The role of pharmacotherapy in the treatment of endometriosis across the lifespan

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The role of pharmacotherapy in the treatment of endometriosis across the lifespan

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ABSTRACT
Introduction: Endometriosis is estimated to affect 10% of reproductive-aged women. The gold standard for treatment is surgery; however, surgery carries a significant morbidity and cost burden. There is an ongoing need for safe, effective medical therapies for endometriosis patients, both in conjunction with and independent of surgical interventions. Most conventional therapies for endometriosis work by a similar mechanism, and efficacy is variable. In recent years, there has been increased interest in the development and testing of novel pharmacotherapies for endometriosis.

Areas covered: This review discusses both conventional and emerging treatments for endometriosis. The authors present the application of these drugs in different presentations of endometriosis across the lifespan and discuss how emerging therapies might fit into future medical management of endometriosis. Conventional therapies include nonsteroidal anti-inflammatory drugs, combined oral contraceptives, progestins, GnRH agonists/antagonists, and aromatase inhibitors. Emerging therapies are focused on disease-specific targets such as endothelial growth factor receptors.

Expert opinion: The field of endometriosis therapy is moving toward modifying the immune and inflammatory milieu surrounding endometrial implants. If these drugs show efficacy in clinical trials, combining them with current medical treatment is expected to result in a profound impact on symptom and disease burden for patients who suffer from endometriosis worldwide.

1. Introduction

Endometriosis is estimated to affect 10% of reproductive-aged women [1] and nearly 50% of women experiencing infertility [2]. These women have lower health-related quality of life and report greater pain, depression, anxiety, and impaired social function as compared to the general population [3]. Furthermore, these patients are utilizing the healthcare system much more than their matched counterparts, creating a financial burden on the healthcare system in the United States and worldwide [4,5]. Given the prevalence and financial burden of endometriosis, finding cost-effective strategies to manage the disease is critically important.

Endometriosis can present with a variety of symptoms including dysmenorrhea, dyspareunia, chronic pelvic pain, dysuria, dyschezia, and infertility [6]. Sampson’s theory of retrograde menstruation (wherein retrograde menstruation leads to the proliferation of endometrial glands and stroma outside of the uterus) is the most commonly accepted hypothesis for pelvic disease. Extra-pelvic disease is thought to arise from lymphatic spread, hematogenous dissemination, or metaplastic transformation. In all forms of the disease, there is believed to be a component of immune dysfunction [7]. The significant pro-inflammatory environment of the peritoneal cavity is thought to be in part responsible for the pathophysiology of endometriosis. Pharmacotherapy directed toward the lesions or the pro-inflammatory milieu are both potential targets for drug therapy.

There are multiple goals for pharmacotherapy in patients with endometriosis, including the improvement of quality of life, pelvic pain, and disease burden. In addition, pharmacotherapy can be used to delay or decrease surgical interventions, improve post-operative pain control, and even achieve disease remission [8]. The use of agents associated with significant side effects has come under scrutiny from patient advocacy groups such as the Institute for Clinical and Economic Review [9]. It is therefore important to select pharmacotherapies that maximize benefits and minimize side effects for patients desiring treatment for endometriosis.

Much of the literature regarding the medical management of endometriosis centers on empiric therapy for women who have not undergone surgical management. This report provides up-to-date, evidence-based recommendations and algorithms to guide healthcare practitioners in their treatment of endometriosis sufferers across the lifespan, from early management of symptoms to post-surgery and menopause.

2. Conventional medical therapies

Conventional medical therapies for endometriosis include non-steroidal anti-inflammatory drugs (NSAIDs), combined oral contraceptives (COCs), progestins, gonadotropin-releasing hormone...
With rare exceptions (such as NSAIDs and dydrogesterone), pharmacologic agents used to treat endometriosis-related symptoms inhibit ovulation and are not useful in women actively trying to conceive. There are no pharmacologic agents that improve fertility outcomes in the setting of endometriosis.

For those patients with pelvic pain and suspected endometriosis without surgical diagnosis, COCs or progestins, alone or in combination with NSAIDs, can be used as first-line empiric therapy. There are no data to support the use of the GnRH antagonist elagolix over COCs or progestins, as there are no direct comparison studies. As these drugs have both significant side effects and cost, they should be considered as secondary or tertiary treatment options.

Postoperative treatment with progestins or COCs for a period of 24 months results in reduced cyclic pelvic pain and endometriosis-related pain compared to COCs taken cyclically. Second-line therapies include GnRH agonists, GnRH antagonists, and aromatase inhibitors.

The utility of oral androgens is limited by androgenic side effects; however, they may be a role for vaginal and intrauterine administration of danazol for refractory symptoms.

Emerging therapies that target molecular pathways, including GnRH receptor antagonists and agonists, and aromatase inhibitors (AIs). NSAIDs, COCs, and progestins all have demonstrated efficacy, favorable side effect profiles, and may be considered first-line agents for the treatment of endometriosis-related pain [10,11] (Figure 1). Progestins are appropriate for women with contraindications to estrogen, including risk factors for thrombosis and migraine with aura; however, most are not approved as contraceptives. For women with symptoms refractory to first-line pharmacotherapies, GnRH agonists, and aromatase inhibitors may be considered; however, both of these medications induce a hypoestrogenic state and carry significant side effects that limit their clinical utility. Although aromatase inhibitors are not FDA approved for the management of endometriosis, prospective and randomized trials demonstrate that their use, in combination with estrogens, progestins, or GnRH agonists, effectively reduces pain and decreases the volume of both rectal nodules and endometriomas [12-15].

Hormonal therapies all address endometriosis-related symptoms by inducing a hypoestrogenic state. Hypoestrogenism results in decidualization and atrophy of both eutopic endometrial tissue and endometriosis lesions outside of the uterus. Table 1 summarizes conventional therapies for endometriosis and their applications.

3. Treatment of endometriosis by presentation

3.1. Empiric medical therapy for the patient with endometriosis-related symptoms

In circumstances where endometriosis is suspected but surgery is not desired, there are many options for empiric medical management (Figure 1). Empiric therapy may be used in women without laparoscopy-proven disease, those with previous surgery and/or recurrent symptoms, or patients with comorbid conditions who are poor surgical candidates. Meta-analysis data show that the prevalence of endometriosis in women with chronic pelvic pain who undergo laparoscopy is approximately 33%. Given that most women with chronic pelvic pain will not have a pathologic diagnosis of endometriosis, the use of medications with significant side effects such as GnRH agonists/antagonists must be carefully considered [9,16].

Empiric therapy has the potential to prevent disease progression and delay the need for invasive procedures [17]. Although international bodies (including ASRM and ESHRE) support the empiric treatment of endometriosis without definitive histopathologic diagnosis, [6,18] forgoing laparoscopy in the setting of suspected endometriosis is a matter of ongoing debate.

Current literature supports using COCs and progestins for empiric therapy for pelvic pain in women without a histopathologic diagnosis of endometriosis. Multiple randomized, placebo-controlled trials of patients with radiographic or clinical evidence of endometriosis found that COCs were superior to placebo in reducing dysmenorrhea and endometrioma size [18,19]. Additionally, data support continuous use of COCs (versus cyclic use) for the reduction of endometriosis-associated pain. In multiple systematic reviews of post-surgical patients, continuous use further reduced dysmenorrhea and delayed pain recurrence as compared to cyclic use [20,21]. Although most studies comparing cyclic and continuous COCs focus on the post-operative period, it is reasonable to apply these results to empiric treatment as well.

Oral and other progestin formulations are also used in the treatment of clinically suspected endometriosis. Oral progestins such as medroxyprogesterone acetate, norethindrone acetate, and dienogest are effective at reducing dysmenorrhea and pelvic pain [22-25]. Other progestin delivery methods such as the levonorgestrel intrauterine system (IUS) or the etonogestrel subcutaneous implant are also effective at reducing pain and improving the quality of life in women with suspected endometriosis [24,25]. Recent literature suggests that the etonogestrel-releasing implant is also effective at reducing pain symptoms in patients with deeply infiltrating endometriosis [26].

A few studies have evaluated the impact of pre-surgical medical therapy on surgical outcomes; however, the data are surprisingly sparse. One notable RCT in 1999 compared the use of GnRH agonist (leuprolide) versus placebo in managing chronic pelvic pain in a population of women in Tennessee with clinically suspected endometriosis [27]. After 12 weeks of therapy, women in the leuprolide group (n = 49) had significant improvements in all pain measures as compared to placebo (n = 46), including physician-rated scores for dysmenorrhea, pelvic pain, and pelvic tenderness. Patients then underwent laparoscopy and an equivalent number in each group had confirmed endometriosis (78% and 87%, respectively).

It is important to note that the ESHRE and ACOG guidelines generally do not recommend pre-surgical medical therapy in order to improve surgical outcome [6,7]. Another RCT in 2008 compared the use of oral contraceptives versus placebo in the treatment of dysmenorrhea in a population of women in...
Japan that included patients with radiographically suspected endometriosis who had not undergone surgery [18]. In this study, use of oral contraceptives decreased dysmenorrhea, non-menstrual pelvic pain, and endometrioma size; however, this study included patients who had undergone surgery and included a mixture of different types of endometriosis. Of the different types of endometriosis, endometriomas are particularly well suited to pre-surgical studies, given their characteristic appearance on ultrasound. A retrospective study comparing dienogest versus norethindrone acetate in a population of women with endometriomas diagnosed on preoperative ultrasound showed that both medications were effective in reducing endometrioma size, dysmenorrhea, dyspareunia, and chronic pelvic pain [28]. However, again, these results are not applicable to a majority of patients without overt endometriomas.

Without surgery, current mainstream therapies are likely to be ineffective in treating endometriosis-related pain for a significant subset of women. A recent systematic review of medical therapies for endometriosis suggests that 11–19% of women with endometriosis ‘derived no pain relief at all from medical therapy’ [29]. Future work is ongoing to better characterize molecular pathways involved in endometriosis pathogenesis in order to design targeted therapies that can alleviate the need for surgery in endometriosis treatment.

It is generally recommended that contraceptive agents (oral or other forms of progestin delivery) can be empirically used to treat chronic pelvic pain that is attributed to potential endometriosis. The use of other more expensive drugs with significant side effects should be reserved for those patients with a documented history of endometriosis.

3.2. Medical therapy following endometriosis surgery

Recurrence rates after operative laparoscopy for endometriosis range from 21.5% at 2 years to 40–50% at 5 years, and may be as high as 72% at 7 years [30–32]. The pathogenesis of recurrent disease remains controversial, with some evidence suggesting that recurrent lesions arise de novo, and other data suggesting the majority represent inadequately treated lesions.
### Table 1. Conventional therapies for endometriosis.

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>How does the mechanism of action affect endometriosis?</th>
<th>How is it used in treatment of endometriosis?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td>Inhibit COX-1 and COX-2 enzymes → lowers prostaglandin levels</td>
<td>Prostaglandin E2 (PGE2) stimulates aromatase and increases estrogen Prostaglandins contribute to inflammation</td>
<td>In combination with hormonal therapies  • Cochrane review shows weak evidence for efficacy  • They are one of the few conventional nonhormonal therapies available</td>
</tr>
<tr>
<td><strong>Combined Oral Contraceptives (COCs)</strong></td>
<td>Estrogen and progestin inhibit GnRH, FSH, and the mid-cycle LH surge</td>
<td>Suppresses ovulation, hypoestrogenic state, decidualization and atrophy of the eutopic and ectopic endometrium</td>
<td>Empiric therapy for: 1. Women with pelvic pain who do not desire immediate fertility 2. Women with confirmed endometriosis and recurrent pain 3. Post-operative secondary prevention  • Rates of dysmenorrhea are improved with continuous compared to cyclic use of COCs.</td>
</tr>
<tr>
<td><strong>Progestins</strong></td>
<td>Interfere with the pulsatile release of GnRH which in turn decreases LH and FSH secretion at the hypothalamus</td>
<td>Anovulation leads to a hypoestrogenic state and decidualization and atrophy of eutopic and ectopic endometrium.</td>
<td>Empiric therapy for: 1. Women with pelvic pain who do not desire immediate fertility 2. Women with confirmed endometriosis and recurrent pain  • Multiple formulations are available: oral, IUS, subcutaneous and intramuscular injection</td>
</tr>
<tr>
<td><strong>GnRH agonists</strong></td>
<td>Bind to GnRH receptors causing an initial gonadotropin flare followed by downregulation. Without pulsatile GnRH, FSH and LH secretion are decreased, which ultimately leads to low estrogen levels and endometrial atrophy.</td>
<td>Low estrogen levels lead to regression of endometriotic lesions.</td>
<td>Reserved for patients with confirmed endometriosis who fail to respond to first-line medications  • These have undesirable side effects include vaginal dryness, hot flushes, headaches, weight gain, acne, decreased bone mineral density</td>
</tr>
<tr>
<td><strong>GNRH antagonists</strong></td>
<td>Same mechanism of action as GnRH agonists, without the gonadotropin flare upon initial administration.</td>
<td>Blocking GnRH secretion ultimately leads to a hypogonadotropic hypogonadal state</td>
<td>Reserved for patients with confirmed endometriosis who fail to respond to first-line medications  • Studies have shown non-inferiority of elagolix as compared to progestins for endometriosis-associated pain.  • The side effect profile is unfavorable as compared to other medical therapies and it is ineffective as a contraceptive, which can lead to unintended pregnancies</td>
</tr>
<tr>
<td><strong>Aromatase inhibitors</strong></td>
<td>Inhibit the action of the enzyme aromatase, which converts testosterone and androstenedione to estradiol and estrone.</td>
<td>Decreases the production of estrogen at the level of endometriotic implants as well as estrogen production in the brain, adipose tissue, and the ovary. Again, a hypoestrogenic state leads to atrophy of endometriosis</td>
<td>Patients with recurrent endometriosis-related pain after surgical or natural menopause  • It is important to rule out malignancy in these post-menopausal and post-hysterectomy patients before initiating aromatase inhibitors.  • When given to pre-menopausal women, aromatase inhibitors lead to high FSH levels and cause superovulation and formation of ovarian cysts.  • This has significant side effects in its oral form</td>
</tr>
<tr>
<td><strong>Danazol</strong></td>
<td>17-ethinyl testosterone derivative that inhibits pituitary secretion of gonadotropin hormone, indirectly causing a hypoestrogenic state AND Directly induces atrophy of the endometrium</td>
<td>Direct (androgen effect) and indirect (hypo-estrogenic effect) atrophy of endometrial tissue</td>
<td>Third-line therapy; rarely used in clinical management of endometriosis due to side effects  • Vaginal and IUS routes of administration minimize side effects</td>
</tr>
</tbody>
</table>
The prevention of recurrent lesions is imperative, as repeat surgery increases the risk of ovarian injury, increases postoperative adhesions, and reduces pregnancy rates in sub-fertile women [31,34–36]. Early trials evaluating short durations of postoperative hormonal suppression (3–6 months) demonstrated little benefit in terms of disease recurrence; however, more recent data suggest that long-term suppression results in significant improvements in postoperative recurrence rates [32].

A 2004 Cochrane Review evaluated the impact of adjuvant hormonal therapy on postoperative recurrence rates and demonstrated improvements in pelvic pain at 12 months post-operatively. However, there was no significant difference in pain recurrence or pregnancy rates at 12 and 24 months [37]. Notably, the duration of postoperative suppression was short, ranging from only 3 to 6 months in the 12 included trials [38]. Longer durations of postoperative therapy have demonstrated a longer duration of symptom suppression. However, symptoms increase with discontinuation of therapy, suggesting continuous postoperative therapy is recommended for secondary prevention of disease [32].

Long-term hormonal therapy with the levonorgestrel intrauterine system (IUS), as well as continuous and cyclic combined oral contraceptives (COCs), all appear to reduce endometriosis recurrence rates when used in the postoperative setting. A 2013 Cochrane meta-analysis including 2 randomized controlled trials of 95 women compared postoperative insertion of a levonorgestrel IUS to no treatment. Results showed a significant decrease in dysmenorrhea at 12 months (RR: 0.22, 95% CI: 0.08, 0.60) and a trend toward improvement in patient satisfaction with IUS placement (RR: 3.00, 95% CI: 0.79, 1.44); however, the latter finding did not reach statistical significance [39]. Additionally, RCT data indicate that a 24-month course of COCs administered in either a cyclic or continuous fashion reduced recurrence of cyclic pelvic pain as compared to no treatment. No significant differences were detected in rates of dyspareunia or chronic pelvic pain [40]. Several studies, including a meta-analysis of 3 RCTs and one prospective cohort trial, support the use of continuous over cyclic COCs to reduce postoperative recurrence of dysmenorrhea [20,40–42]. In the meta-analysis, improvements were seen in rates of dysmenorrhea recurrence with a continuous compared to a cyclic COC regimen; however, there was no difference in dyspareunia, non-cyclic pelvic pain, or reoperation rates [20].

In addition to reducing cyclic pelvic pain, adjuvant hormonal suppression also confers the benefit of preventing endometrioma recurrence. Reducing endometrioma formation is critical given that the presence of an endometrioma itself reduces baseline ovarian reserve, and the surgical treatment of endometriomas may cause further ovarian injury, reducing AMH levels by as much as 30% for a unilateral cystectomy and 53% for a bilateral cystectomy [43,44]. A randomized trial of 239 women showed that a 24-month course of postoperative COCs reduced endometrioma recurrence rates from 29% in untreated patients to 14.7% in cyclic COC users and 8.2% in continuous users [41]. Additionally, in women who did have a recurrence, COC users had smaller endometriomas at the time of initial diagnosis and slower endometrioma growth.

Data specific to the postoperative management of deeply infiltrating endometriosis (DIE) are limited; however, some studies have reported improvements in recurrence rates with postoperative medical treatment [45]. In a prospective cohort study of 500 women who underwent rectal shaving for DIE involving the bowel, the recurrence of pelvic pain occurred in 13% of women treated with continuous COCs or progestins compared to 20% of those who were not treated. The lowest recurrence rate was among women who became pregnant after surgery and immediately began continuous progestins after delivery (2%) [46]. Danazol may also have a role in postoperative suppression for women with DIE, though its utility is limited by side effects; danazol is not frequently prescribed in its oral form. A randomized trial of 60 patients evaluated danazol 200 mg 3 times daily for 6 months after laparoscopy and demonstrated significant improvements in postoperative pain compared to placebo [47]. A second-look laparoscopy at 6 months showed a reduction in the size of recurrent endometriotic implants after danazol treatment. While androgenic side effects are common in oral danazol treatment, including acne and weight gain, recent studies of vaginal or intrauterine danazol have reported substantial improvements in pain associated with DIE with no systemic side effects [48].

The postoperative recurrence of endometriosis is thought to be a result of either de novo and ‘minimal residual’ lesions that were incompletely removed or not identified during the initial surgery or both [31,45]. Because de novo lesions form with continued menstruation, a short interval of hormonal suppression is insufficient to produce significant effects on recurrence rates [45]. Although data from the late 1990s and early 2000s demonstrated no benefit of postoperative hormonal suppression, the short durations of therapy of 3–6 months were insufficient to improve recurrence rates at 1–2 years. RCT data now demonstrate that treatment durations of 18–24 months reduce cyclic pelvic pain as well as endometrioma recurrence. The most recent ESHRE guidelines published in 2013 reflect these data and recommend post-operative use of a levonorgestrel IUS or COCs for the prevention of postoperative recurrence [6]. GnRH agonists and antagonists are generally not recommended for postoperative secondary prevention.

4. Empiric treatment of endometriosis in the patient with postoperative pain recurrence

For recurrent pain after laparoscopy, repeat surgery should be considered only for symptoms refractory to medical management. Repeat surgery has the potential to result in increased adhesion formation, damage to ovarian reserve, and reduced pregnancy rates in infertile women [31,34,49]. COCs and progestins are the mainstay of treatment; however, several studies suggest a role for vaginal or intrauterine danazol. A small prospective Italian study of 21 patients evaluated the efficacy of vaginal danazol for recurrent endometriosis involving the retrovaginal septum [50]. All 21 patients had laparoscopy-confirmed endometriosis involving the uterosacral ligaments.
and rectovaginal septum managed surgically. They presented for recurrent pain and were found to have disease involving the rectovaginal septum based on rectal exam and transvaginal ultrasound. After treatment with 200 mg of vaginal danazol for 12 months, all 21 patients reported absence of non-cyclic pelvic pain and 19 out of 21 patients reported absent dysmenorrhea and dyspareunia; the remaining 2 patients reported only mild dyspareunia and dysmenorrhea. Additionally, the size of the rectovaginal nodules decreased after treatment. The only side effect reported in the study was vaginal irritation that occurred in four participants, and there were no withdrawals from the study. No androgenic side effects were described. Cholesterol and triglycerides were measured after 6 and 12 months of treatment and were found to increase by 10 and 20 points, respectively; however, these changes were not statistically significant. Similarly, another study evaluated a danazol-loaded IUS containing 300–400 mg of danazol in 18 women with recurrent pain at least 6 months after laparoscopy for endometriosis [51]. After 6 months of treatment with the danazol IUS, all patients showed a reduction in pain beginning 1 month after device insertion. Again, no systemic side effects were reported. Vaginally administered danazol is thought to have minimal to no systemic absorption and therefore minimal side effects [48].

Other options for medical management that are usually reserved for postoperative pain recurrence are the GnRH agonists and antagonists. Due to the side effect burden, these therapies are reserved for patients with a histopathologic diagnosis of endometriosis. Per a Cochrane systematic review of multiple randomized control trials, the literature demonstrates GnRH agonists to be superior to placebo and equally as effective as androgen therapy in treating the symptoms of endometriosis without the undesirable side effects of androgen excess [52].

The main GnRH antagonist on the market is elagolix. Two randomized control trials have shown that elagolix decreases both non-menstrual pelvic pain and improve dysmenorrhea as compared to the placebo [53]. However because elagolix suppresses ovulation in a dose-dependent fashion, balancing efficacy versus and side effects presents a challenge [54]. Furthermore, when elagolix was compared to depot medroxyprogesterone acetate, there was no difference in reduction in endometriosis-related pain relief but there were three unintended pregnancies in the elagolix group. Clinicians should proceed with caution when prescribing elagolix.

Due to the substantial menopausal side effects caused by GnRH agonists and antagonists, including vaginal dryness, hot flushes, and decreased bone density, add-back therapy should be used. Add-back therapy may include progesterone alone or estrogen combined with progesterone. A large-randomized trial compared three modes of add-back therapy to leuprolide acetate alone: GnRH agonist plus a progestin (norethindrone acetate 5 mg orally daily); GnRH agonist plus low-dose estrogen and a progestin (conjugated estrogen 0.625 mg and norethindrone acetate 5 mg PO daily); and GnRH agonist plus high-dose estrogen and a progestin (conjugated estrogen 1.25 mg and norethindrone acetate 5 mg PO daily). The authors concluded that all four regimens significantly reduced pelvic pain, but bone density was higher among women who received any of the add-back therapy regimens than those who received a GnRH agonist alone. Additionally, vasomotor symptoms were significantly lower in the add-back therapy groups [55]. Newer studies have shown that add-back therapy with both progestin and estrogen is superior to add-back therapy with progestin alone, especially in preserving bone mineral density and lean body mass [56]. Therefore, it is recommended that women use add-back therapy with both progestin and estrogen while on GnRH agonists or antagonists.

It is not recommended to use GnRH agonists with add-back therapy for longer than 12 months; however, if medical therapy is discontinued, pain is likely to recur. Few studies address the transition off of GnRH agonists; however, some data support a return to oral contraceptives [57].

4.1. Treatment of endometriosis in the infertile patient

Patients with endometriosis who are actively trying to conceive present a unique challenge. Traditional medical therapies are effective in ameliorating endometriosis work by inhibiting ovulation induction and, thereby, eliminating fertility [58]. While NSAIDs may have a role as adjuvant therapy alongside hormonally active drugs [18], when taken independently they show minimal-to-no effect [59].

Multiple RCTs have shown no benefit to medically treating endometriosis with hormonally suppressive therapies in women attempting to conceive spontaneously. The studies vary in the therapy used and duration of use, but all with similar outcomes – the cumulative pregnancy rates are the same at 1 year in the expectant management group as the medically treated [60]. Data does support surgical intervention in the symptomatic patient with infertility. A Cochrane review comparing diagnostic laparoscopy to laparoscopic excision of mild and moderate endometriosis concluded that surgical treatment (excision) reduces overall pain and increases both clinical pregnancy (OR 1.89, 95% CI 1.25 to 2.86, P = 0.003, 3 RCTs, 528 participants) and live birth or ongoing pregnancy rates (OR 1.94, 95% CI 1.20 to 3.16, P = 0.007, 2 RCTs, 382 participants, moderate-quality evidence) [61].

The treatment of infertile women with endometrioma is highly debated and beyond the scope of this discussion. Further information regarding this can be found in recent publications by Llarena et al. and Rehmer et al. [62,63]. In general, in women seeking assisted reproductive technology (ART) with an endometrioma over 4 cm in size, surgical resection may be warranted if associated with pain, difficult oocyte retrieval, or recurrent in vitro fertilization (IVF) failures.

For women undergoing ART, limited data are available regarding the benefits of pharmacotherapy. A meta-analysis of three RCTs that included a total of 165 women demonstrated improved clinical pregnancy rates (OR of 4.28, 95% CI: 2.0–9.15) when a GnRH agonist was given for 2 to 6 months prior to ovarian hyperstimulation for IVF [64]. However, more recent data from an RCT of 120 women concluded there was no difference in number of MII oocytes obtained from patients with mild peritoneal endometriosis who received a GnRH agonist for 3 months postoperatively compared to patients who underwent IVF immediately after surgery [65]. There was no difference in pregnancy rates [64,66]; however, the study was
not powered to evaluate pregnancy rate as an outcome [62, 64]. Overall, the data suggest that there is no difference in pregnancy rate or live birth rate between those pre-treated with a GnRH agonist prior to ovarian stimulation and those who proceed directly to IVF. At this time, more data are needed to support recommending an intervention, be it surgical or suppression with a GnRH agonist prior to IVF. Given this, surgery should arguably be reserved only for those with pain or large endometriomas. One should also consider the longer duration of stimulation and increased amount of medication needed to achieve stimulation for IVF in patients who have undergone down-regulation, which begets increased risk and cost burden to the patient. In addition to GnRH agonists, there is some evidence to support pre-treatment with letrozole or progestins prior to ovarian hyperstimulation for IVF, although many of these studies are small and therefore more evidence is needed [67–69].

Furthermore, it is important to note that medications for ovarian hyperstimulation do not impact disease progression. A 2018 systematic review found that IVF does not increase endometriosis-related pain symptoms or the risk of endometriosis recurrence [70]. There is low-quality evidence that intrauterine insemination could increase the risk of endometriosis recurrence; however the data are very limited [70]. In sum, assisted reproductive technology should not be withheld from endometriosis patients due to concerns about disease recurrence. Assisted reproductive technology, especially IVF, is recommended for infertility treatment in endometriosis patients because this may be the only way that these patients can achieve fertility.

4.2. Treatment of endometriosis in the post-hysterectomy patient

Limited data are available with regard to the management of women who present with recurrent pain after definitive surgical therapy. After hysterectomy with BSO, 90% of women experience long-term relief, and 5-year reoperation rates are low at 8% [71]. Incomplete disease excision may increase the risk of recurrence, particularly in women with extensive disease [72]. In women of less than 40 years of age, conservation of ovaries is recommended, as removal of the ovaries does not significantly improve the surgery-free time [73]. In women over 40, removal of ovaries at the time of hysterectomy improved reoperation rates and can therefore be considered [71], but oophorectomy should be approached with caution, given increased morbidity and mortality in patients who undergo oophorectomy before age 65 [72, 74, 75].

Hormone replacement after hysterectomy with BSO should include both estrogen and progesterone due to concerns that estrogen alone may increase both disease recurrence and the risk of malignant transformation. Endometriosis lesions have been shown to have their own aromatase activity, giving them the ability to produce local estrogen, even after bilateral oophorectomy [71]. While the overall risk appears to be low, case reports are numerous in women with endometriosis treated with unopposed estrogen. Therefore, it is recommended that progestins be added to hormonal replacement therapies in these women to mitigate the risk of developing adenocarcinoma arising from foci of endometriosis [76].

In these patients with suspected disease recurrence, a biopsy is recommended to rule out malignancy. Consideration should also be given to ovarian remnant syndrome, particularly when FSH levels are above 30. Once endometriosis has been confirmed, depending on the size and presenting symptoms, excisional surgery may be warranted. Aromatase inhibitors can also be helpful in these patients [77] (Figure 2).

4.3. Treatment of endometriosis in the postmenopausal patient

Postmenopausal endometriosis is rare [78]. Predisposing factors, associated conditions, and incidence are unknown. As most studies of endometriosis have been performed exclusively on reproductive-aged women, data on the management of endometriosis in the postmenopausal patient are limited. Anecdotal reports suggest a lack of efficacy of GnRH agonists, danazol, and progestins [78].

As endometriosis is an estrogen-dependent disease, postmenopausal endometriosis is maintained through either exogenous (e.g. hormone therapy/HT) or extraovarian sources (adipose, adrenal glands, skin, endometrial stroma) [77, 79]. In the event of postmenopausal endometriosis, surgical excision is recommended for histopathologic confirmation and to rule out malignancy [77] (Figure 2). In postmenopausal patients with post-surgical recurrence or where surgery is contraindicated, aromatase inhibitors (AIs) have been studied as one possible treatment modality [77]. AIs have been extensively studied in postmenopausal breast cancer and premenopausal endometriosis. In an analysis of five case reports, AIs were found to consistently improve pain and bowel/bladder symptoms in postmenopausal patients [77]. However, AIs are also associated with increased vasomotor symptoms, vaginal dryness, and decreased bone mineral density; increased bone mineral density testing and possibly coadministration of bisphosphonates is warranted in this population [77].

While progestins are commonly prescribed as a medical therapy for reproductive-aged women in the treatment of endometriosis, progestin use in menopause – specifically medroxyprogesterone acetate – has been associated with an increased incidence of coronary heart disease and breast cancer [80]. In particular, continuous use (as would be used for endometriosis suppression) of medroxyprogesterone acetate was associated with a higher risk of breast cancer. Given this, natural micronized progesterone is typically recommended in postmenopausal HT for its lack of adverse lipid effects [81]. Of note, for patients with a history of endometriosis who desire HT for vasomotor symptoms, there are no definitive studies linking HT to disease recurrence or malignant transformation, though data are mixed [79].

The use of estrogen receptor agonist/antagonists (also known as selective estrogen receptor modulators), such as bazedoxifene, has been studied in postmenopausal women, but not in the context of postmenopausal endometriosis or patients undergoing HT with a history of endometriosis [79]. To our knowledge, there are likewise no reports of any of the

EXPERT OPINION ON PHARMACOTHERAPY 7
previously mentioned emerging therapies studied in the context of postmenopausal endometriosis.

5. Conclusion

This review intends to simplify the use of pharmacologic strategies for managing endometriosis across the lifespan. While there are numerous drugs available on the market for the treatment of endometriosis-related pain, treatment should be approached in a systematic fashion and tailored to patient treatment goals.

6. Expert opinion

Most currently available pharmacotherapies for endometriosis modulate symptoms by suppressing ovulation or inducing a hypoestrogenic state; none address the underlying pathophysiology of the disease. Although some data demonstrate reductions in the size of endometriomas and colorectal lesions with medical treatment, medical therapies are used primarily for the management of pain and are unable to induce disease regression.

There are no therapies that improve fertility outcomes in women with endometriosis, and nearly all hormonal medications inhibit ovulation. Dydrogesterone, taken twice daily for 21 days during the menstrual cycle, is the only hormonal therapy that is effective at reducing dysmenorrhea symptoms without suppressing ovulation [82,83].

A number of therapies are under study that address immunologic, angiogenic, and hormonal aspects of the disease pathogenesis. These treatments have the potential to better target the mechanisms that underlie the formation of endometriotic lesions to induce disease regression.

Progesterone resistance is a key part of the pathogenesis of endometriosis. Progesterone has an anti-estrogenic effect on the endometrium; however, in endometriosis, stromal cells fail to respond appropriately to progesterone and therefore do not inactivate estrogen. The combination of this failure to inactivate estrogen and this dysregulated aromatase activity results in high levels of estrogen in tissues affected by endometriosis [11]. Selective progesterone receptor modulators

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Figure 2. Management of the patient with suspected endometriosis who has undergone surgical or natural menopause.
vascular endothelial growth factor (VEGF) agents have differential effects on progesterone receptors of different tissues. They can act as pure agonists, pure antagonists, or partial agonist/antagonists depending on progesterone receptor expression in different tissue [58]. The most commonly studied SPRM is mifepristone. A Cochrane review summarizing the evidence for selective progesterone receptor modulators in the treatment of endometriosis concluded that there is moderate evidence that mifepristone is effective in reducing the dysmenorrhea symptoms [84]. There may be a negative side effect of endometrial hyperplasia in patients taking SPRMs that needs to be further investigated.

Anti–vascular endothelial growth factor (VEGF) agents have been studied in animal models as an effective target for endometriosis treatment. In endometriosis, angiogenesis is thought to be altered to promote the survival and proliferation of endometriotic tissue [11]. A meta-analysis of 13 animal studies, including a total of 245 animals, found that VEGF monotherapy had a ‘significant inhibitory effect on endometriosis size (SMD – 0.96, 95% CI – 1.31 to – 0.62), reduction of endometriosis weight (SMD – 1.70, 95% CI – 2.75 to – 0.65), and endometriosis score (SMD – 1.17, 95% CI – 1.65 to – 0.69) when compared to control animals’ [82]. Although the studies included in this meta-analysis were small, the results are encouraging and warrant further study.

In addition to endothelial targets, there is increasing interest in immunological targets for the management of endometriosis. Altered cell-mediated immunity is thought to play a significant role in the pathogenesis of endometriosis. In women with endometriosis, both ectopic and eutopic endometrial cells are more resistant to apoptosis than normal endometrial cells. In the context of the retrograde menstruation theory, this evasion of apoptosis may promote the survival of endometrial cells in the peritoneal cavity and account for the reduced activity of the cellular-mediated immune system in recognizing and clearing ectopic endometrial cells.

Tumor necrosis factor is a major player in the inflammatory milieu of endometriosis. There are many drugs that target tumor necrosis factor alpha including etanercept, infliximab, and imiquimod. Small trials have tested these drugs in animal models of endometriosis with successful results. A rat model comparing etanercept and infliximab found that both successfully decreased endometrial implant size, etanercept more so than infliximab [83]. There are many other small studies looking at newer targets such as janus kinase inhibitors and mTOR inhibitors [85]. The side effects from these drugs seem to be tolerable and they warrant further investigation with clinical trials. Furthermore, with continued improvements in single-cell deep sequencing technology, a knowledge of the individual immune environment may allow for novel targeted treatment options.

Recent literature examines cell-mediated immune factors in the perioperative period of endometriosis treatment; it is hypothesized that in the perioperative period, cell-mediated immunity is impaired by overactivation of the HPA axis [31]. Therefore, any microscopic disease that is left behind after surgery has an ideal environment to proliferate with a down-regulated cellular immunity, and this is suggested to be a possible mechanism for endometriosis pain recurrence after surgery. In one study, a mouse model was developed to compare the size of endometriosis lesions intentionally left behind post-surgically in a control group compared to the group treated with immune modulators (NF-kappaB inhibitors or a beta-blocker) in the perioperative period; in the groups treated with either beta-blockers or NF-kappaB inhibitors, there was a decelerated growth rate compared to control [86]. While the investigation is still in its infancy, cell-mediated immune modulators in the perioperative period offer an exciting avenue for discovery and development in the medical management of endometriosis.

In summary, there is a need for improved therapies for endometriosis that better target the pathogenesis of endometriosis and promote disease regression. These targeted therapies have the potential to function independently or in combination with existing medical therapies.

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References
Papers of special note have been highlighted as either of interest (*) or of considerable interest (+) to readers.


** This reference was cited multiple times throughout the article as it offers a systematic review of multiple RCTs examining the use of oral contraceptives after excision of endometriomas.


** This reference was used extensively as an outline for clinical and pharmacologic management of endometriosis and offers a nice global perspective on the use of pharmacotherapy.


« This Cochrane Review summarizes the data that supports the use of GnRH analogues in treating endometriosis-related pain and was very helpful when writing this section of the review.


« Cochrane review that gives a nice overview of the role of laparoscopy in the management of endometriosis.


« This reference gives excellent data about need for re-operation after initial surgical management of endometriosis.


« Systematic review that highlights pharmacotherapy options specifically in the setting of endometriosis in the postmenopausal woman.


