# Pharmacological Treatment for Endometriosis-associated Pain

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**Abstract.** Endometriosis is recognized as a chronic, estrogen-dependent gynecological disorder, which is clinically defined by the presence and growth of endometrial-like tissue at anatomical sites outside the uterine cavity. The symptom is frequently linked to pelvic pain of prolonged duration, infertility, and ovarian endometriotic cysts. Current therapeutic strategies encompass both surgical intervention and a range of pharmacological approaches. This review focuses on pharmacological management of endometriosis-associated pain, covering established first-line therapies which are used most commonly, such as combined oral contraceptive pills and progestins, second-line options including nonsteroidal anti-inflammatory drugs and gonadotropin-releasing hormone (GnRH) agonists, as well as emerging treatments such as GnRH antagonists and aromatase inhibitors. The discussion begins with an overview of disease pathogenesis and the mechanisms underlying pain generation, followed by a detailed description of drug actions, evidence supporting their efficacy, potential adverse effects, and strategies to mitigate treatment-related complications. By summarizing the advantages and limitations of different pharmacotherapies, this review seeks to provide clinicians with a reference for individualized and safe treatment regimens, while also offering insights to the development of novel drugs and the optimization of therapeutic strategies in the future.

**Keywords:** Endometriosis, Combined oral contraceptive pills, Progestins, Gonadotropin-releasing hormone agonist.

## 1. Introduction

Endometriosis is a persistent, estrogen-dependent disorder of the female reproductive system, defined by the presence of endometrial tissue located outside the uterine cavity. The ovaries, pelvic peritoneum, fallopian tubes are most commonly affected by these ectopic endometrial-like tissues. Those lesions also influence even distant organs like lungs and diaphragm in rare cases. Around 6-10% of women will be influenced by endometriosis in their reproductive age. Typical symptoms of endometriosis involve pelvic pain syndrome (including dysmenorrhea and dyspareunia), ovarian endometriotic cysts (chocolate cysts), and sterility (21% of the women with infertility were diagnosed as having endometriosis by receiving gynecological laparoscopy) [1]. Endometriosis-associated pain profoundly impairs patients' quality of life. Therefore, effective pain management represents a critical aspect of clinical care. At present, multiple pharmacological agents have been shown to effectively relieve endometriosis-induced pain. However, there is still a lack of systematic analysis of pharmacological strategies for pain management in endometriosis. Therefore, this review aims to integrate current evidence regarding the mechanisms of action, clinical efficacy, and adverse effects of commonly used drugs. By summarizing the advantages and limitations of different pharmacotherapies, this review seeks to provide clinicians with a reference for individualized and safe treatment regimens, while also offering insights to the development of novel drugs and the optimization of therapeutic strategies in the future.

## 2. Pathogenesis of Endometriosis

The interaction of hormonal, immunologic, genetic, and environmental influences involve in the pathogenesis of endometriosis, making it's complex and multifactorial. While no single theory fully explains all aspects of the disease, several complementary mechanisms have been proposed.

The retrograde menstruation hypothesis, first proposed by Sampson in 1927, remains the most widely accepted explanation for the pathogenesis of endometriosis. According to this theory, a portion

of menstrual effluent does not exit exclusively through the cervix and vagina but instead refluxes through the fallopian tubes into the peritoneal cavity. This retrograde flow transports viable endometrial fragments, including both glandular epithelial and stromal cells. Upon reaching the peritoneal surface or ovaries, these cells are capable of adhering, invading the extracellular matrix, and establishing ectopic implants. Once established, they exhibit survival and proliferative capacity, closely resembling the eutopic endometrium in both structural characteristics and hormonal responsiveness. During each menstrual cycle, they undergo proliferation and breakdown, leading to cyclical bleeding into the peritoneal cavity. Accumulated blood and cellular debris cause chemical irritation of pelvic tissues and consequently cause pelvic pain syndrome.

Within chronic pelvic pain linked to endometriosis, inflammation and altered innervation are regarded as closely linked mechanisms. Ectopic endometrial tissue produces pro-inflammatory mediators, such as IL-6 and prostaglandins. The resulting inflammatory environment sustains peritoneal immune activation, which directly sensitizes pelvic nociceptors and increases cyclooxygenase-2 activity. This, in turn, promotes excessive prostaglandin synthesis, leading to uterine hypercontractility and menstrual pain. At the same time, endometriotic lesions show marked neurogenesis. Factors including nerve growth factor stimulate the sprouting of sensory and sympathetic fibers into the lesions, creating abnormal patterns of innervation. Neurogenic inflammation is initiated through the crosstalk between nerve fibers and immune cells and is further intensified by neuropeptides which enhance both inflammatory responses and nociceptive transmission. Together, these processes form a reinforcing cycle of inflammation and nerve remodeling, which contributes to the persistence and worsening of pelvic pain in affected individuals.

## 3. First-line Therapy

### 3.1. COCPs

One of the most widely used drugs for endometriosis is combined oral contraceptive pills (COCPs), meanwhile it's included in the first-line therapy for curing the disease. which contain estrogen and progestogen. Exogenous estrogen and progestin act to suppress hypothalamic secretion of gonadotropin-releasing hormone (GnRH), resulting in pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) decrease. FSH level decreases will lead to inhibition of follicular development, while lower LH levels prevent ovulation. Consequently, ovarian estradiol production declines, leading to diminished proliferative stimulation of ectopic endometrial tissue. As estrogen exposure to ectopic endometrium reduction, COCPs relieve estrogen-driven pain.

A clinical study examined whether chronic pelvic pain (CPP) could be mitigated through the long-term administration of COCPs. The average visual analog scale scores of dysmenorrhea declined from 75 at baseline to 31 after 2 years treatment, which indicates that extended administration of COCPs is linked to a significant reduction in CPP [2]. Meanwhile, COCPs have been shown to enhance apoptosis while simultaneously inhibiting cellular proliferation within both the epithelial and stromal compartments of the eutopic endometrial tissue. Short-term exposure to COCPs markedly elevated the level of apoptosis in patients who were diagnosed as having endometriosis compared with the control group. Apoptosis indices at the stromal level were observed at 13.6 versus 15.1, and 2.5 versus 3.4 at the epithelial level, respectively [3]. Inhibition of proliferation of endometrium results in reduction of CPP.

COCPs are among the most widely used pharmacological treatments for endometriosis. Therefore, even though they are associated with a relatively low incidence of adverse effects, these effects still are noteworthy. Breakthrough bleeding (BTB) is a common mild side effect in the first 3-6 months after starting use of COCPs. It's caused by hormonal fluctuations as the levels of estrogen or progestin are irregular, which can cause the endometrium to shed unpredictably. Continuous use of the current regimen can spontaneously resolve most cases of BTB. In addition, risk of venous thromboembolism events (VTE), including pulmonary embolism and deep vein thrombosis, will have a fivefold increase after using COCPs [4]. Therefore, in patients over 40 years of age or in those presenting with risk

factors for venous thromboembolism (e.g., obesity or thrombophilia), alternative therapeutic options for curing endometriosis are generally recommended.

### 3.2. Progestogens

Progestins includes oral, depot (intramuscular and subcutaneous), implant, and intrauterine. Several main types of oral progestins applied widely are dienogest (DNG), medroxyprogesterone acetate, and norethindrone acetate (NETA). DNG is an oral selective progestin that has been widely utilized due to its proved efficacy in relieving chronic pelvic pain due to endometriosis. It exerts a dual mechanism of action. DNG exerts its central effects by acting on the hypothalamus to suppress the pulsatile secretion of GnRH, thereby reducing circulating levels of FSH and LH and inhibiting ovulation. This cascade leads to decreased estrogen production, attenuating the stimulation of ectopic endometrial tissue. Consequently, inflammatory activity and tissue proliferation are diminished, contributing to alleviation of pain linked with endometriosis. In peripheral mechanism, they bind to progesterone receptors (PRs) in endometrial stromal cells, triggering expression of genes like IGFBP-1 and prolactin, which are markers of decidualization. This process causes stromal decidualization, which makes the tissue less proliferative and more functionally inactive. Therefore, less pain generated by lesion expansion. Moreover, endometriotic lesions secrete pro-inflammatory cytokines and prostaglandins that enhance the sensitivity of pelvic nociceptive pathways. DNG exerts anti-inflammatory effects by downregulating mediators, such as prostaglandin E2 and IL-6, thereby attenuating nociceptive signaling and contributing to the amelioration of CPP.

Approximately 90% of patients reflect that the endometriosis-associated pain was improved or completely eliminated after using progestins for 6 months [5]. A clinical study found that both NETA and DNG reduce the severity of dysmenorrhea from 8 score to 0 score after administration for 6 months. Additionally, treatment with NETA was associated with a significant decrease in the proportion of women who experienced moderate to intense pain during sexual activity from 88% to 3%, whereas DNG therapy led to a decrease from 79% to 6%, highlighting the substantial efficacy of these progestins in alleviating endometriosis-associated pain at intercourse [6].

Progestins are generally well-tolerated and often preferred for long-term therapy. The most common issues of using progestins are BTB, same as COCPs, amenorrhea, and mild hormonal side effects such as weight change and breast tenderness. These adverse effects are not serious but may be unbearable for small parts of patients. BTB can be overcome by taking estrogen for 7 days or continually use increased dose of progestins until bleeding stops [7].

## 4. Second-line Therapy

### 4.1. NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are nonhormonal drugs used commonly for relieving pain caused by endometriosis. Ectopic endometrial lesions produce abnormally high amounts of prostaglandins that drive inflammation, uterine contractions, and pain sensitization. NSAIDs can inhibit cyclooxygenase (COX-1 and COX-2), reducing synthesis of prostaglandins. Therefore, the inflammation in the ectopic lesions and pelvic pain are reduced. However, NSAIDs can only treat symptoms of endometriosis but unable to prevent disease progression.

Use of NSAIDs will increase the risk of serious gastrointestinal haemorrhage or perforation twofold or even threefold. In all ulceration, 30% cases are caused by high use of NASIDs [8]. Therefore, patients with history of ulteration are not recommended taking NSAIDs as treatment for endometriosis.

### 4.2. Gonadotropin-Releasing Hormone Agonist

Gonadotropin-Releasing Hormone agonist (GnRH agonist) is a hormonal treatment for endometriosis. The drug binds to GnRH receptors in the anterior pituitary, stimulating the release FSH and LH, which may briefly increase estrogen levels for the first several days. Continuous apply

of GnRH agonists leads to desensitization of pituitary GnRH receptors, which results in FSH and LH secretion drops dramatically. Therefore, ovarian estrogen production declines. Ectopic endometrial tissue shrinks and pelvic pain is relieved as estrogen level decreases. A clinical study found that the percentage of patients who suffer from sever endometriosis-associated pain reduce from around 40% to 5-10% and a surge appears in the percentage of female who suffer no or mild pain, with a 45% increase, after using Nafarelin as treatment for six months [9].

The adverse effect of taking GnRH agonist as treatment involves decreased bone mineral density and hypoestrogenism state which includes hot flashes and vaginal dryness. The duration of administration of GnRH agonist is limited to 3 months unless add-back therapy is used. Add-back therapy involves supplement low-dose of estrogen or progestins in order to counteract side effects. A randomized, controlled trial showed that the spine bone density of mineral was equal to or higher than baseline in groups that used add-back therapy [10]. One limitation of GnRH agonist is the likelihood of recurrence of endometriosis is high as its intake cannot be long-term. The proportions of recurrence after 5 years are 36.9% for patients who have minimal endometriosis and 74.4% for severe endometriosis [11].

## 5. Emerging Therapy of Endometriosis

### 5.1. Gonadotropin-Releasing Hormone antagonist

Gonadotropin-Releasing Hormone antagonist (GnRH antagonist) is a newer hormonal therapy for endometriosis. GnRH antagonists act on GnRH receptors, like GnRH agonists, but more directly. They have complementary shape to GnRH receptors so they bind perfectly and GnRH receptors in the pituitary are fully blocked. This prevents LSH and LH release. Consequently, ovarian estrogen level drops. Hypoestrogenism state causes atrophy of ectopic endometrial lesions and reduction of inflammation.

A study found that GnRH antagonists are available for 60% of patients with Endometriosis to make the ectopic endometrial tissues shrink. After administration of GnRH antagonist over 8 weeks, the severity of endometriosis is alleviated significantly [12]. In another study, dysmenorrhea and non-menstrual pelvic pain can be relieved by administration of both higher doses (200mg per day) and lower doses (150mg per day) of GnRH antagonist. Responder rates for dysmenorrhea reached 52.1% with lower doses and 78.2% with higher doses after one year of administration of GnRH antagonists, which demonstrates that both lower and higher dose of GnRH antagonist are available for alleviating pain [13].

However, the side effects because of hypoestrogenism state also appear during use of GnRH antagonist. Long-term use of high dose (200mg per day) of GnRH antagonist will lead to loss of bone mineral density, so add-back therapy can be used as same as treatment of GnRH agonist to avoid this side effect.

### 5.2. Aromatase Inhibitors

Aromatase inhibitors (AIs) are competitive or non-competitive inhibitors to aromatase. Aromatase is the primary enzyme responsible for transforming androgens, such as androstenedione and testosterone, into estrogens like estrone and estradiol, so it's also celled estrogen synthetase. AIs can bind with aromatase and block activity of the enzyme. Accumulating evidence indicates that they may represent a promising therapeutic option for endometriosis by targeting the estrogen-dependent pathways underlying disease progression. In endometriotic lesions, abnormal aromatase expression has been identified, leading to estrogen production within the ectopic endometrium. Therefore, fewer estrogens are produced by aromatase, leading to reduction of ectopic endometrial lesion proliferation and estrogen-driven inflammation which results in relieving CPP.

It's found that estrogen levels decrease 50% after treatment of AIs and the pelvic pain is relieved and eliminated fully after 2 months. The size of red polyploid viginal lesions decreases significantly after 9 months of administration [14].

Enhanced ovarian cyst formation may be caused by monotherapy of AIs. Since AIs will lower levels of estrogen, leading to diminished negative feedback on the hypothalamus and pituitary. Accordingly, AIs are generally administered in combination with progestins or GnRH agonists, which suppress gonadotropin release and prevent ovarian stimulation. This combined approach ensures more effective suppression of estrogen production and improves therapeutic outcomes in endometriosis management.

## 6. Conclusion

Endometriosis is a prevalent, estrogen-dependent gynecological disorder recognized primarily by chronic pelvic pain, ovarian endometriotic cysts, and infertility, with pain being debilitating symptom affecting quality of life. Pharmacological management remains central to symptom control, and this review outlines the mechanisms, therapeutic efficacy, and adverse effects of current agents for endometriosis-associated pain. First-line treatments mainly include combined oral contraceptives (COCPs) and progestins. COCPs reduce pain by inhibiting ovarian estrogen synthesis and modulating endometrial cell turnover, though their use may be complicated by breakthrough bleeding and an increased risk of venous thromboembolism. Progestins, such as DNG, exert both central and peripheral actions, demonstrating robust analgesic effects with generally favorable tolerability. Other strategies involve nonsteroidal anti-inflammatory drugs, which offer only symptomatic relief without influencing disease progression, and gonadotropin-releasing hormone (GnRH) agonists, which suppress estrogen production and reduce lesion size but are limited by side effects such as bone demineralization, restricting their use to short treatment courses. Emerging options that directly target estrogen signaling, including GnRH antagonists and aromatase inhibitors, have also shown clinical benefit, although hypoestrogenism-related adverse effects remain a major concern. Collectively, these therapeutic approaches highlight the need for individualized treatment strategies and underscore opportunities for the development of novel targeted therapies.

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