



# Current & Emerging Therapies for Endometriosis–Associated Pain

A Review by Ebunoluwa Oluwatimileyin Tijani et al.

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# Understanding Endometriosis: A Global Challenge



## Definition

Chronic gynecological disorder: endometrial-like tissue grows outside the uterus.



## Prevalence

Affects ~10% of women of reproductive age worldwide.



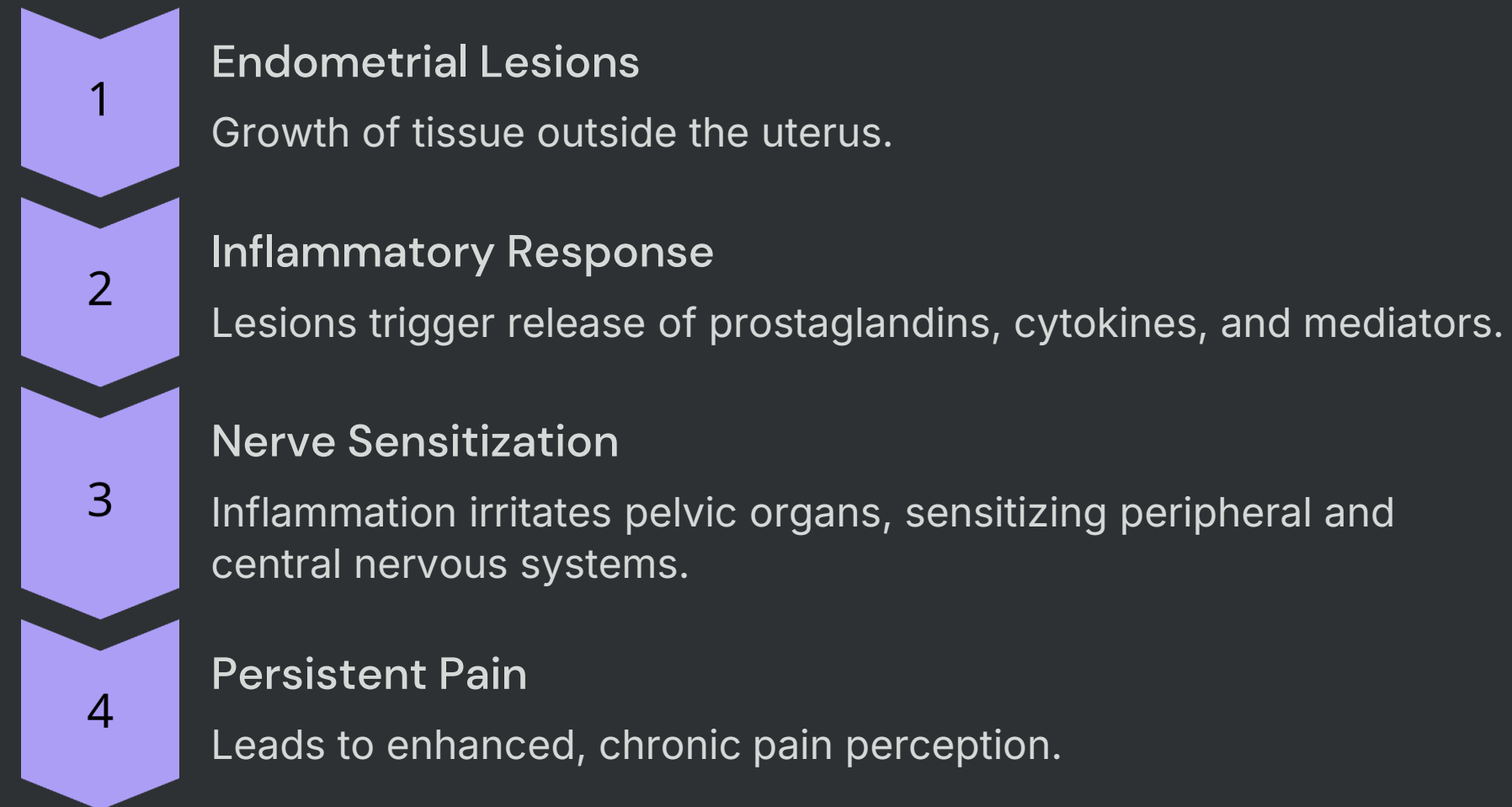
## Impact

Leads to severe pelvic pain, infertility, and reduced quality of life.

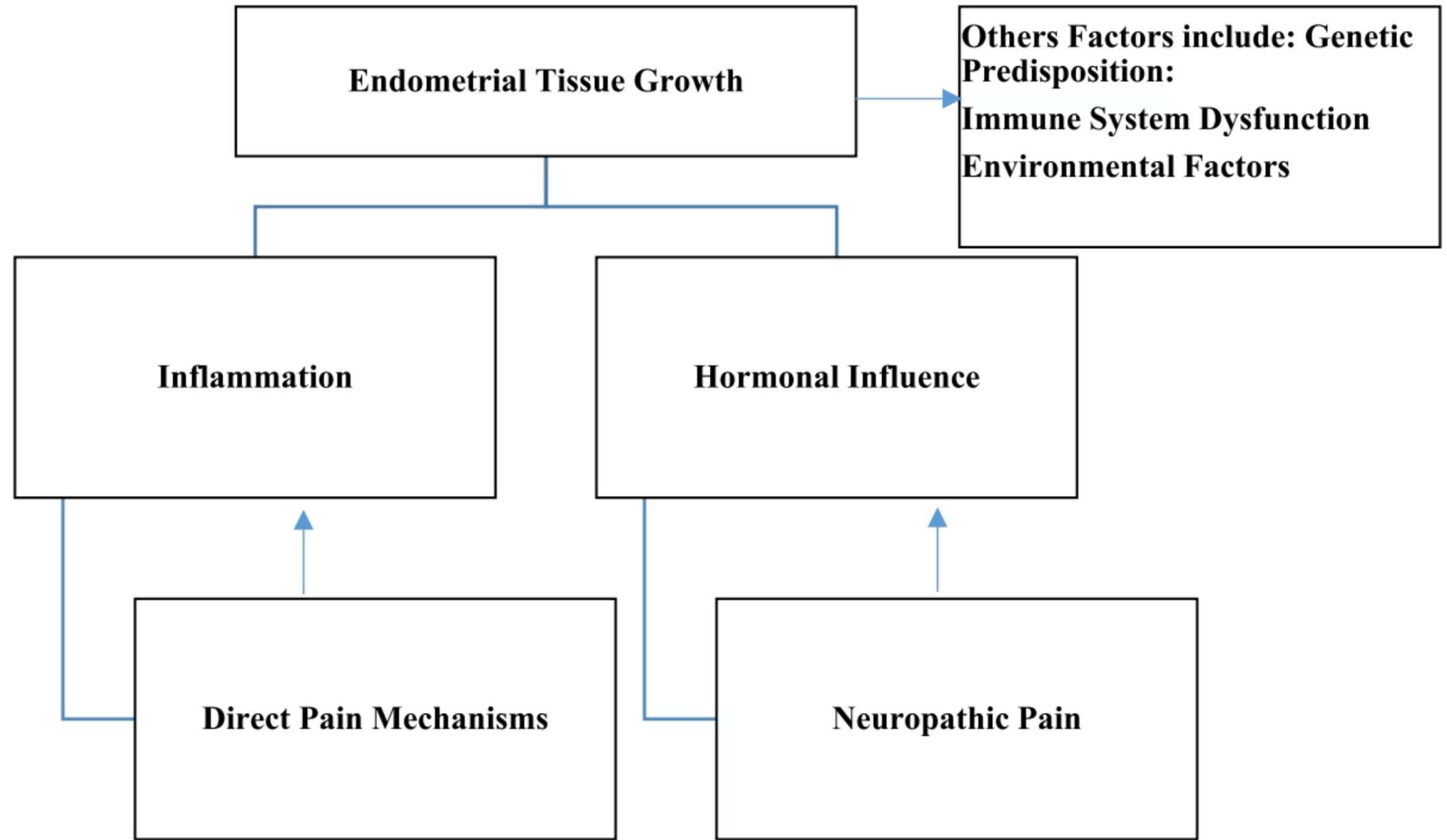
Despite advances, treatment remains challenging due to the disease's complex nature and varied patient responses. Up to 90% of women experience persistent pelvic pain, significantly impacting daily life.



# Pathophysiology of Endometriosis-Associated Pain (EAP)



This chronic pain, often cyclical but also non-cyclical, severely compromises physical, emotional, and social well-being.



**Fig. 1** The primary factors involved in the pathophysiology of endometriosis-associated pain

# Review Purpose & Methodology

## Purpose of the Review

This narrative review assesses established and developing treatments for endometriosis-related pain, covering pharmaceutical, surgical, and complementary options.

It aims to identify strengths and weaknesses of current therapies and the potential of future options to address unmet needs, guiding healthcare providers.



## Search Methodology

An extensive search was conducted across Scopus, PubMed, and Google

Keywords included "endometriosis-associated pain," "treatment," "therapy," "emerging therapies," "deep infiltrating endometriosis," and "pain management."

Focus was on peer-reviewed articles published in English within the last decade, excluding case reports.



# Current Pharmacological Therapies

1

## NSAIDs

First-line, inhibit COX enzymes to reduce inflammation. Moderately effective for pain, but less so for chronic pelvic pain. Side effects: GI discomfort, ulcers.

2

## Hormonal Therapies

Suppress ovulation and regulate estrogen. OCs effective for mild cases, but limited duration. GnRH agonists/antagonists lower pain but induce menopausal symptoms. Progestins (Dienogest) effective, but side effects like breakthrough bleeding.

3

## Opioids

For severe pain, alter perception. Effective short-term, but high potential for addiction and side effects. Not recommended for long-term chronic pain.





# Current Surgical & Complementary Therapies

## Surgical Interventions

- **Laparoscopy**

Standard for identifying and removing lesions. Positive outcomes, but high recurrence rates (up to 50% within 5 years). Requires skilled surgeons.

- **Laparotomy**

More invasive open surgery for severe, extensive cases. Longer recovery time.

- **Nerve Ablation**

Interrupts pain signals. Mixed evidence, not widely practiced, potential complications.

## Complementary & Alternative Therapies

- **Acupuncture**

Stimulates nerves for pain relief. Some evidence, but inconclusive due to lack of large trials.

- **Dietary & Herbal**

Anti-inflammatory diets (omega-3, antioxidants) and supplements (curcumin). Limited but emerging evidence; potential interactions.

- **Physical Therapy**

Pelvic floor therapy improves muscle function. Decreases discomfort and enhances quality of life, especially for urinary/bowel dysfunction.



**Table 1** A comparative overview of the most used treatment modalities for managing endometriosis-associated pain

Treatment Modality	Subcategory	Mechanism of Action	Effectiveness	Limitations	Cost-Effectiveness
Pharmacological	NSAIDs [50, 76]	Inhibit COX enzymes to reduce inflammation; [76]	Moderately effective in pain relief [50]	Limited efficacy for chronic pain [37]	It has a low cost and is suitable for short-term use [7]
	Oral Contraceptives [75]	Suppress ovulation and stabilize hormone levels [75]	Effective in managing mild cases [19]	May not be sufficient for severe cases [73]	Affordable and widely accessible; cost-effective for long-term management of mild cases [83]
	GnRH Agonists and Antagonists	Reduce the production of oestrogen by suppressing the pituitary gland. Zhang et al., [88]	Beneficial in lowering pain [66]	It can cause menopausal symptoms with long-term use [36, 43]	Expensive but highly effective for short-term relief; less sustainable for extended use [83]
	Progestins [65]	Inhibit the growth of endometrial tissue by modifying hormonal balance [22]	Effective pain management [65]	Risk of irregular bleeding, weight gain [82, 83]	Moderately priced; and cost-effective for chronic cases [24]
	Opioids [4]	Bind to brain opioid receptors to inhibit pain signals [4]	Effective for short-term use [4]	High potential for addiction and tolerance [12]	High cost with significant risks; limited cost-effectiveness for long-term pain relief [86]
Surgical	Laparoscopy [40]	Minimally invasive removal of endometrial lesions [77]	Effective symptom relief [31]	High recurrence rates, require skilled surgeons [21]	High upfront cost; cost-effective if performed by experienced surgeons [71]
	Laparotomy [85]	Open surgery to remove large or deep endometrial lesions [85]	Effective for extensive endometriosis [85]	Longer recovery time, more invasive [87]	Expensive with prolonged recovery costs; less favorable compared to laparoscopy [71]
	Nerve Ablation and Resection [60]	Surgical destruction of nerves responsible for transmitting pain [60]	Some success in reducing pain [60]	Effectiveness varies, not widely practiced [81]	Moderate cost; effectiveness varies [55], making sustainability uncertain
Complementary and Alternative	Acupuncture [47, 48]	Stimulates nerves and muscles to promote natural pain relief [47, 48]	Some evidence of effectiveness Mira et al., [57]	Lack of large-scale clinical trials Mira et al., [57]	Moderate per-session cost; effectiveness varies [86], impacting cost-effectiveness
	Dietary Interventions/Herbal Supplements [80]	Anti-inflammatory diets to reduce systemic inflammation [61]	Limited but emerging evidence [80]	Lack of regulation in supplements, variable patient response [80]	Low to moderate cost; effectiveness depends on patient adherence and supplement quality [39]
	Physical Therapy [23]	Targeted exercises to strengthen pelvic muscles and reduce pain [23]	Effective in improving mobility [23]	Requires patient adherence to be effective [23]	Moderate cost with high long-term value for compliant patients [3]



# Deep Infiltrating Endometriosis (DIE)

DIE is one of the most severe forms, with lesions penetrating >5mm, often involving bowel, bladder, and ureters. Pain is frequently refractory to standard pharmacological treatments.

## Surgical Management

Considered the cornerstone due to limited medical efficacy. Techniques include excision of lesions, bowel resections, and ureterolysis.

## Peritonectomy

An emerging radical surgical trend involving complete excision of affected peritoneal tissue, showing promise in reducing pain and improving fertility.

Limitations include high recurrence rates, technically demanding procedures requiring skilled surgeons, and risks of postoperative complications.



**Endometriosis**

# Emerging Pharmacological Approaches

1

## SPRMs

Modulate progesterone receptors, targeting tissue growth and inflammation. Ulipristal acetate is promising, but safety concerns exist.

2

## Aromatase Inhibitors

Reduce local estrogen production. Show positive outcomes, but bone loss limits long-term use.

3

## Newer GnRH Antagonists

Offer rapid estrogen reduction with fewer hypoestrogenic effects. Bone health concerns remain; high cost.

4

## Anti-angiogenic Therapies

Target vascularization of lesions. Show promise in reducing lesion size and pain in early trials.

5

## Cannabinoids

Potential for chronic pain and inflammation. Preclinical studies show promise, but limited clinical data and legal challenges exist.



# Emerging Advanced Techniques & Therapies

## Advances in Surgical Techniques



### Robotic-assisted Surgery

Improves precision, dexterity, and visualization for complex DIE cases. Reduced blood loss, shorter recovery.



### Minimally Invasive

Single-port laparoscopy (single incision) and NOTES (no external incisions, experimental).

## Gene, Stem Cell & Immunotherapy



### Gene & Molecular

Target irregular epigenetic modifications (HDACis, DNMTis). CRISPR-Cas9 for precise gene editing. Experimental, ethical concerns.



### Stem Cell & Immunotherapy

Mesenchymal stem cells (MSCs) and immunotherapy (T cells, vaccines) are experimental. Safety profiles unclear, high costs.

## Non-pharmacological Interventions

### Lifestyle Modifications

Dietary changes (anti-inflammatory foods like omega-3 fatty acids) and exercise to reduce stress and enhance well-being.

### Cognitive-Behavioral Therapy (CBT)

Effectively manages chronic pain by addressing emotional and cognitive elements.



**Table 2** Comparative summary of current and emerging therapies for endometriosis-associated pain

Therapy Type	Efficacy	Safety Profiles	Cost-Effectiveness	Accessibility	Challenges
Current Therapies					
NSAIDs	Effective for mild to moderate pain relief; limited in reducing disease progression [66]	Although generally safe for immediate usage, prolonged use can induce gastrointestinal as well as renal difficulties [66]	Low-cost but may lead to increased long-term costs due to potential side effects requiring further management [73]	Widely accessible over the counter or by prescription [66]	Long-term use associated with risks; doesn't address the underlying cause of endometriosis [10]
Hormonal Therapies	Reduces pain and suppresses disease activity; GnRH agonists are effective for severe cases [66]	Hormonal negative consequences include mood changes, weight gain, and reduced bone density. [73]	Moderate cost: repeated prescriptions or long-term treatment required, increasing overall cost [73]	Widely accessible in most healthcare settings, though GnRH agonists may require specialized prescription [66]	Does not provide a permanent cure; side effects often limit long-term use [36]
Surgical Interventions	Laparoscopy is effective in removing lesions and providing long-term pain relief [77]	Risks include infection, scarring, and potential recurrence of endometriosis [10]	High upfront costs due to surgical procedures, though cost-effective in the long term for some patients [10]	Accessible in regions with advanced healthcare facilities but requires specialized expertise [77]	Risk of recurrence, high costs, and potential complications from surgery [21]
Opioid Analgesics	Effective for short-term pain relief but not a long-term solution [47, 48]	High risk of addiction, tolerance, and opioid-related side effects [47, 48]	Can be costly over time, particularly due to the need for careful management of side effects [57]	Accessible, but there is increasing regulation due to the opioid crisis [47, 48]	High potential for addiction, tolerance, and societal concerns regarding opioid overuse [47, 48]
Emerging Therapies					
Selective Progesterone Receptor Modulators (SPRMs)	Promising in clinical trials with efficacy in reducing lesion size and associated pain [65]	Early evidence suggests fewer side effects than traditional hormonal therapies, though more data is needed [65]	Cost-effectiveness not yet fully established due to the emerging nature of the treatment [70]	Limited accessibility as it is still in experimental stages or early clinical use [70]	Long-term effects and safety are still unknown; further trials needed [54]
GnRH Antagonists	Provides rapid pain relief like agonists but without the initial hormonal flare associated with agonists [54]	Potential side effects include headache, hot flashes, and mood changes [36]	High cost due to the novel nature of the drug and need for repeated administration [43]	Currently available in certain regions but less accessible due to cost and regulatory approvals [29]	Still expensive, with potential side effects requiring careful patient monitoring [29]
Aromatase Inhibitors	Reduces estrogen levels, showing promise in managing pain and reducing lesion size [34]	Risks include bone loss and increased fracture risk [34]	Moderate to high cost, especially considering potential long-term side effects that may require further treatment [34]	Limited availability due to its off-label use in endometriosis, more commonly used for breast cancer [34]	Off-label usage in endometriosis; safety concerns, particularly with long-term use, and higher cost compared to other therapies [34]
Stem Cell Therapies	Early studies show potential in tissue regeneration and reducing inflammation associated with endometriosis [42, 53]	Still experimental; long-term safety and efficacy data are lacking [42, 53]	Currently very expensive due to its novel and experimental nature [42, 53]	Extremely limited accessibility; available only in research settings or specialized clinics [42, 53]	Experimental nature means unknown risks, high costs, and limited accessibility [42, 53]
Immunotherapy	Promising in targeting immune system dysfunction that may contribute to endometriosis pathology [27]	Still in the early stages of research, safety profiles remain unclear [27]	Very high cost due to experimental and targeted nature of treatments [42]	Currently only available in clinical trials or highly specialized centers [42]	Unknown long-term effects, high costs, and accessibility limitations [52]
Gene and Molecular Therapies	Potential to correct underlying genetic and molecular drivers of endometriosis [82, 83]	Early-stage research; unknown safety risks and ethical concerns [82, 83]	Likely to be expensive due to complexity and cutting-edge nature [16]	Limited to experimental or clinical trial settings [30]	High cost, ethical concerns and unknown long-term effects [30]



# Challenges & Future Directions



## Cost-effectiveness

Older hormonal treatments are affordable, but newer therapies and advanced surgical techniques are often expensive, limiting accessibility.



## Patient Adherence

Compromised by therapy side effects (menopausal symptoms, GI issues). Emerging medicines aim for fewer side effects, but treatment complexity remains a hurdle.



## Patient Response Variability

Significant challenge due to diverse clinical manifestations, including lesion location, patient age, and comorbidities, influencing treatment outcomes.



## Research Limitations

Many studies suffer from small sample sizes, brief follow-up periods, and inconsistent outcome measures, often relying on subjective pain scores.



## Socioeconomic & Cultural Factors

Financial limitations and inadequate healthcare infrastructure, coupled with cultural stigmas, restrict access to advanced therapies and delay diagnosis.

Future research needs long-term studies, deeper investigation into fundamental mechanisms (immunology, genetics, microbiome), biomarker validation, and combination therapies. Holistic care must address psychological and social effects.

