, which can be frustrating for patients; furthermore, the occurrence of intolerable side effects poses a barrier to effective long-term management; lastly, current treatment approaches for endometriosis-associated pain, such as those that potentially inhibit ovulation, may not be suitable for patients who wish to conceive and address their infertility [73,74]. Moreover, surgery is of course able to eliminate visible endometriotic lesions, but cannot cure the disease. Thus, postoperative recurrence is common, because persistent foci not detected at the time of surgery may progress under the influence of circulating estrogens. This highlights the importance of performing an adequate postoperative medical treatment aiming to reduce the risk of disease recurrence. Lastly, there is a growing focus on addressing the unique challenges faced by severely symptomatic adolescents who may be at an increased risk of developing endometriosis. These young individuals could potentially benefit the most from medical preventive interventions aimed at reducing their suffering and limiting the hypothetical progression of endometriosis [5]. Currently, there is a wide range of drugs that can be employed for the treatment of symptoms associated to endometriosis (Table 1).

According to major international guidelines, low-dose combined estro-progestins and progestogens should be considered standard first-line treatments for symptomatic endometriosis [36,137]. While COCs have traditionally been widely used for symptomatic endometriosis, progestins were relatively recently recognized as an effective standalone treatment option for managing endometriosis symptoms. Supporting their use, clinical trial data indicate that progestins generally have a favorable safety profile when used in long-term regimens [138]

Some authors highlight concerns about the supraphysiological levels of EE present in low-dose COCs, containing 20–30 mg of EE, advocating for the systematic use of progestogen monotherapies over COCs as the preferred first-line treatment for endometriosis [139]. Nevertheless, at the moment the choice between COCs and progestins as the primary treatment approach depends on various factors, including patient preferences, medical history, and potential contraindications. Furthermore, various methods of drug administration are accessible for these medications, such as depot injections, implants, or IUS, offering diverse options for long-term treatment. Although the lower thrombotic risk is associated with progestins, as opposed to estro-progestins [140], it is crucial to counsel patients on the actual risk of developing venous thromboembolism when using such combined hormonal contraceptives. In an average-risk adolescent population, the baseline incidence of spontaneous venous thromboembolism ranges from 4 to 11 per 100,000 women annually [141]. COCs may result in a 3- to 5-fold increase in the risk of venous thromboembolism, translating to a fluctuating risk between 10 and 30 events per 100,000 women annually among young COC users [142]. This risk may be further slightly reduced if the COC contains EE <20 mg or micronized 17b-E_2, or E_2 valerate, or estetrol [5]. Notably, given the mortality rate from venous thromboembolism in women aged 20–44 years is less than 1% [143], in the worst-case scenario of COC use in healthy adolescents, approximately one additional death would occur per 4–500,000 young women treated annually.

A significant portion of patients does not respond to combined estro-progestins or progestins for endometriosis, potentially due to progesterone resistance, possibly stemming from receptor subtype imbalances or adhesion molecule issues [144,145]. The current discourse often overlooks the diverse molecular and genetic characteristics related to the presence of at least three different phenotypes of endometriosis among patients, impacting their biological responses to estrogen suppression. Recognizing and addressing this heterogeneity will be critical for a nuanced understanding of the efficacy and limitations of hormonal therapies in managing endometriosis. Additionally, lacking in predictive biomarkers for progestin resistance, dynamic monitoring of patient responses is crucial for timely consideration of alternative treatments or optimal surgery scheduling. Limited research distinguishes patients discontinuing treatment due to ineffectiveness from those halting treatment due to hormone-related AEs [12].

For patients who do not respond adequately to first-line therapies, the use of GnRH agonists can be considered for a limited time, although they are associated with a less favorable tolerability profile. The optimal schedule for the dosages and duration of treatment with GnRH agonists remains a subject of controversy. It is important to note that long-term administration of these drugs is characterized by with a significant incidence of AEs related to hypoestrogenism, including a negative impact on BMD. These side effects can limit patients' adherence to the therapy. Therefore, when considering treatment with GnRH agonists for a duration longer than six months, it is crucial to incorporate an appropriate add-back therapy for mitigating the onset of estrogen-deprivation-related symptoms [12].

In light of the above, there is a growing demand for new alternative treatment options that can provide effective management of endometriosis with improved tolerability and fewer side effects. The development of such alternatives is crucial to meet the needs of patients who do not respond to standard therapies or experience intolerable side effects.

Over the last decade, there have been few notable advancements, prompting a significant emphasis on the evaluation of GnRH antagonists' efficacy and safety [91]. The principal advantages attributed to oral GnRH antagonists include dose-dependent estrogen suppression, with partial suppression at lower doses and nearly complete suppression at higher doses. These antagonists also offer the benefits of rapid reversibility and restoration of normal hormone secretion upon treatment discontinuation. Moreover, they provide immediate suppression of gonadotropins, effectively avoiding the flare-up effect [146,147].

Attaining a balance in hypoestrogenism levels is crucial, given its direct correlation with the clinical response. In simpler terms, mitigating side effects may compromise complete pain relief, as supported by Vercellini et al. [148]. This holds even greater significance considering the diverse phenotypes of endometriosis and the varying extent of the disease prevalent in patients, necessitating different degrees of estrogenic suppression. Existing data indicates that lower dosages of GnRH antagonists, which aim to maintain estrogen levels within a range favorable for preserving BMD, may not fully address endometriosis-associated pain. Moreover, studies on oral GnRH antagonists seem to suggest that hormonal add-back therapy is still required to prevent bone loss and mitigate menopausal side effects [146,147]. When comparing these drugs with GnRH agonists, the choice between a daily oral pill and a trimestral intramuscular injection is a matter of personal preference [107]. In comparison to GnRH agonists, it has been hypothesized that the faster recovery of normal E_2 levels and the onset of ovulation could potentially be advantageous for patients planning a pregnancy, although there is currently no available data on spontaneous pregnancy rates following discontinuation of GnRH antagonists [37]. In this perspective, further studies should aim to provide a more comprehensive definition of the long-term efficacy and safety of GnRH antagonists and ascertain the necessity for add-back therapy.

Most studies on AIs have involved a limited number of women who received relatively short therapy durations, typically around 6 months. Furthermore, it has been firmly established that both ANA and LTZ are associated with a significant incidence of AEs, including hot flushes, myalgia, and arthralgia. Consequently, these medications may not be well-tolerated by young patients dealing with a chronic benign disease, unlike in the oncologic context where these drugs are more extensively utilized. However, the current administration of AIs for endometriosis is off-label and therefore they should be given to patients with severe symptoms resistant to other conventional therapies. Up to now, no SERM and SPRM have been shown to be effective and to have an adequate safety profile for patients with endometriosis, despite the previous promising results on animals and limited data on humans [149]. The exploration of therapeutic targets within endometriotic lesions reveals potential interventions, such as STS inhibitors like E2MATE and 17β-HSD1 inhibitors like FOR-6219 [132]. These compounds, showcased in clinical trials, exhibit promising outcomes in reducing estrogenic activity and hold potential for addressing endometriosis-associated pain.

Current investigational trials on drugs for endometriosis encounter several limitations that warrant critical consideration. First, the frequent absence of a double-blinding design in trials investigating medical therapies poses a significant challenge. The recognition of active therapy by patients may compromise the integrity of blinding procedures, particularly given the subjective nature of symptoms. In terms of inclusion criteria, trials often focus on women with proven endometriosis, typically diagnosed through laparoscopy. However, this method frequently involves the previous removal of superficial and deep lesions, potentially biasing the representation of endometriosis severity in study cohorts.

More importantly, as already mentioned, endometriosis exhibits considerable heterogeneity in lesions, encompassing biochemical and likely genetic-epigenetic differences. Unfortunately, current trials inadequately address and stratify these variations, risking oversight of critical factors influencing treatment responses. The consideration of dysmenorrhea in the context of therapies abolishing menstruation introduces another limitation. As treatments aim to suppress or eliminate menstrual cycles, the assessment of dysmenorrhea becomes inherently challenging, complicating the interpretation of pain management outcomes.

As of the present, there is no sanctioned medical intervention exclusively designed for the management of adenomyosis, despite the widespread use of LNG-IUD in this setting [150]. The available evidence guiding the selection of optimal medical treatments is notably restricted, primarily attributed to the intricacies associated with diagnosis and the prevalent coexistence of other gynecological conditions, such as endometriosis and uterine leiomyomas. The presence of these concurrent conditions often complicates the determination of the most efficacious medical approach, occasionally necessitating recourse to surgical interventions. The well-established co-occurrence of endometriosis in individuals with adenomyosis is extensively documented, with a substantial number of cases presenting with both pathologies concurrently. This simultaneous manifestation poses intricate challenges in the symptomatic management and decisions pertaining to treatment modalities. Nevertheless, it has been observed that medical interventions targeting adenomyosis can confer favorable effects on symptoms associated with endometriosis.

As sustained by the academic group coordinated by Vercellini et al. [37], a stepped-care approach is emerging in endometriosis treatment to reduce financial and healthcare burdens. While about two-thirds of combined estro-progestins users, especially those on continuous regimens, find satisfaction, alternative therapies are needed for the remaining third of patients. Combined estro-progestins and progestins serve as a first-line option, while GnRH-agonists, GnRH-antagonists, or other medical therapies are considered second-line interventions [31]. This stepwise approach aims to offer tailored and effective management strategies, ensuring optimal treatment outcomes for individuals with endometriosis. Concerning this point, GnRH antagonists, possibly with add-back therapy for prolonged use (i.e. exceeding 6 months), may offer a valuable therapeutic avenue for cases unresponsive to first-line treatments like combined estro-progestins and progestins. Nevertheless, it is important to bear in mind that patients with extensive deep endometriosis (such as intestinal and bladder nodules) have used hormonal therapies for years to control pain and/or for contraception, but the impact of these therapies on the progression of unoperated deep nodules remain to be elucidated. Limited data showed that, in some patients, deep endometriosis can progress despite the use of hormonal therapies. More importantly, imaging exams, such as transvaginal ultrasound, should not only be performed only women reporting a worsening of clinical symptoms, as the progression of the disease might not be correlated with the worsening of clinical symptoms [151,152].

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