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REVIEW

Why do oestrogens matter: systematic review and meta-analysis assessing GnRH antagonists, considering add-back therapy, for endometriosis-associated pain

BIOGRAPHY

Manuela Viviano is an Obstetrics and Gynaecology Resident at Geneva University Hospitals, Switzerland. She has published over 30 articles on women's health, including topics such as cervical cancer screening, contraception and adolescents, most of which have been presented to national Swiss and international congresses.

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KEY MESSAGE

Gonadotrophin-releasing hormone antagonists are effective for endometriosis-associated pain, although, as their administration is restricted to short periods of time, the use of add-back therapy represents a promising option for long-term treatment.

ABSTRACT

Gonadotrophin-releasing hormone (GnRH) antagonists have been demonstrated to reduce endometriosis-associated pain. Because of the hypo-oestrogenic state they induce, however, higher dosages of GnRH antagonists are not recommended for used long term. This unwanted effect may be eliminated by so-called add-back therapy (ABT). This review was conducted to assess the safety and efficacy of GnRH antagonists, with or without add-back hormonal replacement therapy. Out of the 345 studies selected through the initial search, seven randomized controlled trials were included, comparing different oral GnRH antagonists at varying dosages, from a minimum of 50 mg to a maximum of 200 mg once or twice daily. Women treated with the lowest dose of GnRH antagonists had significantly greater mean pain score reductions from baseline throughout treatment compared with those treated with placebo (odds ratio [OR] −13.12, 95% CI −17.35 to −8.89 and OR −3.08, 95% CI −4.39 to −1.76 for dysmenorrhoea and non-menstrual pelvic pain, respectively). Compatible with the dose−response effect, a positive correlation was found between response rates and adverse event rates. While GnRH antagonists offer an advantage in terms of pain reduction for endometriosis, the more recent literature suggests using GnRH antagonists with ABT, which, while mitigating the hypo-oestrogenic effects of GnRH antagonists, maintain their efficacy, while allowing their long-term use.

INTRODUCTION

Endometriosis is a chronic disease producing an inflammatory reaction and is characterized by ectopic endometrial-like tissue implanted outside the uterus (*Sutton et al., 1997*). It affects approximately 10% of women of reproductive age and may be associated with infertility and pain symptoms, including dysmenorrhoea, chronic pelvic pain and dyspareunia (*Giudice, 2010*; *Zondervan et al., 2020*). These symptoms depend on the extent of proliferation of the endometriotic lesions, which occurs mainly under the influence of oestradiol (*Zondervan et al., 2020*), as well as on the extent of lesional fibrosis

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1472-6483/
Declaration: The authors report no financial or commercial conflicts of interest.

KEYWORDS

Add-back
Dysmenorrhoea
Endometriosis
Gonadotrophin-releasing hormone antagonists
Pelvic pain

(*Huang et al., 2021*; *Nie et al., 2022*). Based on this principle, current guidelines recommend the use of medical treatment to lower oestradiol synthesis by inhibiting ovulation and to counteract oestradiol activity in the lesional microenvironment (*Practice committee of the American Society for Reproductive Medicine, 2014*).

Combined oral contraceptives (COC) and progestin-only (PO) contraceptives are among the first-line treatments for endometriosis-associated pain (EAP). They can be administered in a cyclic or continuous fashion, although their side effects, which include increased risk of arterial or venous thromboembolism and breast tenderness for COC, and abnormal uterine bleeding for both COC and progestin-only contraceptives, may limit their use (*Barra et al., 2018*; *Rafique and Decherney, 2017*; *Tepper et al., 2016*). Additionally, approximately 30% of treated individuals do not respond to COC or progestin-only treatment due to progesterone resistance (*Vercellini et al., 2016*), which has been shown to be a consequence of a deficit or inactivity in progesterone receptors within endometriotic lesions. It has been linked to the proliferation and persistence of endometriotic implants and to the response to progestin-based treatment (*Donnez and Dolmans, 2021b*).

Another line of treatment is provided by gonadotrophin-releasing hormone (GnRH) agonists. These bind to the pituitary GnRH receptors and, after an initial flare-up effect, down-regulate the pituitary–ovarian axis due to an intrinsic negative feedback control; this translates into an hypo-oestrogenic state, decreasing blood oestradiol concentrations to 20 pg/ml or less (*Brown et al., 2010*). The hypo-oestrogenic state is responsible for the appearance of vasomotor menopausal symptoms and a decline in bone mineral density (BMD), limiting the duration of treatment to periods of 6–24 months, depending on the dose of the agonist administered. In addition, GnRH agonists can only be administered via a nasal spray twice daily or a daily or monthly injection, with unpredictable reversibility of treatment effects when the injectable depot form is used (*Practice committee of the American Society for Reproductive Medicine, 2014*).

In this context, the more recently introduced GnRH antagonists provide a valuable alternative for the medical treatment of endometriosis (*Küpker et al., 2002*). They induce a dose-dependent down-regulation of the hypothalamic–pituitary–gonadal axis by competitively binding to GnRH receptors. Unlike GnRH agonists, GnRH antagonists do not produce an initial flare-up effect and they can be administered orally, thus facilitating treatment compliance. The oral formulation also provides the possibility of titration, allowing partial oestradiol suppression at lower doses and full suppression at higher doses. GnRH agonists, in contrast, achieve full oestradiol suppression without the need for dose titration (*Donnez and Dolmans, 2021a*). Several orally active compounds are at present under investigation for the treatment of EAP.

With the aim of reducing the effects of hypo-oestrogenism on BMD, so-called 'add-back hormonal replacement therapy' (add-back therapy, ABT) has been advocated when using GnRH antagonists (*Donnez et al., 2022*). Yan and colleagues have published a systematic review and meta-analysis on the subject that includes studies published up to April 2022 (*Yan et al., 2022*).

Two recently published randomized controlled trials (RCT) from Giudice and co-workers have assessed the efficacy and safety of the orally active agent relugolix, with or without ABT. They evaluated the effects of the combined treatment, concluding that the combined regimen has the same efficacy as using GnRH antagonists alone in reducing EAP, since the hormonal replacement therapy allows oestradiol concentrations to remain within the therapeutic range of 30–60 pg/ml (*Giudice et al., 2022*). This type of combination treatment may provide a solution for the long-term management of EAP, although at an increased cost.

To determine whether GnRH antagonists can produce the same effects on EAP when administered with or without ABT, a systematic review of the literature was conducted. This was carried out because, if combined treatment is found to be as effective as a GnRH antagonist alone, it will offer a valuable long-term medical treatment, reducing the need for surgical treatment and analgesic use.

MATERIAL AND METHODS

As detailed below, the systematic literature search was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (*Moher D et al., 2009*). The protocol was registered on the International Prospective Register for Systematic reviews (PROSPERO) with the identification number CRD42022370617.

Search strategy

The search was performed on the MEDLINE, Web of Science and EMBASE databases. No language or date restrictions were applied. The following key keywords were used: "GnRH antagonists" or "Elagolix" or "Cetrorelix" or "Linzagolix" or "Relugolix" or "gonadotropin-releasing hormone antagonists" and "add-back" or "combination" and "therapy" and "endometriosis" and "randomized". The PRISMA flowchart is reported in FIGURE 1.

Eligibility criteria

The review included studies conducted on premenopausal women with a surgically proven diagnosis of endometriosis who were experiencing moderate to severe pain, comparing the use of GnRH antagonists, either alone or in combination with hormonal replacement therapy, with that of a placebo. Pain could be described as dyspareunia, chronic pelvic pain or dysmenorrhoea, or all of them.

Studies conducted on non-human subjects, and those providing insufficient data, including participants taking other medications, or evaluating non-EAP symptoms, were excluded.

Study selection

The screening process included the titles and abstracts of published articles. Case reports, editorials, reviews and short communications were excluded, as they did not provide sufficient information to assess the primary end-point. Two investigators independently performed the literature search and study selection.

Quality assessment

The investigators independently assessed the risk of bias using the Cochrane Risk of Bias tool (*Higgins et al., 2011*) and visualization using the robvis (Risk-Of-Bias VISualization) tool (*McGuinness and Higgins, 2020*).

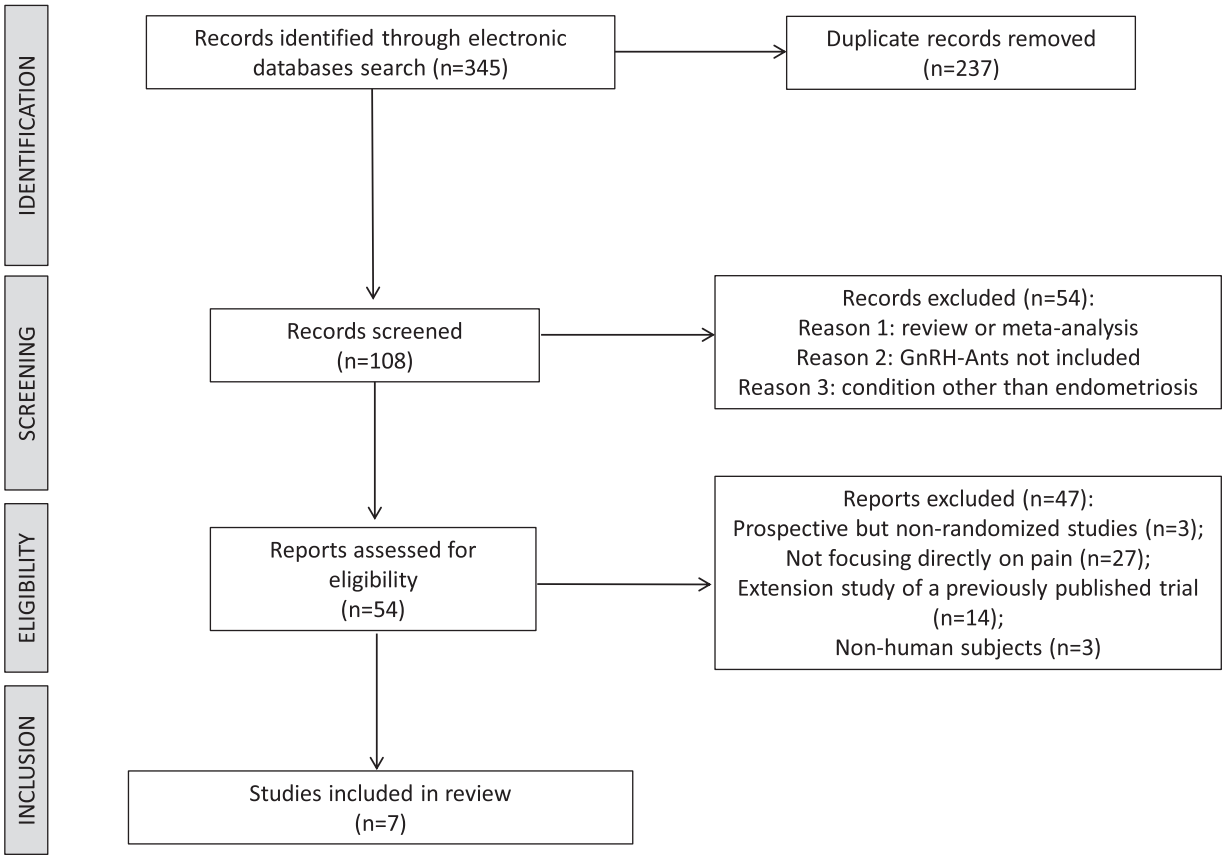

FIGURE 1 PRISMA flow diagram of the systematic review process. The electronic databases were MEDLINE, Web of Science and EMBASE. GnRH-Ants, gonadotropin-releasing hormone antagonists.

Statistical analysis

A chi-squared test for heterogeneity among means was performed to verify the presence of a statistical heterogeneity among the selected studies. The pooled mean and standard deviation (SD) were calculated using a random effects model. To facilitate comparability between different studies, the mean differences in terms of pain score were all converted to a visual analogue scale (VAS) score, which varied from a minimum of 0 to a maximum of 4, using the following formula: for any score *x* that ranged from 0 to *n*, the conversion would be *x* / *n* * 4 (*Giannoulis, 2023*). When necessary, 95% confidence intervals (CI) were converted to standard deviations following the Cochrane handbook guidelines (*Higgins et al., 2023*). The pooled means were represented as a square in the forest plot, their size corresponding to the relative standard deviation. A *P*-value of ≤0.05 was considered significant (*Amrhein et al., 2019*). The data extracted from the studies and included in the meta-analysis were analysed using Review Manager (*RevMan, Version 5.4, Copenhagen; The Nordic Cochrane Centre, The Cochrane Collaboration, 2014*).

The correlation between responder rates and overall adverse event rates was calculated using the immediate form of two-sample test of proportions on STATA 14 software (StataCorp LLC, USA). Spearman's correlation coefficient was calculated using R (version 4.3.1; The R Foundation, Austria), when possible, to test the association between responder rate and adverse event rate at dosages for elagolix of 150 mg once daily or 200 mg twice daily, linzagolix 50 mg, 75 mg, 75 mg titrated dose, 100 mg or 200 mg daily, and relugolix 40 mg daily combination therapy and delayed combination therapy.

RESULTS

The initial search carried out in November 2022 yielded 326 articles; of these, seven were selected for inclusion in the systematic review. A new search was conducted as per 1 October 2023, allowing the screening of a total of 345 articles. The 18 additional articles were all excluded because they were either duplicates ($n = 5$), literature or systematic reviews ($n = 7$) or case reports ($n = 1$), or did not concern endometriosis ($n = 5$). Following the previously stated inclusion and exclusion criteria, seven articles were selected to be included in the present review.

Population characteristics

All the included studies were RCT. Of these, the study by Harada and colleaues was a non-inferiority one, whereas the rest were all superiority trials. Five out of the seven studies were conducted in the USA (*Carr et al., 2013*; *Diamond et al., 2014*; *Donnez et al., 2020*; *Giudice et al., 2022*; *Taylor et al., 2017*). Of these, three also included European countries (*Donnez et al., 2020*; *Giudice et al., 2022*; *Taylor et al., 2017*). The two remaining studies were conducted exclusively in Japan (*Harada et al., 2022*; *Osuga et al., 2021b*).

FIGURE 2 Risk of bias assessment, using the Cochrane Risk of Bias tool. (A) Summary plot. (B) Traffic light plot. 'Judgement' refers to the risk of bias assessment and 'low' indicates a low risk of bias. Figure drawn using the robvis (Risk-Of-Bias VISualization) tool (*McGuinness and Higgins, 2020*).

The number of participants included varied between a minimum of 137 in the study by Carr and colleagues and a maximum of 872 in the trial by Taylor and collaborators (*Carr et al., 2013*; *Taylor et al., 2017*). The mean age of the patients varied from 31 to 37.1 years according to Diamond and colleagues and Harada and co-workers, respectively (*Diamond et al., 2014*; *Harada et al., 2022*). The mean body mass index varied from a minimum of 21.2 kg/m^2 to a maximum of 28.2 kg/m^2 (*Carr et al., 2013*; *Osuga et al., 2021b*). Overall, the quality of all the included studies was excellent.

FIGURE 2 illustrates the studies' risk of bias according to the Cochrane Risk of Bias assessment.

Efficacy outcomes

The included trials compared the oral formulations of relugolix, elagolix and linzagolix, either alone at different dosages or with ABT, with a placebo. Endometriosis had been surgically diagnosed in all patients except for those in the study by Harada and co-workers, in which up to 38.2% of women had a clinical, non-surgical diagnosis of endometriosis (*Harada et al., 2022*). The follow-up duration varied from a minimum of 4 weeks (*Osuga et al., 2021b*) to a maximum of 12 months (*Taylor et al., 2017*).

TABLE 1 reports the pain assessment methods and efficacy measures used in each trial. As the efficacy measure of the primary outcome, most studies assessed the change in mean monthly pain score from baseline throughout the treatment period. The adopted assessment measures included the 4-point Biberoglu and Behrman scale (*Biberoglu and Behrman, 1981*), the 11-point Numeric Rating Scale (NRS; *Gloth et al., 2001*), the 4-point Visual Rating Scale (*Sung and Jeng-Wu, 2018*), and the 0–100 Visual Analog Scale

TABLE 1 **PAIN ASSESSMENT METHODS USED IN THE INCLUDED STUDIES**

Study	Molecule	Dysmenorrhoea	Non-menstrual pelvic pain	Dyspareunia	Overall pelvic pain	Definition of response	Response rate (%)	Amenorrhoea rate (%)
Carr et al. (2013)	Elagolix 150 mg	Biberoglu and Behrman (0–3)	Biberoglu and Behrman (0–3)	Biberoglu and Behrman (0–3)	NA	Changes in monthly mean scores at 8W and 24W compared with baseline (CPSSS)	62.5% (dysmenorrhoea and non-menstrual pelvic pain at 8W)	25.8% in the first 8W, of whom 7.6% remained amenorrhoeic throughout the 24W
Diamond et al. (2014)	Elagolix 150 mg, elagolix 250 mg	Biberoglu and Behrman (0–3)	Biberoglu and Behrman (0–3)	CPSSS (dyspareunia component)	NRS (0–10)	Changes in monthly mean scores at 12W and 24W compared with baseline	NA	NA
Taylor et al. (2017) (Elaris-I)	Elagolix 150 mg, elagolix 200 mg twice daily	NRS (0–10)	NRS (0–10)	NRS (0–3)	NRS (0–3)	Changes in the proportion of women with at least a −0.81 change in dysmenorrhoea and −0.36 for NMPP; decreased or stable use of analgesics at 3Mo and 6Mo	46.4%, 75.8%.	3.2%, 5.6%
Taylor et al. (2017) (Elaris-II)	Elagolix 150 mg, elagolix 200 mg twice daily	NRS (0–10)	NRS (0–10)	NRS (0–3)	NRS (0–3)	Changes in the proportion of women with at least a −0.85 change in dysmenorrhea and −0.45 for NMPP; decreased or stable use of analgesics at 3Mo and 6Mo	43.4%, 72.4%	4.9%, 8.7%
Donnez et al. (2020)	Linzagolix 50 mg, linzagolix 75 mg, linzagolix 100 mg, linzagolix 200 mg, linzagolix 75 mg[a]	VRS (0–3)	VRS (0–3)	VRS (0–3)	NRS (0–10)	Reduction of ≥30% in the mean overall pelvic pain score from baseline to 12W	49.4%, 61.5%, 56.4%, 56.3%	11.1%, 36.3%, 55.8%, 80.9% at 12W
Osuga et al. (2021)	Relugolix 10 mg, relugolix 20 mg, relugolix 40 mg	VAS (0–100 mm)	VAS (0–100 mm)	VAS (0–100 mm)	VAS (0–100 mm)	Mean change from baseline in the VAS score for 28 days before the end of the treatment period	NA	NA
Giudice et al. (2022) (SPIRIT 1)	Relugolix 40 mg, CT relugolix 40 mg DCT	NRS (0–10)	NRS (0–10)	NRS (0–10)	NRS (0–10)	Proportion of responders at 24W for dysmenorrhoea and pelvic pain based on NRS score	75%/59%, 72%/58% (dysmenorrhoea/pelvic pain)	NA
Giudice et al. (2022) (SPIRIT 2)	Relugolix 40 mg, CT relugolix 40 mg DCT	NRS (0–10)	NRS (0–10)	NRS (0–10)	NRS (0–10)	Proportion of responders at 24W for dysmenorrhea and pelvic pain based on NRS score	75%/66%, 73%/53% (dysmenorrhoea/pelvic pain)	NA
Harada et al. (2022)	Relugolix 40 mg	VAS (0–100)	VAS (0–100)	VAS (0–100)	VAS (0–100)	Change in maximum and mean VAS score from baseline to 24W	NA	94.20%

3Mo, 3 months; 6Mo, 6 months; 8W, 8 weeks; 24W, 24 weeks; CPSSS, composite pelvic signs and symptoms score; CT, relugolix combination therapy (1 mg oestradiol, 0.5 mg norethisterone acetate); DCT, delayed relugolix combination therapy (relugolix alone for 12 weeks followed by relugolix CT for the following 12 weeks); NA, not assessed; NMPP, non-menstrual pelvic pain; NRS, Numeric Rating Scale; VAS, Visual Analog Scale; VRS, Visual Rating Scale.

[a] Titrated dose.

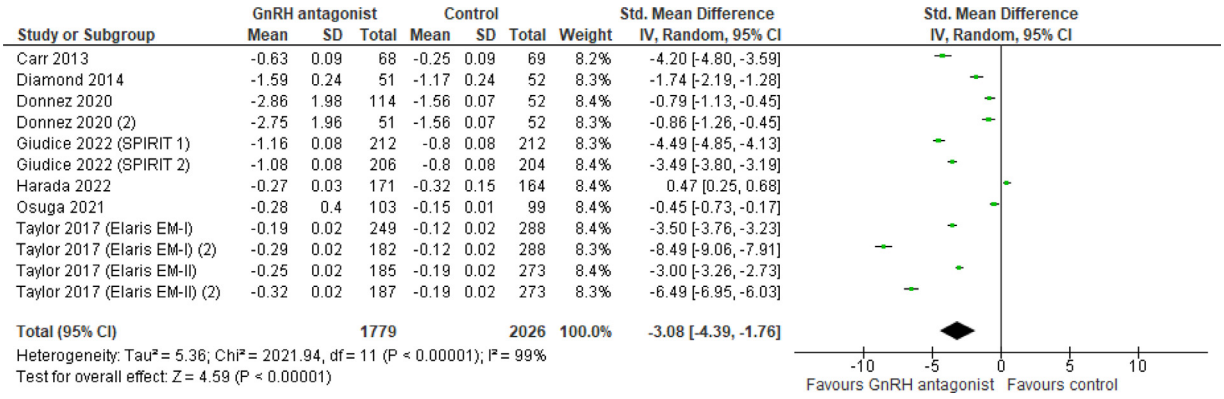

FIGURE 3 Change in non-menstrual pelvic pain from baseline: pooled analysis of mean score reductions in non-menstrual pelvic pain. Each study refers to the lowest dose used with the exception of: Taylor 2017 (Elaris EM-I) (2), elagolix 200 mg twice daily; Taylor 2017 (Elaris EM-II) (2), elagolix 200 mg twice daily; Donnez 2020, linzagolix 75 mg; Donnez 2020 (2), linzagolix 200 mg. GnRH, gonadotrophin-releasing hormone; IV, inverse variance.

(*Hayes and Patterson, 1921*; *Yeung and Wong, 2019*).

Pelvic pain

EAP was measured using the VAS by Harada and co-workers, with scores varying from a minimum of 0 (no pain) to a maximum of 100 (excruciating pain) (*Harada et al., 2022*); the authors found that the maximum VAS pain score decreased by 52 ± 1.3 points from baseline to week 24 of treatment among women treated with relugolix; in addition, this reduction proved to be non-inferior to that obtained among women treated with the GnRH agonist leuprorelin (*Harada et al., 2022*).

Carr and colleagues assessed EAP using a 4-point modified Biberoglu–Behrman scale, ranging from 0 (no pain) to a maximum of 3 (severe pain); the authors found significantly greater mean reductions of non-cyclic pelvic pain among women treated with elagolix 150 mg (−0.47 versus −0.19 for placebo, $P = 0.0066$) after 8 weeks of treatment (*Carr et al., 2013*). The same authors found significantly greater mean reductions from baseline to week 8 in monthly cumulative pain among women treated with elagolix compared with placebo (−0.55 versus −0.21, respectively, $P = 0.0011$) (*Carr et al., 2013*).

According to Donnez and co-workers, treatment with linzagolix 50, 75, 100 or 200 mg daily yielded a significantly higher percentage of women experiencing an overall pain reduction of 30% more more compared with placebo (61.5%, 56.4% and 56.3% versus 34.5%, respectively) (*Donnez et al., 2020*). In the Elaris EM-I trial, 50.4% of women treated with elagolix 150 mg and 54.5% of women treated with elagolix 200 mg twice daily experienced a clinically meaningful reduction in non-menstrual pelvic pain, compared with only 36.5% in the placebo group (*Taylor et al., 2017*). The outcome in the Elaris EM-I and Elaris EM-II trials was measured using a 4-point NRS (*Yeung and Wong, 2019*).

In their primary study, Osuga and collaborators assessed pain on the 10-point VAS scale and found that women treated with relugolix had statistically significant differences in pelvic pain compared with placebo (−2.9 for relugolix 10 mg, −4.3 for relugolix 20 mg and −6.8 for relugolix 40 mg) (*Osuga et al., 2021b*). The same authors observed a progressive reduction in the mean VAS score for pelvic pain throughout the treatment period in the relugolix groups (*Osuga et al., 2021b*).

In the SPIRIT 1 and SPIRIT 2 trials, Giudice and colleagues assessed the efficacy and safety of relugolix combination therapy, consisting of oral relugolix 40 mg combined with 1 mg of oestradiol and 0.5 mg of norethisterone acetate daily for 24 weeks, with delayed combination therapy, consisting of oral relugolix 40 mg daily for the first 12 weeks, followed by oral relugolix 40 mg combined with 1 mg oestradiol and 0.5 mg norethisterone acetate daily throughout the following 12 weeks (*Giudice et al., 2022*). The authors observed a substantial decrease in the NRS score for non-menstrual pelvic pain from baseline to week 24 of treatment among women treated with combination therapy compared with placebo (−2.9 and −2.8 for relugolix combination therapy and delayed relugolix combination therapy,respectively, versus −2.0 for placebo in the SPIRIT 1 trial) (*Giudice et al., 2022*).

As reported in **FIGURE 3**, the comparison of the mean score reduction for non-menstrual pelvic pain across the included studies revealed that women treated with GnRH antagonists at the lowest dose had significantly greater mean pain score reductions from baseline throughout treatment compared with women treated with placebo (odds ratio [OR] −3.08, 95% CI −4.39 to −1.76).

FIGURE 4 depicts the comparison in terms of mean non-menstrual pelvic pain between relugolix 40 mg given alone or administered with ABT. There was no significant difference in terms of non-menstrual pelvic pain between the relugolix alone and combination therapies ($P = 0.41$).

Dysmenorrhoea

According to Harada and co-workers, the maximum VAS score for dysmenorrhoea decreased significantly from 63.3 at baseline to 2.1 at week 24 among women treated with relugolix. These results were also obtained for dyspareunia and non-cyclic pelvic pain, all of which proved to be non-inferior to those obtained among women treated with leuprorelin (*Harada et al., 2022*). Diamond and colleagues used the NRS to assess efficacy in pain management, finding that the reduction in dysmenorrhoea was significantly greater among women treated with elagolix 150 mg or 250 mg compared with placebo ($P = 0.0021$ and $P = 0.0003$, respectively) (*Diamond et al., 2014*).

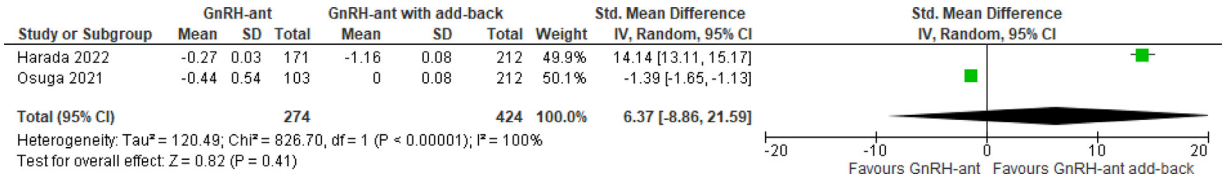

FIGURE 4 Comparison of the change in mean non-menstrual pelvic pain between relugolix 40 mg alone and relugolix 40 mg with add-back therapy. Values for GnRH antagonists with add-back therapy were obtained from the SPIRIT-1 trial. GnRH-ant, gonadotrophin-releasing hormone antagonist; IV, inverse variance.

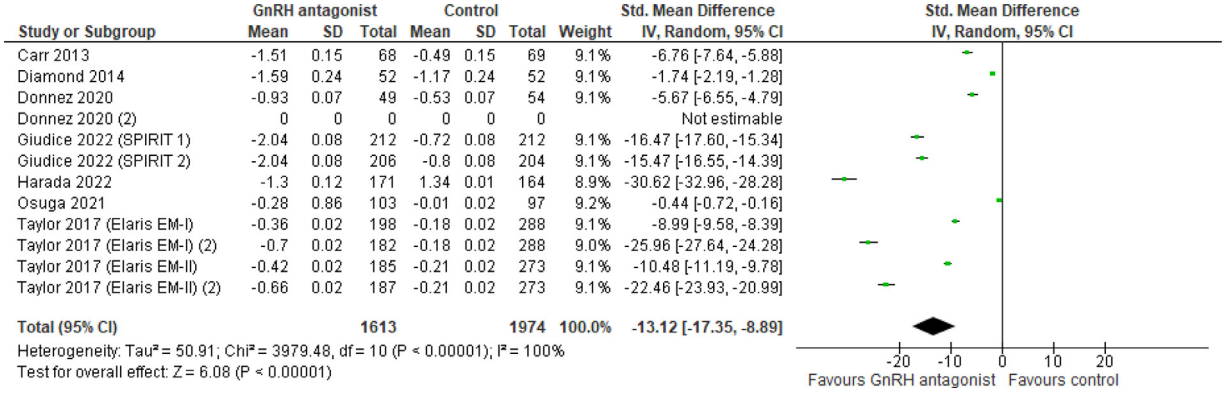

FIGURE 5 Mean change in dysmenorrhoea score from baseline. Each study refers to the lowest dose used, with the exception of: Taylor 2017 (Elaris EM-I) (2), elagolix 200 mg twice daily; Taylor 2017 (Elaris EM-II) (2), elagolix 200 mg twice daily; Donnez 2020, linzagolix 75 mg; Donnez 2020 (2), linzagolix 200 mg. GnRH, gonadotrophin-releasing hormone; IV, inverse variance.

Carr and colleagues reported a higher percentage of patients who had at least a 30% reduction in pain scores from baseline to week 8 for dysmenorrhoea (62.5% versus 32.8% with elagolix 150 mg and placebo, respectively; $P = 0.0008$) (*Carr et al., 2013*). In Elaris EM-I, as many as 46.4% of women treated with elagolix 150 mg and up to 75.8% of women treated with elagolix 200 mg twice daily experienced a clinically meaningful decrease in dysmenorrhoea, compared with only 19.6% of women who had received placebo (*Taylor et al., 2017*). The reductions in dysmenorrhoea and non-menstrual pelvic pain were apparent after 1 month and persisted at 6 months of treatment. In their trials evaluating the efficacy of relugolix combination therapy, Giudice and colleagues found that the NRS score for dysmenorrhoea decreased significantly, with up to a −5.1 difference versus −1.8 among women treated with relugolix combination therapy versus placebo, respectively, in the SPIRIT 1 trial (*Giudice et al., 2022*).

As reported in FIGURE 5, the comparison of the mean score reduction for dysmenorrhoea across all the included studies revealed that women treated with GnRH antagonists at the lowest dose had significantly greater mean pain score reductions from baseline throughout treatment compared with those treated with placebo (OR −13.12, 95% CI −17.35 to −8.89).

FIGURE 6 shows the comparison in terms of mean changes in dysmenorrhoea between relugolix 40 mg and the same GnRH antagonist when administered with ABT. There was no significant difference in terms of dysmenorrhoea between relugolix given alone or in combination therapy ($P = 0.15$).

Dyspareunia

According to Diamond and colleagues, the NRS score for dyspareunia decreased significantly with elagolix 150 mg compared with placebo at weeks 8 and 12 of treatment, whereas — surprisingly — women treated with elagolix 250 mg had a significantly smaller reduction in dyspareunia compared with placebo at weeks 4 and 8 (*Diamond et al., 2014*); the scores were also lower at week 12, although the mean reduction did not reach statistical significance (*Diamond et al.,*

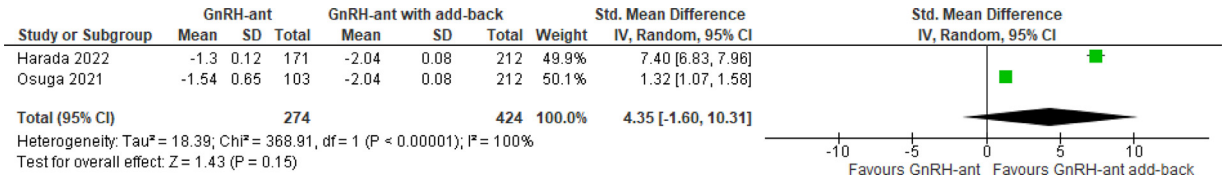

FIGURE 6 Comparison of the change in mean dysmenorrhoea score between relugolix 40 mg and relugolix 40 mg with add-back therapy. Values for GnRH antagonists with add-back therapy were obtained from the SPIRIT 1 trial. GnRH-ant, gonadotrophin-releasing hormone antagonist; IV, inverse variance.

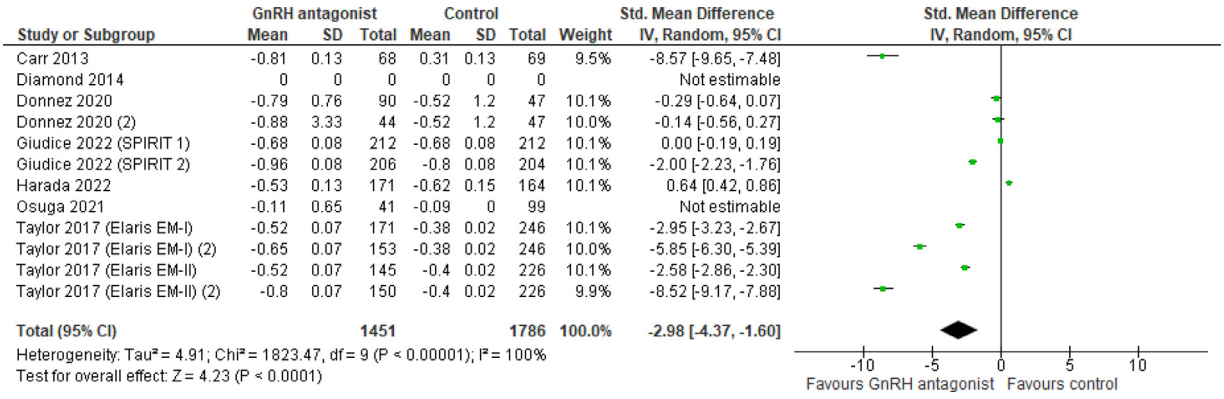

FIGURE 7 Change of mean dyspareunia score from baseline. Each study refers to the lowest dose used, with the exception of: Taylor 2017 (Elaris EM-I) (2), elagolix 200 mg twice daily; Taylor 2017 (Elaris EM-II) (2), elagolix 200 mg twice daily; Donnez 2020, linzagolix 75 mg; Donnez 2020 (2), linzagolix 200 mg. GnRH, gonadotrophin-releasing hormone; IV, inverse variance.

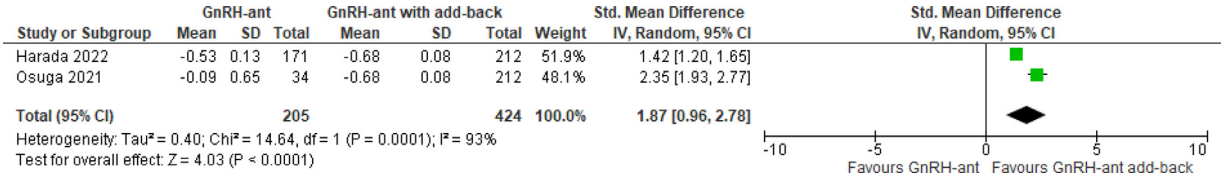

FIGURE 8 Comparison of the change in mean dyspareunia score between relugolix 40 mg and relugolix 40 mg with add-back therapy. Values for GnRH antagonists with add-back therapy were obtained from the SPIRIT 1 trial. GnRH-ant, gonadotrophin-releasing hormone antagonist; IV, inverse variance.

2014). Similar to the results obtained for non-cyclical pelvic pain and dysmenorrhoea, Carr and colleagues found a significantly greater mean reduction from baseline to week 8 among women treated with elagolix 150 mg compared with placebo (−0.61 versus −0.23, respectively; $P = 0.0070$) (*Carr et al., 2013*).

According to Donnez and co-workers, NRS scores for dyspareunia decreased significantly in the group of women treated with linzagolix 200 mg compared with placebo ($P = 0.023$) (*Donnez et al., 2020*). Osuga and collaborators found no clear trend of change in the dyspareunia and dysmenorrhoea scores among women treated with either 10, 20 or 40 mg of relugolix compared with leuprorelin (*Osuga et al., 2021b*). Similarly, Giudice and colleagues observed a significant reduction in dyspareunia NRS score among women treated with relugolix combination therapy (−2.4 versus −1.7 for relugolix combination therapy versus placebo, respectively, in the SPIRIT 1 trial).

FIGURE 7 reports the reduction in dyspareunia scores across selected studies. The analysis revealed a modest reduction in dyspareunia among women treated with GnRH antagonists at the lowest dose compared with placebo (OR −2.98, 95% CI −4.37 to −1.60).

FIGURE 8 shows the comparison in terms of the mean change in dysmenorrhoea score between relugolix 40 mg and the same GnRH antagonist when administered with ABT. There was a significant difference in terms of dyspareunia reduction between relugolix alone and in combination therapy, the latter being associated with greater pain reduction ($P < 0.0001$).

FIGURE 9 reports the response rates according to the different molecules, for studies in which such data were available. Spearman's correlation coefficient was calculated to test for a correlation between the response rate and the dosage, obtaining values of 0.86 ($P = 0.057$), 0.97 ($P = 0.005$) and −0.94 ($P = 0.057$) for Taylor and collaborators (elagolix 150 mg and 400 mg daily), Donnez and co-workers (linzagolix 50 mg, 75 mg, 75 mg titrated dose, 100 mg and 200 mg daily) and Giudice and colleagues (relugolix 40 mg in combination therapy and delayed combination therapy), respectively (*Donnez et al., 2020*; *Giudice et al., 2022*; *Taylor et al., 2017*). The data appear to suggest that, first, there is substantial heterogeneity among the different GnRH antagonist molecules, and second, that there is a positive correlation between the dosage and the response rate for linzagolix. However, for elagolix and relugolix, the correlation did not reach significance, with the directionality for relugolix appearing counterintuitive.

Use of analgesics

Harada and co-workers found that the mean number of days of analgesics decreased from baseline to week 24 both in women treated with relugolix (from 9.3 to 0.4) and in those treated with leuprorelin (from 11.2 to 0.4) (*Harada et al., 2022*). According to Diamond and colleagues, prescription of analgesics showed a modest decrease from baseline throughout week 12 across the three groups of women treated with either placebo, elagolix 150 mg or elagolix 250 mg, although the reductions were slightly greater in the group of women treated with elagolix 150 mg and elagolix 250 mg (−3.3, −2.6 and −2.2 for elagolix 250 mg, elagolix 150 mg and placebo, respectively) (*Diamond et al., 2014*). According to Carr and colleagues, treatment with elagolix 150 mg was associated with a greater mean reduction of the percentage of days of analgesic use

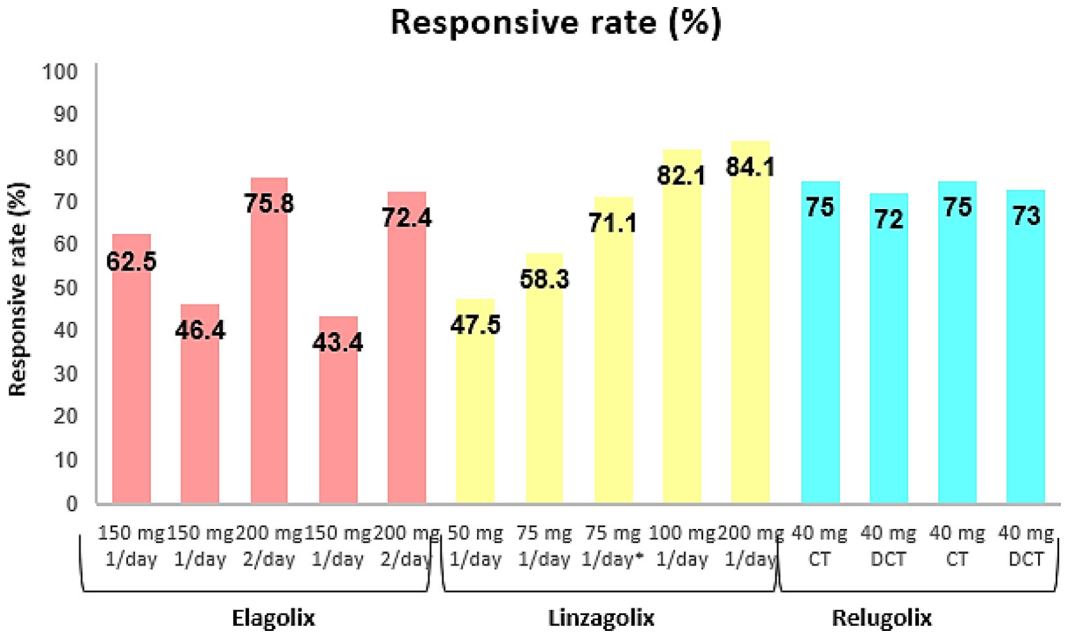

FIGURE 9 Response rates according to the different molecules and dosages. 1/day*, titrated linzagolix dose; CT, combination therapy; DCT, delayed combination therapy.

from baseline to week 8 when compared with placebo (−21.6% versus −9.2%; $P = 0.0019$, for any analgesic use) (*Carr et al., 2013*). Similarly, Donnez and co-workers found that although more than 95% of women were using analgesics for EAP at baseline, the rate decreased to 76.1–68.9% among those treated with linzagolix between the doses of 75 mg ($P = 0.030$), 100 mg ($P = 0.012$) and 200 mg ($P = 0.024$) (*Donnez et al., 2020*).

According to Taylor and collaborators, women treated with elagolix at high doses (250 mg twice daily) required a significantly lower amount of any rescue analgesic drug compared with women who received placebo (*Taylor et al., 2017*). On the other hand, women treated with elagolix 150 mg once daily did not show a significantly different reduction in rescue analgesic use after either 3 or 6 months of treatment when compared with women who received a placebo (*Taylor et al., 2017*). In a dose–response study, Osuga and collborators observed a progressive reduction in the frequency of analgesic use with the increase in relugolix dose (*Osuga et al., 2021b*).

According to Giudice and colleagues, more women treated with relugolix combination therapy were opioid-free at treatment week 24 of treatment compared with the placebo group (56% and 58% for relugolix combination therapy and delayed combination therapy, respectively, versus 31% in the placebo group in the SPIRIT 1 trial). Although the same authors found that the change in daily analgesic use was not significantly different between women treated with placebo and those treated with relugolix combination therapy (−0.4 ± 0.1 and −0.5 ± 0.1, respectively; $P = 0.41$), the proportion of patients not using analgesics for EAP was significantly higher among women treated with relugolix combination therapy compared with those treated with placebo (31% versus 56%, respectively; $P < 0.0001$) (*Giudice et al., 2022*).

The results of the meta-analysis showed a greater reduction in daily analgesic use among women treated with GnRH antagonists compared with the respective control groups (OR −0.13, 95% CI −0.24 to −0.02).

Quality of life

TABLE 2 reports the methods used to assess quality of life across the included studies.

The Endometriosis Health Profile-30

The Endometriosis Health Profile-30 (EHP-30) questionnaire evaluates five domains concerning quality of life, namely, pain, control and powerlessness, emotional well-being, social support and self-image (*Jones et al., 2004*).

The EHP-30 scores improved among women treated with relugolix and leuprorelin in a similar manner in the non-inferiority study conducted by Harada and co-workers (*Harada et al., 2022*). Diamond and colleagues found improvements in the three treatment groups (elagolix 150 mg, elagolix 250 mg and placebo) with regard to all five domains explored with the EHP-30 questionnaire at 12 weeks of treatment, with the greatest improvement found among women treated with elagolix 150 mg (the pain dimension mean change from baseline was −11.9 ± 3.3, −23.1 ± 3.0 and −19.2 ± 3.1 among women treated with placebo, elagolix 150 mg and elagolix 250 mg, respectively) (*Diamond et al., 2014*). For four of the five dimensions of the EHP-30 (redefined as EHP-5 by the authors), namely, pain, control and powerlessness, emotional well-being, social support and self-image, Carr and colleagues found a greater mean reduction at week 8 with elagolix compared with placebo (for the pain domain, −28.3 ± 2.9 versus −13.0 ± 2.9 for women treated with elagolix or placebo, respectively) (*Carr et al., 2013*).

Similarly, Donnez and co-workers found that, based on the results of the EHP-30 questionnaire, the quality of life of women treated with linzagolix improved, in particular with respect to the pain, control and powerlessness domains, regardless of the GnRH antagonist dose (*Donnez et al.,*

TABLE 2 QUALITY OF LIFE ASSESSMENT METHODS USED IN THE INCLUDED STUDIES

Study	Molecule(s)	Questionnaire
Carr et al. (2013)	Elagolix 150 mg	EHP-5, PGIC (7-point scale)
Diamond et al. (2014	Elagolix 150 mg, elagolix 250 mg	EHP-5, PGIC
Taylor et al. (2017) (Elaris-I)	Elagolix 150 mg, elagolix 200 mg twice daily	PGIC, EHP-30
Taylor et al. (2017) (Elaris-II)	Elagolix 150 mg, elagolix 200 mg twice daily	
Donnez et al. (2020)	Linzagolix 50 mg, linzagolix 75 mg, linzagolix 200 mg, linzagolix 75 mg [a]	PGIC, EHP-30
Osuga et al. (2021b)	Relugolix 10 mg, relugolix 20 mg, relugolix 40 mg	EHP-30
Giudice et al. (2022)	Relugolix 40 mg, CT relugolix 40 mg DCT	PGIC, EHP-30
Harada et al. (2022)	Relugolix 40 mg	EHP-30, Work Productivity and Activity Impairment Questionnaire: General Health

CT, relugolix combination therapy (1 mg oestradiol, 0.5 mg norethisterone acetate); DCT, delayed relugolix combination therapy (relugolix alone for 12 weeks followed by relugolix CT for the following 12 weeks); EHP-5, Endometriosis Health Profile-5; EHP-30, Endometriosis Health Profile-30; PGIC, Patient Global Impression of Change.
[a] Titrated dose.

2020). In the SPIRIT 1 and SPIRIT 2 trials, Giudice and colleagues obtained a significant improvement in EHP-30 scores among women treated with relugolix combination therapy compared with placebo (−33.8 ± 1.8 versus −18.7 ± 1.8 for relugolix combination therapy and placebo, respectively in SPIRIT 1 and −32.2 ± 1.7 versus −19.9 ± 1.7 for relugolix combination therapy and placebo, respectively in SPIRIT 2) (*Giudice et al., 2022*). In line with the previously mentioned studies, Osuga and collaborators found an improvement in EHP-30 scores among women treated with relugolix (*Osuga et al., 2021b*).

As reported in FIGURE 10, the results of the meta-analysis on the EHP-30 mean change from baseline show a consistent improvement in quality of life among the selected studies (OR −5.01, 95% CI −8.34 to −1.68).

The Patient Global Impression of Change questionnaire

Diamond and colleagues evaluated the Patient Global Impression of Change (PGIC) and found that the relative scores changed from 'no change' or 'minimal improvement' at the end of the placebo lead-in period to 'much improved' at week 12 among women treated with elagolix (*Diamond et al., 2014*). In the study by Carr and colleagues, at week 8 up to 60.3% of patients treated with elagolix reported feeling that their overall condition was 'much improved' or 'very much improved', compared with 30% of patients who had received placebo (*Carr et al., 2013*).

According to Donnez and co-workers, a significantly higher percentage of women treated with linzagolix 75, 100, and 200 mg reported they were 'much' or 'very much' improved on the PGIC scale when compared with women treated with placebo (*Donnez et al., 2020*). According to Taylor and collaborators, significantly more women taking elagolix either 150 mg once daily or 200 mg twice daily of reported 'much' or 'very much' improvement on the PGIC scale at 6 months of treatment (*Taylor et al., 2017*).

Work Productivity and Activity Impairment Questionnaire: General Health

The Work Productivity and Activity Impairment Questionnaire: General Health showed an improvement among women treated with relugolix and leuprorelin in a similar manner in the non-inferiority study conducted by Harada and co-workers (*Harada et al., 2022*).

Hormone concentrations

Serum concentrations of oestradiol, LH and FSH hormone decreased from baseline to week 24 of treatment in both groups of women receiving either relugolix or leuprorelin in the non-inferiority study by Harada and co-workers. Serum oestradiol concentrations recovered during the follow-up period for patients in the group treated with relugolix, but not in the group treated with leuprorelin (*Harada et al., 2022*). In the study by Diamond colleagues, mean serum oestradiol concentrations at week 8 of treatment were 57.0, 35.8 and 32.6 pg/ml for the placebo, elagolix 150 mg and elagolix 250 mg groups, respectively. Oestradiol

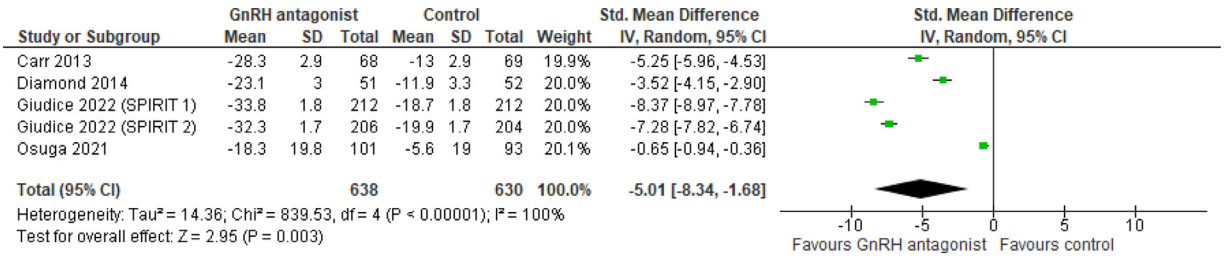

FIGURE 10 Mean change from baseline in the Endometriosis Health Profile-30 (EHP-30) score. Each study refers to the lowest dose used. GnRH, gonadotrophin-releasing hormone; IV, inverse variance.

TABLE 3 MOST FREQUENTLY REPORTED ADVERSE EVENTS

Study	Molecule(s)	AE type and frequency (%)	Overall incidence of any AE (%)
Carr et al. (2013)	Elagolix 150 mg	Nausea (9.9), headache (9.9), hot flushes (9.9)	51.5
Diamond et al. (2014)	Elagolix 150 mg, elagolix 250 mg	Headache (9.8, 7.7), nausea (9.8, 5.8), anxiety (5.9, 5.8)	31.4, 42.3
Taylor et al. (2017) (Elaris-I)	Elagolix 150 mg, elagolix 200 mg twice daily	Hot flushes (23.7, 42.3), headache (15.3, 17.3), nausea	80.7, 82.7
Taylor et al. (2017) (Elaris-II)	Elagolix 150 mg, elagolix 200 mg twice daily	Hot flushes (22.6, 47.6), headache (18.6, 22.7), nausea	79.2, 84.7
Donnez et al. (2020)	Linzagolix 50 mg, linzagolix 75 mg, linzagolix 100 mg, linzagolix 200 mg	Hot flushes (14.3, 19.3, 26.9, 42.1), headache (20.4, 20.2, 23.1, 29.8)	57.1, 64.9, 65.4, 71.9
Osuga et al. (2021b)	Relugolix 10 mg, relugolix 20 mg, relugolix 40 mg	Nasopharyngitis (20.4, 19.0, 21.4), metrorrhagia (25.2, 30.0, 24.3), hot flushes (8.7, 19.0, 52.4)	79.6, 89.0, 94.2
Giudice et al. (2022) (SPIRIT 1)	Relugolix 40 mg, CT relugolix 40 mg DCT	Headaches (27, 32), nasopharyngitis (6, 5), hot flushes (10, 34)	71, 77
Giudice et al. (2022) (SPIRIT 2)	Relugolix 40 mg, CT relugolix 40 mg DCT	Headaches (39, 38), nasopharyngitis (14, 7), hot flushes (14, 35)	81, 82
Harada et al. (2022)	Relugolix 40 mg	Hot flushes (42.7), metrorrhagia (31.0), headache (10.5)	90.1

AE, adverse events; CT, relugolix combination therapy (1 mg oestradiol, 0.5 mg norethisterone acetate); DCT, delayed relugolix combination therapy (relugolix alone for 12 weeks followed by relugolix CT for the following 12 weeks).

concentrations remained unchanged in the two groups treated with elagolix up to week 12 and up until week 24, while they increased among women who received a placebo (*Diamond et al., 2014*).

According to Donnez and co-workers, women treated with 200 mg of linzagolix experienced a rapid and full suppression of oestradiol concentrations to 11 pg/ml by week 4 of treatment, and this remained unchanged at week 24. Participants treated with linzagolix at lower doses showed a dose-dependent partial suppression of oestradiol, with values ranging from 20 to 60 pg/ml (*Donnez et al., 2020*).

Safety outcomes

Type and frequency of adverse events

In the non-inferiority study conducted by Harada and co-workers, the incidence of drug-related adverse events was 75.9% and 90.9% in the groups treated with relugolix 40 mg and leuprorelin, respectively. The most frequently reported adverse events were hot flushes, metrorrhagia and headache (*Harada et al., 2022*). Diamond and colleagues found that the most frequently reported adverse events were headache (1.9%, 9.8% and 7.7% for placebo, elagolix 150 mg and elagolix 250 mg, respectively), nausea (1.9%, 9.8% and 5.8%) and anxiety (0.0%, 5.9% and 5.8%) (*Diamond et al., 2014*). Similarly, Carr and colleagues found that the most frequently reported adverse events were nausea, headache, and hot flushes, each of which occurred in 9.9% of women treated with elagolix 150 mg. The frequency was comparable to that found among women treated with placebo (*Carr et al., 2013*).

According to Donnez and co-workers, the most frequently reported adverse events were hot flushes and headaches, the former being more frequent with linzagolix 200 mg (*Donnez et al., 2020*). In the Elaris EM-I and Elaris EM-II trials, more than 70% of women in each trial group reported at least one adverse event, the most frequent being hot flushes, headache or nausea. Discontinuation due to hot flushes occurred in less than 3% of participants treated with elagolix 200 mg twice daily in the Elaris EM-I trial (*Taylor et al., 2017*).

In their 24-week extension study, Osuga and collaborators observed that the adverse events reported with a frequency of 10% or more were nasopharyngitis, headache, metrorrhagia, irregular menstruation, menorrhagia, oligomenorrhoea, hyperhidrosis and hot flushes (*Osuga et al., 2021a*). In their SPIRIT 1 and SPIRIT 2 trials, Giudice and colleagues observed a higher incidence of hot flushes among women treated with delayed relugolix combination therapy compared with the other groups, and this mostly occurred throughout the first 12 weeks of treatment (34% in the delayed combination therapy group versus 10% in both the relugolix combination therapy and placebo groups in SPIRIT 1) (*Giudice et al., 2022*).

TABLE 3 summarizes the most frequently reported adverse events and their relative incidence across the selected studies.

FIGURE 11 depicts the most frequently reported adverse events by molecule used. When comparing high-dose antagonists with combination therapy, the rate of hot flushes was lower with the latter, while the rate of headache remained stable despite the use of ABT.

TABLE 4 shows the correlation between response rates for overall pelvic pain and adverse event rates. In the Elaris EM-I and EM-II trials, the administration of elagolix 200 mg twice daily corresponded to a response rate of 75.8% and of 72.4% in the Elaris EM-I and Elaris EM-II trials, respectively. The corresponding adverse event rates were 82.7% (Elaris EM-I) and 84.7% (Elaris EM-II) ($P = 0.053$ and 0.002 for Elaris EM-I and Elaris EM-II, respectively). A significant correlation was also found between the response rates obtained with elagolix 150 mg (46.4% and 43.4% in Elaris EM-I and Elaris EM-II,

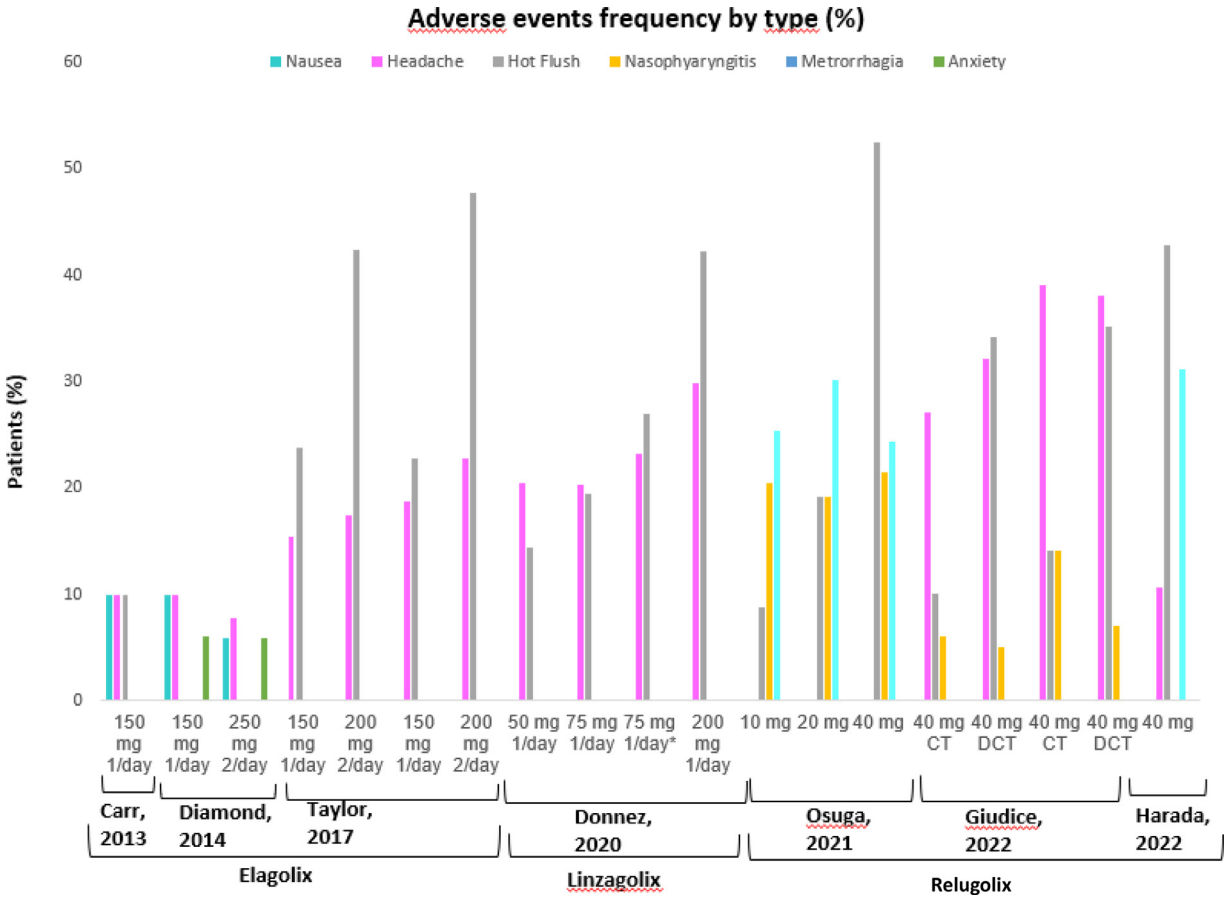

FIGURE 11 Adverse event frequency according to the type of molecule used. CT, combination therapy; DCT, delayed combination therapy.

respectively) and the relative adverse event rates (80.7% and 79.2% in Elaris EM-I and Elaris EM-II, respectively) ($P < 0.001$ for the same comparison in the two trials).

In the SPIRIT 2 trial, there was a significant association between the rate of response obtained with relugolix delayed combination therapy (73%) and the adverse event rate obtained with the same combination therapy (82%) ($P = 0.029$).

BMD

Changes in BMD from baseline to week 24 of treatment were comparable between women treated with relugolix (−4.80%) and women treated with leuprorelin (−4.84%) in the study by Harada and co-workers (*Harada et al., 2022*). Diamond and colleagues found significantly higher mean BMD percentage changes at the spine at week 12 for women treated with elagolix 250 mg (−0.937 and 0.375 with elagolix 250 mg and placebo, respectively) and at the femur at week 24 for both 150 mg (−0.743) and 250 mg (−1.024) elagolix compared with placebo. These patients underwent repeat bone density (dual-energy X-ray absorptiometry) scans at week 48, at which their BMD had either slightly increased or remained stable (*Diamond et al., 2014*).

According to Donnez and co-workers, 19.0% and 52.6% of women treated with linzagolix 75 mg and 200 mg, respectively, experienced a reduction of more than 3% in BMD at week 24 (*Donnez et al., 2020*). Moreover, a decrease of over 8% in BMD was observed among 2.6% of women treated with linzagolix 200 mg (*Donnez et al., 2020*). In the Elaris EM-I trial, 20.9% of women treated with elagolix 200 mg twice daily experienced a 5% or greater decrease in BMD at 6 months, compared with 1.8% in the placebo group (*Taylor et al., 2017*). In their 24-week extension study, Osuga and collaborators observed that the decrease in BMD was dose dependent and time dependent in women treated with relugolix. Moreover, changes in spinal BMD at 24 weeks were −4.9 (2.9%) for relugolix 40 mg, compared with −0.2 (2.0%) for placebo (*Osuga et al., 2021a*).

In the SPIRIT 1 and SPIRIT 2 trials with combination therapy, Giudice and colleagues observed that spinal and total hip BMD decreased in the first 12 weeks of treatment in the delayed combination therapy group, whereas it stabilized with the transition to relugolix combination therapy (*Giudice et al., 2022*). Moreover, in the two trials the least squares mean percentage changes in BMD from baseline to week 12 and 24 in BMD were less than 1% in women who received relugolix combination treatment (*Giudice et al., 2022*).

Time to return of menses

According to Harada and co-workers, menstruation returned earlier among women treated with relugolix (median 38 days) compared with women treated with leuprorelin (median 68 days) (*Harada et al., 2022*). In the 24-week extension study conducted by Osuga and collaborators, return of menses was not confirmed in 24 (5.0%) out of 483 women, the main reasons being either loss to follow-up, pregnancy, surgery or the start

TABLE 4 CORRELATION BETWEEN RESPONSE RATES AND ADVERSE EVENT RATES

Study	Molecule(s)	Response rate (%)	AE rates (%)	*N* tot	*P*-value	Spearman's correlation	*P*-value
Carr et al. (2013)	Elagolix 150 mg	62.5	51.5	68.0	0.195		
Diamond et al. (2014)	Elagolix 150 mg	NA	31.4	51	–		
	Elagolix 250 mg	NA	42.3	52	–		
Taylor et al. (2017) (Elaris-I)	Elagolix 150 mg	46.4	80.7	249	<0.001	0.86	0.057
	Elagolix 200 mg twice daily	75.8	82.7	248	0.053		
Taylor et al. (2017) (Elaris-II)	Elagolix 150 mg	43.4	79.2	226	<0.001		
	Elagolix 200 mg twice daily	72.4	84.7	229	0.002		
Donnez et al. (2020)	Linzagolix 50 mg	47.5	57.1	49	0.341	0.97	0.005
	Linzagolix 75 mg	58.3	64.9	56	0.472		
	Linzagolix 75 mg[a]	71.1	64.9	58	0.489		
	Linzagolix 100 mg	82.1	65.4	51	0.051		
	Linzagolix 200 mg	84.1	71.9	56	0.125		
Osuga et al. (2021)	Relugolix 10 mg	NA	79.6	103	–		
	Relugolix 20 mg	NA	89	100	–		
	Relugolix 40 mg	NA	94.2	103	–		
Giudice et al. (2022) (SPIRIT 1)	Relugolix 40 mg CT	75	71	212	0.354	−0.94	0.057
	Relugolix 40 mg DCT	72	77	211	0.239		
Giudice et al. (2022) (SPIRIT 2)	Relugolix 40 mg CT	75	81	206	0.142		
	Relugolix 40 mg DCT	73	82	206	0.029		
Harada et al. (2022)	Relugolix 40 mg	NA	90.1	171	–		

AE, adverse events, CT, relugolix combination therapy (1 mg oestradiol, 0.5 mg norethisterone acetate); DCT, delayed relugolix combination therapy (relugolix alone for 12 weeks followed by relugolix CT for the following 12 weeks); *N* tot, number of participants over which the percentage was calculated; NA, (data) not available.

[a] Titrated dose.

of an alternative hormonal treatment before the return of menses. The mean duration from the last dose of the drug to the return of menstrual periods was 21.0, 26.0 and 36.9 days for the relugolix 10, 20 and 40 mg groups, respectively, compared with 17.3 days in the placebo group (*Osuga et al., 2021a*). In their trials on combination therapy, Giudice and colleagues observed a median return to menses of 31 days (interquartile range 21–36 days) in both the relugolix combination group and the delayed relugolix combination group (*Giudice et al., 2022*).

Financial aspects

The price estimates of commercially available GnRH antagonists vary depending on individual countries' pricing and insurance reimbursement policies. The cost of elagolix in the USA has been estimated to be around $10,000 a year, corresponding to $845 per month. Obviously, the price of treatment can affect both the choice of this treatment and a patient's adherence to it, thus impacting the effectiveness (*Vercellini et al., 2019*). The cost of linzagolix in the UK is £99 for 100 or 200 mg tablets, which translates to £1287 (around $1610) a year. According to the UK National Institute of Health and Care Excellence, the cost of ABT alone, which includes oestradiol and norethisterone acetate, is £13.20, translating to £1353 for 12 months of treatment. The price of treatment with relugolix combination therapy is about $100 per month in the USA and in Europe, although treatment may be reimbursed by insurance companies, as is currently the case in France and Switzerland.

The cost of oestro-progestins and progestin-only pills also varies based on each country's reimbursement policies. A study conducted in the UK estimated the cost of a 6-month treatment as £11–£18 for progestin-only pills, £8 for oestro-progestins and £1035 and £1145 for goserelin without or with ABT, respectively (*Pearson and Pickersgill, 2004*).

While medical treatment comes with a cost, it has been estimated that the annual indirect costs arising from endometriosis amount to $1023 per patient, including outpatient and hospital care (*Simoens et al., 2007*). However, a head-to-head comparison of GnRH antagonists with or without ABT against other standards of care, along with a cost–benefit analysis, is lacking.

DISCUSSION

As stated by the American Society for Reproductive Medicine Practice Committee, the long-term management of endometriosis should entail an optimization of medical treatment, while also avoiding repeated surgical procedures (*Practice committee of the American Society for Reproductive Medicine, 2014*).

Up to 33% of women do not respond to the first line of treatment, such as oestro-progestins and progestin-only pills, and second-line treatment with GnRH agonists is burdened by adverse effects related to oestrogen deficiency. In this scenario, GnRH antagonists represent a valid

alternative (Donnez, Dolmans, 2021), since they suppress, in a dose-dependent manner, the release of FSH and LH, which translates into anovulation for most users (*Ng et al., 2017*). This effect is immediate and rapidly reversible, as most women experience a return to menses within 21–37 days (*Huirne and Lambalk, 2001*; *Osuga et al., 2021b*; *Zajec et al., 2022*).

Unlike GnRH agonists, which only exist in the parenteral form, GnRH antagonists are administered orally, which may potentially increase patient compliance and satisfaction (*Armer and Smelt, 2004*), as well as the possibility of titration. GnRH antagonists are also a suitable option for women of advanced reproductive age, for whom oestro-progestins may be contraindicated due to a higher risk of venous or arterial thrombosis (*Manzoli et al., 2012*). Although progestin-only pills do not increase the risk of thromboembolic events, they can be burdened by an increased frequency of abnormal uterine bleeding, which may lead to decreased user compliance and treatment discontinuation. On the positive side, GnRH antagonists are associated with lower rates of moderate to heavy uterine bleeding, as well as lower rates of breakthrough bleeding (*Carr et al., 2013*).

In one of the first double-blind RCT assessing the efficacy of GnRH antagonists compared with placebo in reducing EAP, Carr and colleagues observed a significantly greater pelvic pain reduction among women treated with elagolix compared with those treated with placebo (−0.55 versus −0.21, respectively) after 8 weeks of treatment (*Carr et al., 2013*). Elagolix has since then been assessed in the Elaris EM-I and Elaris-EM II trials, proving its efficacy in terms of pain management in a dose-dependent fashion, with a responder rate of 75.8% (Elaris EM-I) and 72.4% (Elaris EM-II) with elagolix 200 mg twice daily compared with a responder rate of 46.4% (Elaris EM-I) and 43.4% (Elaris EM-II) at a dose of 150 mg/day (*Taylor et al., 2017*).

Relugolix has been studied both alone and with ABT for the treatment of endometriosis, showing a responder rate of 75% in the SPIRIT 1 trial in terms of dysmenorrhoea pain reduction at 24 weeks of treatment (*Giudice et al., 2022*). While relugolix combined therapy is available upon presentation of a medical prescription in Europe and the USA, relugolix alone is only available for sale in Japan.

Another molecule, linzagolix, approved by the European Medicines Agency as of June 2022, but not yet by the US Food and Drug Administration, has been evaluated in an RCT by Donnez and co-workers, obtaining a responder rate up to 61.5% at a dose of 75 mg/day (*Donnez et al., 2020*; *Taylor et al., 2019*). Linzagolix has been assessed both alone, at a dose of 75 mg daily, and with ABT, at a dose of 200 mg daily, in a recently published trial by Donnez and co-workers. The results in terms of pain management efficacy are comparable to the ones obtained in the present systematic review and meta-analysis, with a responder rate for linzagolix with ABT of 72% and 47.3% for dysmenorrhoea and non-menstrual pelvic pain, respectively (*Donnez et al., 2024*). As the publication date of the study by Donnez and co-workers falls after the cut-off date for the present review, the trial has not been included in the analyses.

Although an overall significant mean change was observed for dyspareunia, the results across the different studies suggest that higher doses of GnRH antagonists are needed to achieve such an effect. As with linzagolix, an improvement of dyspareunia was observed with doses of 200 mg daily (*Donnez et al., 2020*). Similarly, women treated with elagolix improved their dyspareunia mean score from baseline to 3 months more significantly with elagolix 200 mg twice daily compared with elagolix 150 mg once daily (*Taylor et al., 2017*). Relugolix 40 mg alone, in contrast, produced no significant change in dyspareunia, whereas an improvement was observed for women treated with relugolix in combination with ABT (*Giudice et al., 2022*; *Osuga et al., 2021b*).

While the goal of treatment is to lower oestradiol concentrations within a therapeutic window, the hypo-oestrogenic state also comes with adverse effects, the most commonly reported being hot flushes, headache and BMD loss. Headache was reported at a frequency of up to 22.7% with the use of elagolix at a dose of 200 mg twice daily in the Elaris EM-II trial, with even higher rates with relugolix 40 mg combination therapy (39%) and delayed combination therapy (38%) in the SPIRIT 2 trial (*Giudice et al., 2022*; *Taylor et al., 2017*). The use of linzagolix obtained a similar dose-dependent effect, with a reported frequency of headache of up to 29.8% at the dose of 200 mg daily (*Donnez et al., 2020*). Nevertheless, the adverse effects are similar to those described with GnRH agonists. In their non-inferiority study comparing the GnRH antagonist relugolix with leuprorelin, Harada and co-workers found relugolix to be non-inferior to leuprorelin in reducing EAP, with a similar rate of adverse effects, such as hot flushes and headache (*Harada et al., 2022*).

Hot flushes were reported with a frequency up to 47.6% among women treated with elagolix 200 mg twice daily, and a similar rate of 42.1% among women treated with linzagolix 200 mg daily (*Donnez et al., 2020*; *Taylor et al., 2017*). Among women treated with relugolix combination therapy, however, the reported frequency of hot flushes was lower, at only 10% and 34% in the relugolix combination therapy and delayed combination therapy groups, respectively, in the SPIRIT 1 trial (*Giudice et al., 2022*). In the case of hot flushes, combination therapy may have a beneficial effect, while maintaining treatment efficacy. In the case of headache, however, the use of ABT does not seem to have the same positive effect, and other solutions, such as lower-dose protocols, may be more appropriate for women suffering from this type of vasomotor symptom.

Such side-effects may reduce treatment compliance and lead to discontinuation of the treatment (*Donnez et al., 2020*). Donnez and co-workers state that, as GnRH antagonists induce a dose-dependent oestradiol suppression, their adverse effects can also be mitigated by the use of lower-dose protocols (*Donnez and Dolmans, 2021a*). Moreover, the goal of treatment is to maintain their efficacy in pain management while also balancing out adverse effects derived from the induced hypo-oestrogenic state. According to the threshold hypothesis, partial oestradiol suppression (oestradiol concentrations of 30–60 pg/ml), as opposed to full suppression (oestradiol concentrations <20 pg/ml), may be the best solution to balance efficacy and safety of treatment (*Donnez et al., 2017*).

According to Osuga and collaborators, mean BMD decreases in a dose- and time-dependent manner in women treated with relugolix, with a significantly higher change in BMD at 24 weeks compared with placebo (−4.9 and −0.2, respectively) (*Osuga et al., 2021a*). This BMD reduction is comparable to that obtained with the use of GnRH agonists, as found by Harada and co-workers in their non-inferiority trial

comparing relugolix 40 mg daily with leuprorelin, obtaining a reduction in BMD of −4.80% and −4.84% in the relugolix and leuprorelin groups, respectively (*Harada et al., 2022*). For this reason, treatment with GnRH antagonists alone is not the most attractive option for endometriosis, where the goal of treatment should be the long-term management of the symptoms as well as of disease progression. In this scenario, the use of GnRH antagonists in association with ABT, which has previously been approved for women with uterine fibroids, has recently been introduced for women with endometriosis (*Donnez et al., 2022*).

The main rationale to support the use of combination therapy is the fact that, while GnRH antagonists alone suppress hormonal production by directly antagonizing the hypothalamic–hypophyseal–gonadal axis, the use of combination therapy maintains a low but constant oestrogen concentration, compatible with that observed in the early follicular phase of the menstrual cycle, which is considered sufficient to mitigate the oestrogen-deficient side effects of treatment with GnRH antagonists alone while maintaining the efficacy in terms of pain management (*Nakata et al., 2014*).

Giudice and colleagues tested the use of relugolix in association with ABT, which included 1 mg of oestradiol and 0.5 mg of norethisterone acetate to achieve efficacy and minimize oestrogen-deficient effects, such as vasomotor symptoms and BMD loss (*Giudice et al., 2022*). In the SPIRIT 1 and SPIRIT 2 trials, the authors found that the least square mean percentage changes in BMD from baseline to week 12 and 24 were less than 1% in patients treated with relugolix combination therapy (*Giudice et al., 2022*). Among women treated with delayed combination therapy, BMD substantially declined at week 12 with relugolix monotherapy, while it was stabilized when transitioning to combination therapy (*Giudice et al., 2022*). Additionally, women in the combination therapy group experienced significantly less frequent hot flushes compared with participants treated with the delayed relugolix regimen (*Giudice et al., 2022*).

The proportion of responders varies from a minimum of 43.4% with the use of elagolix 150 mg once daily, to a maximum of 75.8% with elagolix 200 mg twice daily (*Taylor et al., 2017*). Moreover, the current meta-analysis comparing relugolix 40 mg with the same dose of relugolix with ABT shows no significant difference in terms of a reduction in dysmenorrhoea and non-menstrual pelvic pain. The response rate with relugolix combination therapy was homogenous across the SPIRIT 1 and SPIRIT 2 trials, ranging between 72% with delayed combination therapy and 75% with relugolix combination therapy (*Giudice et al., 2022*). However, a higher response rate goes hand in hand with higher rates of adverse events. In addition, the rates of non-response are comparable to those observed with combined oestro-progestins and progestin-only pills, for which up to one-third of women do not respond to therapy.

Progesterone resistance has been suggested as a potential explanation for non-response to treatment (*Patel et al., 2017*). In addition, lesional progesterone receptor expression levels also have also been proposed as being responsible for the treatment response (*Flores et al., 2018*). A recent study suggested that *KRAS* mutations are associated with resistance to progestin treatment in adenomyosis. While their association with medical treatment response has yet to be proved, lesional *KRAS* mutations have been found to be associated with deep infiltrating endometriosis and greater surgical difficulties (*Bulun et al., 2023*; *Inoue et al., 2019*; *Orr et al., 2023*). However, one important factor contributing to treatment non-response may be the extent of lesional fibrosis, since a higher fibrotic content in lesions correlates negatively with vascular density as well as epigenetic aberrations (*Liu et al., 2018*). Indeed, reduced vascularity engenders increased difficulty in delivering drugs to the target tissues. In addition, many cancer driver mutations found in endometriotic lesions, such as *KRAS* mutations, are intimately related to lesional fibrogenesis (*Guo, 2018*).

While GnRH agonists and antagonists, as well as COC and progestins, could induce amenorrhoea and thus stop dysmenorrhoea, they may not completely control other forms of pain resulting from pain mediators released by lesions or from adhesions.

Finally, for those patients who respond to GnRH antagonist treatment, one lingering question is whether the long-term treatment might increase the risk of malignant transformation. Presumably, the effective control of oestrogen concentrations at the local level resulting from the GnRH antagonist treatment may render endometriotic lesions atrophic or dormant, but nonetheless viable. As such, the lesions may still undergo low-grade proliferation and thus cell division, leaving the door ajar for mutations (*Guo, 2020*). Clearly, this question cannot yet be addressed and will await future investigations.

A limitation of the present review is represented by the fact that only seven RCT could be included, thereby making it more difficult to generalize the current findings to large populations. On the other hand, all the included RCT were judged to have a very low risk of bias, which boosts the strength of the current analyses, despite the limited data available.

Future trials should compare GnRH antagonists alone and with ABT for endometriosis-associated pain, focusing both on efficacy and safety end-points. Moreover, the tolerability of GnRH antagonists with and without ABT, with particular attention to commonly reported vasomotor symptoms, such as headaches and hot flushes, and abnormal uterine bleeding, should be carefully assessed. The impact of such symptoms on quality of life should be evaluated in order to determine whether their impact may be such as to induce women to discontinue treatment. In addition, a head-to-head comparison along with a cost–benefit analysis of GnRH antagonists with or without ABT against other standards of care is desirable. Lastly, the long-term effect of GnRH antagonist treatment on the risk of malignant transformation should also be investigated.

Further trials should be conducted to identify whether the population of women who do not respond to oestro-progestin combinations overlaps that of women who do not respond to GnRH antagonists (*Vercellini et al., 2019*). While some women who do not respond to oestro-progestins may benefit from GnRH antagonists and vice versa, others may not respond to either line of medical treatment, in which case an ulterior alternative type of treatment, such as surgery, may be their best option.

CONCLUSION

The present study assesses the efficacy and safety of oral GnRH antagonists for the treatment of EAP. The global tendency that emerges from this systematic review

and meta-analysis is that GnRH antagonists are effective in reducing EAP, whether it be dysmenorrhoea, non-cyclic pelvic pain or dyspareunia. While the hypo-oestrogenic effect afforded by GnRH antagonists alone limits their use to short periods of time, the recent introduction of combination hormonal replacement therapy offers a valid alternative, potentially capable of extending the use of GnRH antagonists beyond 24 weeks of treatment. The balance between efficacy and adverse effects should be carefully managed with the use of either low-dose protocols or combination therapy, the choice between the two options being tailored based on the patient's specific context.

DATA AVAILABILITY

Data will be made available on request.

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Received 23 January 2024; received in revised form 28 May 2024; accepted 5 June 2024.