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Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist

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CLINICAL QUESTION

Are two doses of oral elagolix (150 mg once daily and 200 mg twice daily) effective and safe for treating moderate-to-severe endometriosis-associated pain over 6 months?

STUDY DESIGN

Two identical, phase 3, double-blind, randomized, placebo-controlled trials (Elaris EM-I and EM-II).

POPULATION

1,689 premenopausal women with surgically diagnosed endometriosis and moderate or severe pain.

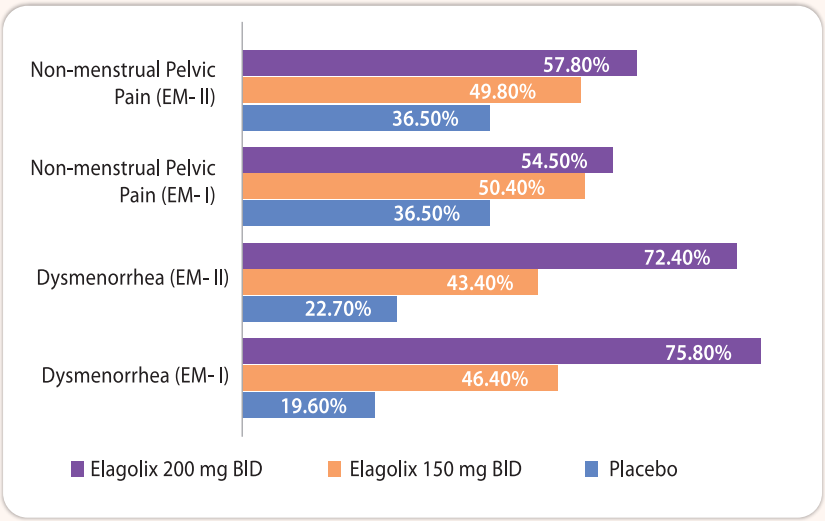
KEY FINDINGS

Both doses of elagolix were significantly more effective than placebo at reducing the two primary pain endpoints at 3 & 6 months.

Dysmenorrhea: Up to 76% of patients had a clinical response with Elagolix 200 mg BID vs. ~21% with placebo.

Nonmenstrual Pelvic Pain: Up to 58% responded with Elagolix vs. 37% with placebo.

Sustained Relief: Pain reduction was significant at 1 month & maintained over 6 months.



SAFETY

Consistent with its mechanism of action, elagolix demonstrated a dose-dependent hypoestrogenic safety profile.

CONCLUSIONS

Both higher and lower doses of elagolix were effective in improving dysmenorrhea and nonmenstrual pelvic pain during a 6-month period in women with endometriosis-associated pain. The two doses of elagolix were associated with hypoestrogenic adverse effects.

Ref.: Taylor, Hugh S et al. "Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist." The New England journal of medicine vol. 377,1 (2017): 28-40. doi:10.1056/NEJMoa1700089

Elagolix: An Oral GnRH Antagonist for Endometriosis pain

Elagox®

Elagolix 150, 200 mg Tablet

Drug Review

Introduction[1]

Endometriosis affects about 1 in 10 women of reproductive age and remains one of the leading gynecologic causes of hospitalization. Its chronic, inflammatory nature results in dysmenorrhea, non-menstrual pelvic pain, and dyspareunia, which are the most distressing symptoms and contribute substantially to impaired daily functioning. Pain severity often does not correlate with disease stage, making management particularly challenging.

Gaps in current treatment options

- Analgesics such as NSAIDs are commonly used to alleviate pain, but high-quality evidence for meaningful benefit is limited, and no single NSAID is preferred.[2]
- Surgical options (e.g., laparoscopy) can relieve symptoms for some, yet evidence for durable pain relief is of low to moderate quality and recurrence is not uncommon.[3]
- Hormonal therapies (e.g., GnRH agonists) are effective but often limited by hypoestrogenic adverse effects (hot flashes, bone loss) and treatment duration caps.[4]
- Older GnRH antagonists are synthetic peptides require subcutaneous injections, implantation of long-acting depots. The peptide structure is responsible for histamine-related adverse events & the tendency to elicit hypersensitivity reactions.[4]

Elagolix: Breakthrough treatment for moderate to severe endometriosis pain[1]

- Elagolix is an oral, non-peptide GnRH receptor antagonist that competitively blocks pituitary GnRH receptors, lowering LH/FSH and thereby reducing estradiol & progesterone to relieve endometriosis pain.

Elagolix competitively & reversibly binds with GnRH receptor → Blocks the binding of endogenous GnRH to the receptor → Inhibits pituitary Gonadotropin (FSH,LH) release → Inhibits estrogen and progesteone release from ovary → **Decreases endometriosis pain**

- Its rapid onset (Tmax ≈ 1 h) and short half-life (4–6 h) allow faster reversibility than GnRH agonists.
- Quick and reversible dose-dependent suppression: 150 mg QD maintains low estradiol, while 200 mg BID produces near-complete suppression-enabling titration to balance efficacy and hypoestrogenic effects.

Clinical efficacy

- In two Phase 3 trials (ELARIS EM-1/EM-2), elagolix significantly improved dysmenorrhea response rates vs placebo (e.g., 46.4% [150 mg QD] and 75.8% [200 mg BID] vs 19.6% placebo in EM-1) and improved non-menstrual pelvic pain at both doses vs placebo.[5]
- Elagolix 200 mg BID dose showed statistically significant benefit for dyspareunia.[6]
- Long-term extensions (EM-3/EM-4) showed maintained responses through 12 months (dysmenorrhea ~51–78% responders; non-menstrual pelvic pain ~66–69%; dyspareunia ~46–60% depending on dose/study).[5]
- Elagolix is well tolerated, with less pronounced hypoestrogenic effects compared with GnRH agonists.[5]

Ref.: 1. Urits, Ivan et al. "An Evidence-Based Review of Elagolix for the Treatment of Pain Secondary to Endometriosis." Psychopharmacology bulletin vol. 50,4 Suppl 1 (2020): 197-215.; 2. Brown J, et al. NSAIDs for pain in women with endometriosis (Cochrane). 2017.; 3. Duffy JMN, Arambage K, Correa FJS, Olive D, Farquhar C, Garry R, Barlow DH, Jacobson TZ.Laparoscopic surgery for endometriosis. Cochrane Database of Systematic Reviews. 2014.; 4. Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hor-mones by elagolix in healthy premenopausal women. J Clin Endocrinol Metab. 2017;102(5):1683–1691.; 5. Agarwal, Sanjay K et al. "Endometriosis-Related Pain Reduction During Bleeding and Nonbleeding Days in Women Treated with Elagolix." Journal of pain research vol. 14 263-271. 2 Feb. 2021, doi:10.2147/JPR.S284703.; 6. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, Diamond MP, Surrey E,Johnson NP, Watts NB, Gallagher JC, Simon JA, Carr B, Dmowski WP, Leyland N, Rowan JP,Duan WR, ... Chwalisz K. Treatment of endometriosis-associated pain with elagolix, an oral GnRHantagonist. N Engl J Med. 2017

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