Efficacy and safety of Elagolix in the treatment of endometriosis associated pain: a systematic review and network meta-analysis

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Abstract

Background: *Endometriosis commonly presents with dysmenorrhea, non-menstrual pelvic pain, and infertility. Elagolix is an oral, short-acting, gonadotropin-releasing hormone antagonist acting through complete estrogen suppression.*

Objective: *To evaluate the evidence from published randomized controlled trials (RCTs) about the efficacy and safety of Elagolix in the treatment of endometriosis associated pain.*

Search strategy: *Electronic databases containing articles published between January 2000 and February 2020 were searched using the MeSH terms (Elagolix OR gonadotropin-releasing hormone antagonist OR GnRH antagonist OR antigonadotropin) AND (endometriosis) AND (pelvic pain).*

Selection criteria: *All RCTs assessing the efficacy of Elagolix in the treatment of pain associated with endometriosis were considered for this network meta-analysis, where five studies were deemed eligible for this review.*

Data collection and analysis: *The mean difference (MD) and confidence intervals (95% CI) for continuous outcomes including analgesic use, dysmenorrhea, non-menstrual pelvic pain, and quality of life were calculated.*

Main results: *Elagolix 250 mg reduced dysmenorrhea significantly, as compared to placebo, (MD = -0.41, 95% CI [-0.7, -0.13]) at 12 weeks, while Elagolix 200 mg reduced dysmenorrhea significantly (MD= -1.2, 95% CI [-1.9, -0.57]) compared to placebo after 24 weeks of treatment.*

Conclusions: *Elagolix 200 mg seems to be an effective drug with fewer side effects when used to reduce dysmenorrhea and non-menstrual pelvic pain after 24 weeks of treatment in patients with endometriosis.*

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Introduction

Endometriosis is characterized by the presence of endometrial-like tissue outside the uterus.[1,2] Ectopic tissue deposits are mainly found on the pelvic peritoneum, ovaries, and rectovaginal septum.[2] The percentage of affected females of reproductive age among the general population has been estimated to be between 2-10%.[3-5] The range of symptoms caused by endometriosis includes pelvic–abdominal pain, heavy menstrual bleeding, non-menstrual pelvic pain, pain at ovulation, dyschezia and dysuria.[6] Patients may additionally suffer from chronic fatigue with deleterious effects on patients' quality of life.[1]

The specifics of the pathophysiology of endometriosis are still a subject of controversy.[2] One explanation --"the estrogen threshold hypothesis" -- on which current medical treatments for endometriosis have been based, has shown favorable results as an alternative to surgery in selected cases.[7] Currently available medical therapies include non-steroidal anti-inflammatory drugs (NSAIDs), progestin-only oral contraceptives, combined hormonal contraceptives (CHCs), the 52mg Levonorgestrel-releasing intrauterine system and injectable gonadotropin-releasing hormone (GnRH) agonists.[8] However, the side effect profiles of these therapies still represent a gap in finding a treatment that better balances the favorable side of estrogen suppression with its unfavorable associated side effects (e.g., bone density loss, vasomotor symptoms).[8-11]

Complete estrogen suppression may not be required to control endometriosis associated pain.[7] Elagolix, a novel therapy for endometriosis, is a potential solution to the issue owing to its dose-dependent estrogen suppressing properties.[12-14] Elagolix is an oral, short-acting GnRH antagonist which can potentially induce complete estrogen suppression when given at higher doses while also being capable of causing partial estrogen suppression at lower doses.[15,16] This dose-dependent property could be the key for providing treatment with a better safety profile, as compared to current therapies, while maintaining efficacy in relieving pain experienced by endometriosis patients. There are only two doses of Elagolix approved by the FDA: 150 mg once daily for up to 24 months and 200 mg twice daily for up to 6 months.[17] However, these standards do not apply worldwide, and some of the applicable studies addressed a wider range of dosages. We performed this systematic review and meta-analysis to establish the evidence from all published randomized, controlled trials (RCTs) addressing outcomes for Elagolix in the treatment of endometriosis associated pain as compared to other available

treatment options.

Materials and Methods

We followed PRISMA statement guidelines during the preparation of this systematic review and meta-analysis.[18] Additionally, we performed all steps in strict accordance with the *Cochrane handbook of systematic reviews of intervention.*[19] Because the study was a systematic review, it was exempt from ethical approval.

Search strategy

We performed a comprehensive search in four electronic databases: PubMed, Scopus, Cochrane Library and International Scientific Indexing (ISI), using a combination of the following MeSH terms (Elagolix OR gonadotropin-releasing hormone antagonist OR GnRH antagonist OR antigonadotropin) AND (endometriosis) AND (pelvic pain), for articles published between January 2000 and February 2020.

Eligibility criteria

We included all studies satisfying the following criteria:

- Population: women diagnosed with endometriosis and suffering from associated pain,
- Intervention: Elagolix,
- Comparator: any other medications or placebo,
- Outcomes: The main outcome measures were analgesic use at 12 weeks, the rate of dysmenorrhea at 12 and 24 weeks, the rate of non-menstrual pelvic pain at 24 weeks, quality of life at 12 weeks and side effects at 24 weeks of treatment,
- Study design: randomized controlled trials.

We excluded the following:

- non-randomized trials
- in vitro and animal studies
- studies whose data were unreliable for extraction and analysis
- studies in non-English languages
- materials from conferences, books, review articles, posters, theses and editorials.

Study selection

The three authors of this article independently conducted database searches, retrieved the results and removed duplicated studies using *EndNote* X7.4 software. We additionally manually searched the reference citations of included studies for additional relevant records that were not identified by the search itself.

Data extraction and analysis

We independently extracted relevant data from included studies. Disagreements were resolved through discussion and consensus among the reviewers. The extracted data included the study design, population, risk of bias domains and study outcomes.

We used the "gemtc" package in *R* software, Supplemental File 1, to conduct our Bayesian network meta-analysis. We calculated mean difference (MD) and confidence intervals (95% CI) for continuous outcomes including analgesic use, dysmenorrhea, non-menstrual pelvic pain and quality of life. We used odds ratios (ORs) and confidence intervals (95% CI) for dichotomous outcomes such as side effects. We assessed heterogeneity between the results using I-square test values, where I^2>50% was used as a measure of significant heterogeneity.

Quality of included studies and risk of bias assessment

Both planned and unintentional biases can affect research outcomes. To control for this factor, two of our authors used the Cochrane risk of bias assessment tool, provided in chapter 8.5 of the *Cochrane handbook of systematic reviews of interventions 5.1.0.*[20] (Supplemental File 1) Risk of bias assessment included the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The reviewers' judgment is categorized as 'Low risk,' 'High risk' or 'Unclear risk' of bias. Any discrepancies between the two reviewers were resolved through discussion.

Results

Search results characteristics of included studies

The search process returned a total of 124 records. We removed duplicates using *Endnote* software. Of the remaining 90 records screened by title/abstract, ten records seemed to be eligible. After reading the full text of the ten studies, we excluded five studies which were ineligible according to the criteria. (Figure 1) Five RCTs were finally included in the meta-analysis.[12,21-24]

Characteristics of included studies

A total of five RCTs[12,21-24] with a total of 1590 patients met our inclusion criteria and were evaluated in this analysis. All women included in the studies had laparoscopically confirmed endometriosis and moderate to severe endometriosis associated pain. Elagolix was used with different doses and for different durations of treatment in the included studies. Taylor et al., compared two different doses of Elagolix (150 mg once daily and 200 mg twice daily) versus placebo for three months.[12] Carr et al., 2013, compared Elagolix 150 mg once daily versus placebo for 6 months.[21] In the 2014 study by Carr et al., two different doses were used (150 mg once daily and 75 mg twice daily), which were compared to depot medroxyprogesterone acetate (DMPA) injections for six months.[22] Another study utilized Elagolix in two doses of 150 and 250 mg once daily versus placebo for three months.[23] Similarly, Acs et al., compared the same two doses versus Leuprorelin Acetate (LA)

again over a three-month period.[24]

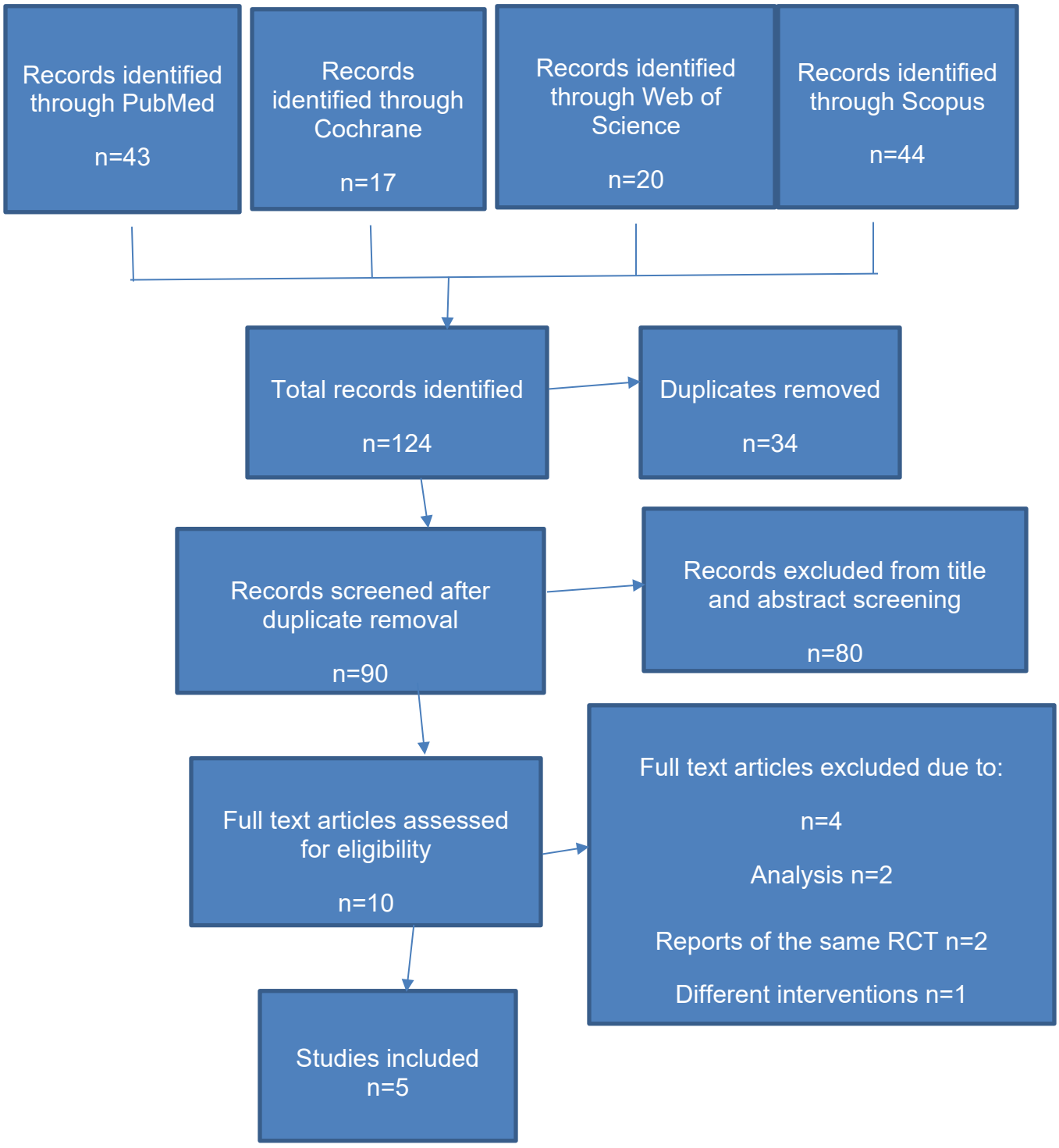

Figure 1: PRISMA Flow Chart of the study selection process

Risk of bias assessment

Using the *Cochrane* tool as described above,[20] we found the included studies to be of high or moderate quality, having a low risk of bias as shown in Figures 2 and 3.

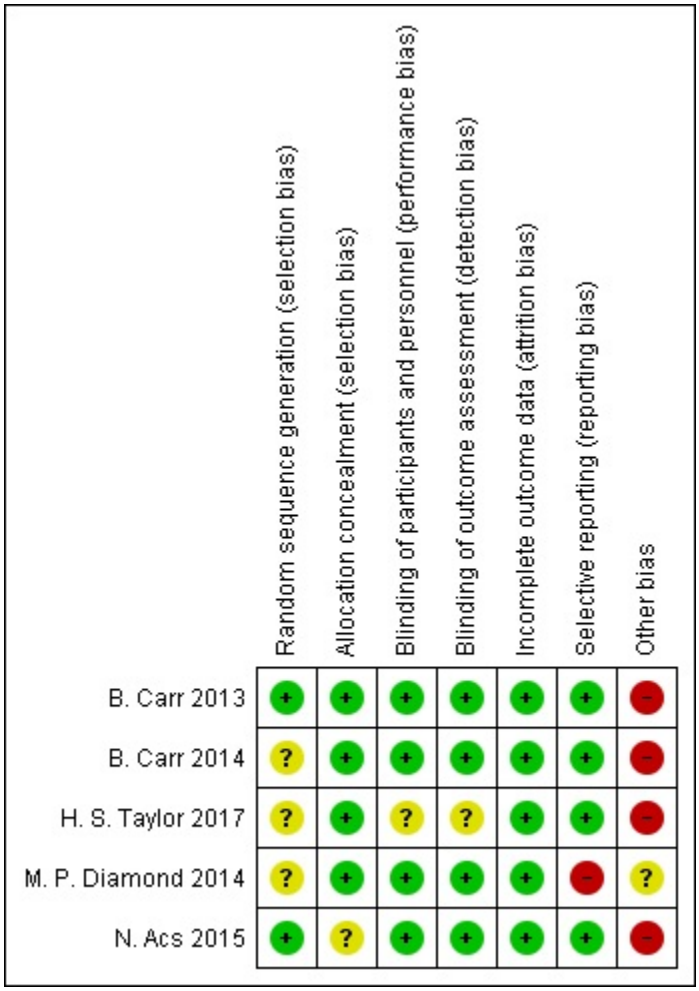

Figure 2: Diagram of the overall quality of included studies

Outcomes

Analgesic use at 12 weeks

Our results showed no significant difference between Elagolix as compared to placebo. In the study by Acs et.al., LA significantly reduced analgesic use at 12 weeks (MD= -4.7, 95% CI [-7.5, -2]) when compared with placebo.[24] (Supplemental File 2: Figure A) Treatment rank probabilities showed LA to be the best treatment to reduce analgesic use. (Supplemental File 3: Figure A)

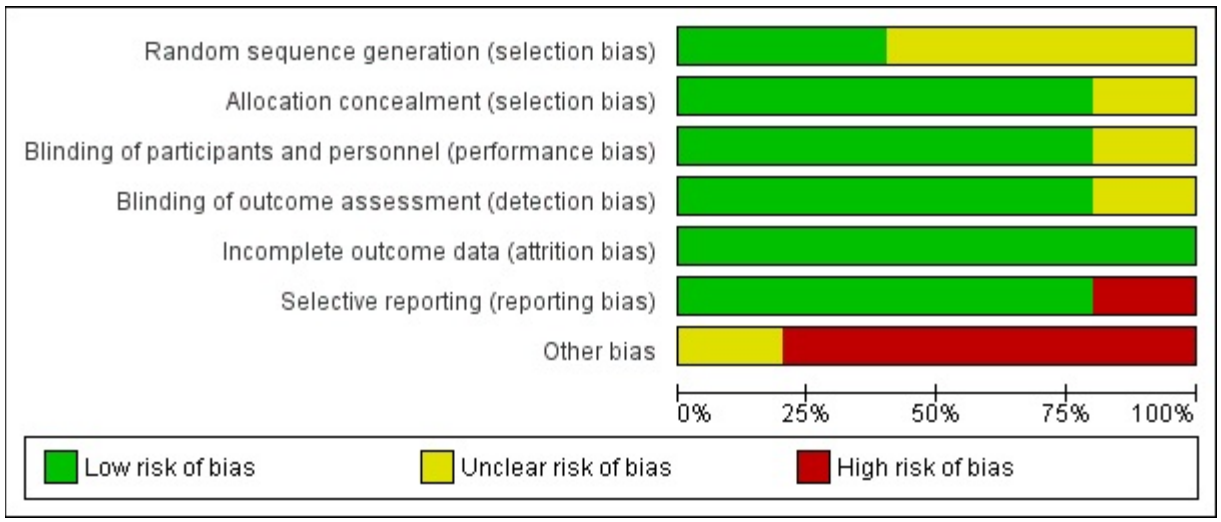

Figure 3: Risk of bias summary graph

Dysmenorrhea at 12 weeks

The meta-analysis results showed that Elagolix 75, 150 and 250 mg reduced dysmenorrhea significantly compared to placebo (MD= -0.62, 95% CI [-1.1, 0.12], -0.32, 95% CI [-0.6, -0.031, and-0.41, 95% CI [-0.7, -0.13] respectively). LA also showed significant reduction in dysmenorrhea compared with placebo (MD= -0.53, 95% CI [-0.9, -0.16]). However, no significant difference was seen between placebo and DMPA. (Supplemental File 2: Figure B) LA and Elagolix 250 mg are the best treatments to reduce dysmenorrhea at 12 weeks according to the treatment rank probabilities. (Supplemental File 3: Figure B)

Dysmenorrhea at 24 weeks

Elagolix 200 mg was the only drug that reduced dysmenorrhea significantly (MD= -1.2, 95% CI [-1.9, -0.57]) compared to placebo after 24 weeks of treatment. All other comparisons showed no significant results. (Supplemental File 2: Figure C) Therefore, Elagolix 200mg was the most effective treatment to reduce dysmenorrhea at 24 weeks based on the treatment rank probabilities. (Supplemental File 3: Figure C).

Non-menstrual pelvic pain at 24 weeks

Similarly, Elagolix 200 mg reduced non-menstrual pelvic pain significantly (MD= -0.36, 95% CI [-0.59, -0.14]) as compared to placebo after 24 weeks of treatment while there were no significant findings with regard to this parameter for the other treatments considered. (Supplemental File 2: Figure D) Treatment rank probabilities showed Elagolix 200 mg is the most effective treatment to reduce the non-menstrual pelvic pain at 24 weeks. (Supplemental File 3: Figure D)

Quality of life at 12 weeks

LA scored higher on the quality-of-life scale at 12 weeks (MD= -18, 95% CI [-35, -1.6]) as compared to placebo (Supplemental File 2: Figure E) and was the most effective based on the treatment rank probabilities.

Side effects

Headache

Headache was more common with Elagolix 150 and 200 mg than placebo (OR= 1.5, 95% CI [1.1, 2.2]), (OR= 1.8. 95% CI [1.3, 2.5] respectively) after 24 weeks of treatment. No significant results were found amongst all other comparisons. (Supplemental File 4: Figure A) Treatment rank probabilities showed Elagolix 200 mg is the drug most likely to cause headache at 24 weeks. (Supplemental File 5: Figure A)

Back pain

There was no significant difference between placebo and all other comparators regarding back pain. (Supplemental File 4: Figure B) Among treatment rank probabilities Elagolix 250 mg is the most likely drug to cause back pain at 24 weeks. (Supplemental file 5: Figure B)

Depression

Similarly, there was no significant difference between placebo and all other comparators in producing depression. (Supplemental File 4: Figure C) Elagolix 75 mg is the most likely drug to produce depression at 24 weeks according to treatment rank probabilities. (Supplemental File 5: Figure C)

Analysis of heterogeneity

Efficacy outcomes showed moderate to high heterogeneity, which we resolved using a random-effects model. The side effects showed low heterogeneity.

Discussion

To the best of our knowledge, no previous systematic reviews that investigate the efficacy and safety of Elagolix in the treatment of endometriosis-associated pain have been published. We conducted this network meta-analysis to provide evidence of the performance of Elagolix relative to these factors and in comparison with placebo and with other common treatment modalities, including LA.

Regarding efficacy, the network meta-analysis showed that both Elagolix 250 mg and LA reduced dysmenorrhea significantly when compared to placebo. However, LA was superior to Elagolix in the reduction of analgesic use and increasing quality of life after 12 weeks of treatment. Our results are consistent with another meta-analysis, which proved that LA is better in reduction of dysmenorrhea than Gestrinone in cases of endometriosis.[25] Elagolix 200 mg was the best choice for reducing dysmenorrhea and non-menstrual pelvic pain after 24 weeks when compared to placebo, other doses of Elagolix (75 mg and 150 mg) and depot-medroxyprogesterone acetate (DMPA).

There are multiple choices for treating endometriosis-associated pain and

dysmenorrhea. According to ESHRE guidelines, first-line hormonal therapies include combined-hormonal contraceptives (CHCs) or the 52mg Levonorgestrel-releasing intrauterine system.[1] Dienogest is a progestogen-only hormone preparation previously used in some trials for the treatment of endometriosis associated pain through suppression of estradiol production for the prevention of endometrial growth.[26,27] Elagolix, as a GnRH antagonist, is effective in reducing non-menstrual pelvic pain and dysmenorrhea based on results of clinical trials only.[28] No RCT has been conducted to compare Elagolix and dienogest for treatment of endometriosis-associated pain.

Regarding side effects, Elagolix at all its dosages, as well as DMPA, did not differ from placebo in causing back pain. However, Elagolix 250 mg is the most likely drug to produce back pain after 24 weeks of treatment according to treatment ranking when compared to placebo, DMPA, and Elagolixitself in doses at 75, 150 and 200 mg. Those findings may suggest that Elagolix, as GnRH antagonist, does not affect bone density, but more research and investigations are needed to confirm this theory. Neither Elagolix nor DMPA differed from placebo in causing depression. Elagolix 200 and 250 mg showed a significant difference in causing headache.

Because this network meta-analysis depended on combined evidence from direct and indirect comparisons, it was able to provide evidence about the different doses of Elagolix. These results depended on the high-quality of RCTs according to the *Cochrane assessment tool for risk of bias*. We used rank order for relative efficacy to conclude that Elagolix 200mg is an effective choice in the reduction of dysmenorrhea and non-menstrual pelvic pain after 24 weeks with minimal side effects.

The results of this study are limited by the small number of studies that were evaluated and by the fact that they depended on a short duration to follow-up. The presence of indirect comparison gave us a small number of patients in each study arm. More and larger studies are needed to this point to provide strong evidence for the safety of Elagolix for long-term use.

Conclusion

This systematic review and meta-analysis suggests that Elagolix 200 mg could be a very effective choice to reduce dysmenorrhea and non-menstrual pelvic pain with fewer side effects after 24 weeks of treatment in patients with endometriosis.

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Supplemental Figures

Supplemental Figure 1: Geometry of network meta-analysis

Supplemental Figure 2: Forest plot showing the efficacy outcomes of different interventions

Supplemental Figure 3: The ranking probability of the interventions for the efficacy outcomes

Supplemental Figure 4: Forest plot showing the side effects of different interventions

Supplemental Figure 5: The ranking probability of the interventions for side effects