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## **Effectiveness of Pharmacological Pain Management Strategies for Severe Symptoms in Endometriosis in Sport**

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**Abstract:**

**Background.** Endometriosis is a chronic, estrogen-dependent inflammatory disease characterized by the presence of endometrial-like tissue outside the uterus, leading to severe pelvic pain, dysmenorrhea, dyspareunia, and reduced quality of life. Despite multiple therapeutic options, effective pain control remains challenging, particularly in patients with severe or recurrent disease.

**Aim.** This study aimed to synthesize current evidence on hormonal and non-hormonal pain-management strategies for severe symptoms in endometriosis.

**Material and methods.** A systematic literature review was conducted using PubMed, ScienceDirect, ResearchGate, and Google Scholar. Randomized controlled trials, cohort studies, and case-control studies published between 2022 and 2025 were included. Studies evaluating pain outcomes using validated pain assessment tools were eligible. Data were extracted regarding intervention type, patient characteristics, follow-up duration, pain outcomes, and risk of bias.

**Results.** Hormonal therapies, including progestogen-based treatments, combined estrogen–progestogen regimens, and gonadotropin-suppressing agents, demonstrated effectiveness in reducing dysmenorrhea and inflammation however outcome varies by formulation, dose, and patient hormonal responsiveness. Non-hormonal approaches, such as anti-inflammatory analgesics, neuromodulatory agents, physical therapies, and multidisciplinary care, provided additional symptom relief, although responses varied considerably among patients. Treatment effectiveness was influenced by reproductive plans, tolerability, contraindications, and long-term safety.

**Conclusions.** Hormonal therapies remain the most effective first-line option for pain reduction in patients with moderate-to-severe endometriosis who are not seeking pregnancy. Individualized, multimodal treatment strategies are essential to address symptom variability and optimize long-term outcomes.

**Key words:** Endometriosis, Menstrual pain, Pain management, Pharmacotherapy, Sport

## **1 Introduction**

Endometriosis is a chronic gynecological condition characterized by the presence of endometrial-like tissue outside the uterus, leading to inflammation, fibrosis, and adhesion formation. It is a leading cause of pelvic pain and infertility in women of reproductive age. The condition is highly heterogeneous, with symptoms ranging from mild to debilitating, often including dysmenorrhea, dyspareunia, chronic pelvic pain, and gastrointestinal or urinary disturbances. The exact etiology remains unclear, but retrograde menstruation, immune dysfunction, hormonal factors, and genetic predisposition are considered key contributors.[1]

Endometriosis affects approximately 10% of women of reproductive age, though prevalence may be underestimated due to delays in diagnosis, which often exceed several years. Many patients experience cyclical or chronic pelvic pain that significantly impairs their quality of life, work productivity, and mental health. Up to 30% of affected individuals report symptoms severe enough to cause psychological distress, including anxiety and depression. Additionally, the disease has been associated with an increased risk of irritable bowel syndrome, interstitial cystitis, and central sensitization syndromes, which may contribute to pain chronicity.[2]

Risk factors for endometriosis include early menarche, short menstrual cycles, heavy menstrual bleeding, nulliparity, and family history. Estrogen-dependent pathophysiology suggests that hormonal fluctuations play a critical role in disease progression, and suppression of ovarian function has been a mainstay of treatment. Protective factors include late menarche, multiparity, prolonged lactation, and the use of combined hormonal contraceptives. Diagnosis remains challenging, as symptoms often overlap with other gynecological, gastrointestinal, and urological disorders. While imaging modalities such as transvaginal ultrasound and MRI can aid in diagnosis, definitive confirmation requires laparoscopic visualization with histopathological analysis of ectopic endometrial tissue.[3]

The differential diagnosis for endometriosis includes adenomyosis, uterine fibroids, chronic pelvic inflammatory disease, irritable bowel syndrome, interstitial cystitis, and musculoskeletal disorders such as myofascial pelvic pain syndrome. Given the complexity of symptomatology, a multidisciplinary approach is often necessary for accurate diagnosis and management.[4]

A comprehensive clinical history is essential and should include an evaluation of menstrual cycle characteristics, pain onset and progression, and the presence of associated symptoms such

as dysmenorrhea, dyspareunia, dyschezia, dysuria, and chronic pelvic pain. The impact of symptoms on daily activities, including work, relationships, and psychological well-being, should also be assessed. A thorough sexual history, including past or current infections, contraceptive use, and fertility concerns, can provide additional diagnostic insights. Physical examination may reveal findings such as uterosacral ligament nodularity, adnexal masses, or pelvic tenderness, though many cases present with a normal examination.[5]

The pathophysiology of endometriosis is complex and multifactorial, involving hormonal, immunological, and inflammatory mechanisms. Ectopic endometrial-like tissue is believed to establish and proliferate due to aberrant immune responses, increased angiogenesis, and resistance to apoptosis. These lesions exhibit estrogen-dependent growth, with local production of estradiol and dysregulated progesterone response contributing to sustained inflammation and pain. Proinflammatory cytokines, oxidative stress, and neural sensitization further exacerbate symptom severity and chronicity. The frequent co-occurrence of neuropathic pain features suggests that central sensitization plays a role in the persistence of symptoms beyond the menstrual cycle.[6]

Treatment strategies for endometriosis aim to reduce pain, prevent disease progression, and preserve fertility when desired. First-line pharmacological therapy includes NSAIDs and hormonal suppression using combined oral contraceptives, progestins, or gonadotropin-releasing hormone (GnRH) analogs. In refractory cases, second-line options such as GnRH antagonists, aromatase inhibitors, and selective progesterone receptor modulators may be considered. Surgical intervention, including laparoscopic excision or ablation of endometriotic lesions, is recommended for patients with severe pain or infertility unresponsive to medical therapy. However, recurrence rates remain high, necessitating long-term management strategies.[7]

Beyond conventional pharmacotherapy and surgery, complementary and alternative treatments have gained interest for symptom relief. This review will examine the role of pharmacological interventions- hormonal therapies (progestogens, combined oral contraceptives, GnRH analogues), non-hormonal analgesic approaches, including NSAIDs and neuromodulators, and non-pharmacological interventions, including pelvic physical therapy, acupuncture, herbal medicine, dietary modifications, relaxation techniques, and psychological support in the management of endometriosis-associated pain.

## **2. Methodology**

A comprehensive literature search was conducted using PubMed, ScienceDirect, ResearchGate, and Google Scholar databases. The primary search yielded 450 studies published between 2018 and 2025. The search strategy incorporated the following terms:

((VAS OR NRS OR PPI) AND (Dysmenorrhea OR "Menstrual pain" OR "Menstrual disorders" OR Endometriosis) AND ("Pain management" OR "Analgesic ladder" OR "Non-pharmacological treatment" OR "Pain relief" OR "Treatment efficacy" OR "Non-steroidal anti-inflammatory drugs" OR NSAIDs OR "Opioid analgesics" OR "Physical therapy" OR Acupuncture OR "Herbal remedies" OR "Heat therapy" OR "Cognitive behavioral therapy" OR CBT OR "Relaxation techniques" OR "Complementary therapies" OR Pharmacotherapy)).

Randomized controlled trials (RCTs), cohort studies, and case-control studies published between 2022 and 2025 were included for analysis. Three independent reviewers screened titles, abstracts, and full texts based on predefined inclusion criteria.

## **3. Results and Discussion**

### **3.1 Hormonal Drugs**

Hormonal therapy represents the first-line management option for most patients with endometriosis who are not actively seeking conception. These agents primarily target the underlying hormonal mechanisms responsible for the debilitating symptoms of the disease. Ectopic endometrial lesions express both estrogen and progesterone receptors, making them highly responsive to fluctuations in circulating hormone levels. Such lesions contribute to pain and other symptoms through local inflammatory responses and the secretion of cytokines and prostaglandins, depending on their anatomical distribution.[8]

Progestogens exert their therapeutic effect mainly by suppressing the hypothalamic–pituitary–ovarian (HPO) axis, thereby reducing gonadotropin release and subsequent ovarian estrogen production. This inhibition limits the growth and activity of ectopic endometrial tissue. Additionally, hormonal agents decrease prostaglandin synthesis, which contributes to the alleviation of pain and inflammation.[9]

It is essential to note that most hormonal drugs used in endometriosis were originally developed as contraceptives; thus, they are contraindicated in patients attempting to conceive. Clinicians

should also be mindful of their potential contraindications and systemic effects, including an increased risk of thromboembolic events, metabolic disturbances, and mood changes, depending on the specific pharmacological agent used.[10]

Hormonal agents, particularly progestogens and combined oral contraceptives (COCs), remain a cornerstone in the management of endometriosis-associated pain. Among progestins, dienogest (DNG) has been extensively studied and consistently demonstrated efficacy in reducing pelvic pain and endometrioma size across diverse populations. Long-term treatment with DNG provides sustained symptom control and reduction of lesion size without major adverse effects, with tolerability improving over time and the first treatment year serving as a strong predictor of long-term adherence.[11] Moreover, DNG therapy has been associated with improvement not only in pelvic pain but also in urinary symptoms, without negatively impacting sexual function. Evidence also suggests that DNG enhances quality of life (QoL) and health-related QoL outcomes, with particular benefit in reducing dyspareunia compared to combined preparations such as ethinylestradiol/dienogest.[12]

Comparative studies between DNG and COCs containing ethinylestradiol or estradiol valerate found no significant differences in biochemical markers or overall efficacy, indicating that cost-effective contraceptive formulations may serve as a viable alternative for some patients. However, other analyses suggest that DNG may provide superior pain relief and QoL improvement compared with standard COCs, though results remain heterogeneous depending on pain subtype and disease localization. Alternative progestins such as norethisterone acetate (NETA) and dydrogesterone have also demonstrated comparable pain reduction, with NETA achieving greater decreases in endometrioma size and lower treatment discontinuation rates, while dydrogesterone showed additional benefits in sexual well-being.[13]

In patients with deep endometriosis (DE) and adenomyosis (AD), extended COC regimens have led to significant clinical and sonographic improvement over prolonged follow-up. Conversely, the response to hormonal therapy in cesarean scar endometriosis appears limited, with minimal pain reduction and no significant change in lesion size. Newer hormonal combinations, including estetrol/drospirenone, have shown promise in reducing pain and improving gynecological parameters while potentially lowering thromboembolic risk. Similarly, relugolix combination therapy, a newer oral GnRH antagonist-based regimen, has demonstrated efficacy, convenience, and tolerability for long-term management of endometriosis-associated pain.[14]

Overall, the collective evidence supports the efficacy and safety of various hormonal approaches in alleviating pain and controlling disease progression in endometriosis. While dienogest remains one of the most studied and effective options, therapy should be individualized based on patient comorbidities, symptom profile, reproductive intentions, and treatment tolerability.[15]

### **3.2 Other Pharmacological Agents for Pain Management**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used agents for managing pain in endometriosis. Their primary mechanism of action involves the inhibition of cyclooxygenase (COX) enzymes, particularly COX-2, which reduces prostaglandin synthesis in inflammatory pathways. Since prostaglandins are key mediators of uterine contractions, inflammation, and pain sensitization, COX inhibition theoretically alleviates the dysmenorrhea and pelvic pain associated with endometriosis. However, despite their widespread use, clinical evidence regarding NSAID efficacy remains inconsistent. Current data suggest insufficient high-quality evidence to confirm the analgesic effectiveness of commonly used agents such as naproxen in endometriosis-related pain. Likewise, the potential therapeutic role of aspirin has not been established, with existing studies emphasizing the need for further research to clarify its safety, efficacy, and optimal dosing strategies in this population.[16]

Emerging evidence indicates that selective COX-2 inhibitors may offer advantages over traditional NSAIDs. Observational data suggest a potential reduction in endometriosis incidence among women using COX-2-selective agents, implying a possible protective or disease-modifying effect. Such findings highlight their potential as targeted options for pain management, particularly in younger women or those with contraindications to hormonal therapy, though further controlled studies are warranted to confirm these observations.[17]

Another non-hormonal compound that has gained attention is N-acetylcysteine (NAC), a glutathione precursor with antioxidant and anti-inflammatory properties. Oral administration of NAC has been shown to improve endometriosis-related pain, reduce endometrioma size, and lower serum CA-125 concentrations. Some studies also suggest a beneficial impact on fertility outcomes, possibly due to its antioxidative modulation of the peritoneal environment. However, when used as an adjunct to low-dose oral contraceptives following conservative laparoscopic surgery, NAC did not significantly affect pain recurrence or endometrioma regrowth compared with contraceptive therapy alone.[18]

In summary, while NSAIDs remain a common first-line symptomatic therapy, robust evidence supporting their long-term benefit in endometriosis pain management is limited. COX-2 inhibitors and NAC represent promising adjunctive or alternative options, particularly for patients seeking non-hormonal interventions or fertility preservation. Nonetheless, further large-scale, randomized studies are required to establish their precise therapeutic roles and long-term safety profiles.[19]

#### **1. 3.3 Surgical and Interventional Approaches**

Minimally invasive and image-guided interventions are increasingly used as adjuncts or alternatives to conventional surgery for selected presentations of endometriosis, particularly

extraperitoneal or focal lesions and acute pain exacerbations. Percutaneous image-guided cryoablation has accumulated the most consistent evidence for extraperitoneal disease: studies of abdominal-wall and other extraperitoneal endometriosis report that cryoablation is safe, can be performed in an outpatient setting, and produces clinically meaningful pain reduction beginning around three months after treatment with sustained benefit to 12 months and beyond. These data support cryoablation as a tissue-sparing option that achieves good local control for well-circumscribed nodules, although controlled trials and longer comparative data versus excision are still required to define durability, recurrence rates, and patient selection criteria.[20]

Regional and perineural techniques have a role for acute exacerbations or refractory pelvic pain. Case reports and early series demonstrate that ultrasound-guided nerve blocks — for example, erector spinae plane (ESP) blocks — can promptly relieve endometriosis-related pain in emergency settings and serve as opioid-sparing alternatives in patients with medication intolerance. Such blocks are primarily temporizing measures that can facilitate diagnostic evaluation, bridge to definitive therapy, or be incorporated into a multimodal analgesic plan.[21]

Chemical and neuromuscular modulation with botulinum toxin (BoNT) targeting pelvic floor hypertonia or myofascial contributors to genito-pelvic pain penetration disorder (GPPD) and chronic pelvic pain (CPP) is biologically plausible and attractive because it can be combined with hormonal and other medical therapies. However, the current literature is dominated by small studies and reviews; high-quality randomized controlled trials are lacking and are needed to determine optimal dosing, injection targets, duration of effect, and long-term safety.[22]

In summary, percutaneous cryoablation and image-guided nerve blocks offer effective, low-morbidity options for selected patients with focal extraperitoneal disease or acute pain flares, while botulinum toxin shows promise for pelvic floor-related pain syndromes but requires rigorous evaluation. Clinicians should individualize procedural choice according to lesion localization, symptom pattern, fertility goals, and available expertise, and consider these interventions as components of a multidisciplinary, multimodal treatment pathway rather than as standalone cures.[23]

### **3.4 Complementary, Alternative, and Supportive Approaches**

Complementary and integrative therapies are increasingly incorporated into multimodal management plans for endometriosis, particularly for patients seeking non-hormonal options, experiencing medication intolerance, or requiring additional symptom control. Among these, acupuncture, physiotherapy and exercise-based interventions, dietary modification, and selected supplements or herbal formulations show potential benefits—although the overall evidence base remains heterogeneous and often limited by small sample sizes and methodological variability.

Acupuncture-related interventions have been investigated most extensively. Network meta-analyses and randomized trials suggest that modalities such as acupoint catgut embedding, auricular therapy, acupoint applications, and multimodal combination regimens may effectively

reduce endometriosis-associated pain. Manual acupuncture alone has demonstrated improvements in dysmenorrhea severity, pain duration, and overall quality of life, with an acceptable safety profile; however, therapeutic effects often diminish after the cessation of treatment.[24] Evidence for acupuncture combined with moxibustion remains insufficient, though some single studies report symptom improvement. [25] More consistently, acupuncture combined with Chinese herbal medicine appears superior to herbal therapy alone, offering enhanced pain reduction and quality-of-life improvement. While these findings support the potential integration of acupuncture into care pathways for patients who cannot or prefer not to use hormonal treatments, robust confirmation through large-scale, high-quality randomized trials is still required.[26]

Exercise- and physiotherapy-based approaches represent another promising area. A single session of digital health–delivered exercise, including virtual reality–assisted formats, has been shown to provide immediate relief from pelvic pain comparable to supervised telehealth physiotherapy. Although short-term, these results support the utility of accessible, self-managed interventions for acute symptom modulation and suggest a role for exercise-based strategies as part of long-term pain management.[27]

Herbal and supplement-based therapies also demonstrate potential benefits. Sanjie Analgesic Capsules appear well tolerated and may alleviate dysmenorrhea, though evidence remains preliminary. Antioxidant vitamin supplementation has shown more consistent efficacy, reducing dysmenorrhea, dyspareunia, and chronic pelvic pain while improving patient-reported quality of life—likely through mitigation of oxidative stress, which contributes to the pathophysiology of endometriosis.[28] Curcumin, when used as an adjunct to dienogest, significantly improved pain scores, sexual function, and quality of life, supporting its role as a synergistic anti-inflammatory supplement. Network pharmacology analyses of patented Chinese herbal formulations further highlight biologically plausible mechanisms for symptom relief, although these findings primarily provide experimental and mechanistic support rather than definitive clinical evidence.[28]

Dietary interventions such as the Mediterranean diet offer an additional supportive strategy. Adherence to a Mediterranean dietary pattern, characterized by high antioxidant and anti-inflammatory nutrient intake, has been associated with decreased pain perception and improved symptom control in women with endometriosis. These findings suggest that long-term dietary modification may contribute meaningfully to chronic pain management, particularly alongside other therapeutic modalities.[29]

Overall, complementary and supportive therapies can offer meaningful symptom relief, improve quality of life, and enhance patient empowerment within a multimodal treatment framework. However, their integration into clinical practice should be guided by patient preference, safety considerations, and an acknowledgment of the variable strength of evidence. Continued high-quality research is essential to determine optimal combinations, dosing strategies, and long-term outcomes.[30]

## 4 Conclusion

Effective pain management in endometriosis requires a multidimensional, individualized, and evidence-based approach. The chronic and heterogeneous nature of the disease, characterized by inflammatory, hormonal, neuropathic, and myofascial components, necessitates treatment strategies that extend beyond simple analgesia to address quality of life, functional impairment, fertility considerations, and psychological well-being. Personalized care and shared decision-making remain central to optimizing adherence, minimizing treatment burden, and improving long-term outcomes.

This review synthesizes current evidence across pharmacological, surgical, and complementary modalities. Hormonal therapies remain the cornerstone of medical management for patients not seeking conception, with agents such as progestins, combined oral contraceptives, and GnRH analogues demonstrating reliable reductions in pain and lesion activity. Among these, dienogest shows broad efficacy across endometriosis phenotypes, though its superiority over other regimens depends on symptom profile and patient tolerance. Emerging agents—including estetrol/drospirenone combinations and oral GnRH antagonists—offer promising alternatives with favorable safety profiles. Non-hormonal pharmacotherapies such as N-acetylcysteine and targeted anti-inflammatory supplements may provide additional symptom relief, although evidence for NSAIDs remains inconsistent and requires higher-quality investigations.

Interventional and surgical innovations broaden the therapeutic landscape for patients with refractory symptoms or localized extraperitoneal disease. Image-guided cryoablation demonstrates durable pain reduction and effective local control of abdominal wall and extraperitoneal lesions. Regional anesthesia techniques, such as erector spinae plane blocks, may offer opioid-sparing relief during acute pain flares, while botulinum toxin presents a biologically plausible option for pelvic floor-related pain syndromes, though robust clinical trials are still needed.

Complementary and lifestyle-based approaches—including acupuncture, physiotherapy and digital exercise platforms, antioxidant supplementation, curcumin, herbal formulations, and adherence to a Mediterranean diet—show potential as adjunctive therapies capable of improving pain, physical function, and quality of life. These modalities are particularly valuable for patients seeking non-hormonal strategies or requiring multimodal management; however, the evidence base remains variable and often limited by methodological constraints.

Despite advances across therapeutic domains, many individuals continue to experience persistent or recurrent symptoms. This underscores the need for integrative, multimodal strategies that combine pharmacological, interventional, and supportive therapies tailored to disease phenotype and patient priorities. Future research should prioritize high-quality

randomized trials, standardized outcome measures, mechanistic studies of pain chronicity, and the development of precision medicine tools—including biomarkers and individualized risk stratification models. Progress in minimally invasive technologies, targeted therapeutics, and integrative care pathways holds significant promise for improving long-term outcomes and enhancing the quality of life for people living with endometriosis

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**AI.**

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. **AI** were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

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