# A COST-EFFECTIVENESS ANALYSIS OF VAGINAL $CO_2$ LASER THERAPY COMPARED TO STANDARD MEDICAL THERAPIES FOR GENITOURINARY SYNDROME OF MENOPAUSE-ASSOCIATED DYSPAREUNIA

Shannon L. Wallace, MD, Brad ST. Martin, MD, Kyueun Lee, MS, Eric R. Sokol, MD

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(FIRST NAME INITIAL LAST NAME): Shannon L. WALLACE, MD1, Brad ST MARTIN, MD1, Kyueun LEE, MS2, Eric R. SOKOL, MD1

Place of research: Stanford, CA USA

INSTITUTIONS (ALL): 1. Department of Obstetrics and Gynecology, Division of Urogynecology, Stanford University Hospital, Palo Alto, CA, United States, 2. Department of Health Research and Policy, Stanford University, Palo Alto, CA, United States

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Corresponding author:

Shannon Wallace, 300 Pasteur Drive, Grant S285, Palo Alto, CA, 94035 303 880 7809 (phone), 650-498-5346 (fax), shanwall@stanford.edu, shannon.wallace0605@gmail.com,

**CONDENSATION:** Vaginal estrogen cream, oral ospemifene and vaginal $CO_2$ laser therapy are all cost-effective strategies for the treatment of menopausal dyspareunia.

**SHORT TITLE:** COST-EFFECTIVENESS ANALYSIS OF VAGINAL $CO_2$ LASER THERAPY

**AJOG at a Glance:**

A. Why was the study conducted?

We sought to perform a cost-effectiveness analysis of three therapies for dyspareunia associated with genitourinary syndrome of menopause (GSM) including vaginal estrogen, oral ospemifene and vaginal $CO_2$ laser therapy and determine if vaginal laser therapy is a cost-effective treatment for this condition.

B. What are the key findings?

All three treatment methods were found to be cost-effective at a threshold of <$50,000 per QALY for both moderate dyspareunia and severe dyspareunia. Vaginal $CO_2$ laser is the optimal cost-effective strategy with the highest effectiveness (QALYs) below the WTP threshold of $50,000 per QALY.

C. What does this study add to what is already known?

This study suggests that the vaginal fractional $CO_2$ laser is a cost-effective strategy for the treatment of dyspareunia associated with GSM, as are vaginal estrogen and oral ospemifene.

**Key Words:** (alphabetized) cost-effectiveness analysis, dyspareunia, energy-based devices, fractional $CO_2$ vaginal laser, genitourinary syndrome of menopause, ospemifene, vaginal estrogen cream, vaginal laser

**STRUCTURED ABSTRACT:**

**ABSTRACT BODY** (250-500 words):

Background: Topical vaginal estrogen is considered the gold standard therapy for GSM-associated dyspareunia, but early investigations of energy-based devices show promise for patients with contraindications or who are refractory to vaginal estrogen cream. While evaluating safety, efficacy and long-term outcomes for novel technologies is critically important when new technologies become available to treat unmet healthcare needs, evaluation of the costs of these new technologies compared to existing therapies is also critically important, but often understudied.

Objectives: We sought to perform a cost-effectiveness analysis of three therapies for GSM including vaginal estrogen, oral ospemifene and vaginal $CO_2$ laser therapy and determine if vaginal laser therapy is a cost-effective treatment for dyspareunia associated with GSM.

Study Design: An IRB-exempt cost-effectiveness analysis was performed by constructing a decision tree using decision analysis software (TreeAge Pro; TreeAge Software, Inc., Williamstown, MA) using integrated empirical data from the published literature. Tornado plots, one-way and two-way sensitivity analyses were performed to assess how changes in the model's input parameters altered the overall outcome of the cost-effectiveness model.

Results: All three treatment methods were found to be cost-effective below the WTP threshold of $50,000 per QALY for moderate dyspareunia. The ICER for vaginal $CO_2$ laser treatment of moderate dyspareunia was $16,372.01 and the ICER for ospemifene was $5,711.14. Although all three treatment strategies were on the efficient frontier, vaginal $CO_2$ laser treatment was the optimal strategy with the highest effectiveness. In a one-way sensitivity analysis of treatment adherence, the vaginal $CO_2$ laser was no longer cost effective when the adherence fell below

38.8%. Vaginal estrogen cream and ospemifene remained cost-effective strategies at all ranges of adherence. When varying the adherence to 100% for all strategies, oral ospemifene was "dominated" by both vaginal fractional $CO_2$ laser therapy and vaginal estrogen cream. In a two-way sensitivity analysis of vaginal $CO_2$ laser adherence and vaginal $CO_2$ laser cost, vaginal $CO_2$ laser therapy still remained the optimal strategy at 200% of its current cost ($5,554.00) if the adherence was greater than 55%. If the cost fell to 20% of its current cost ($555.40), it was the optimal strategy at all adherence values above 29%.

Conclusion: The present study showed that the vaginal fractional $CO_2$ laser is a cost-effective strategy for the treatment of dyspareunia associated with GSM, as are vaginal estrogen and oral ospemifene. In our model, the vaginal $CO_2$ laser is the optimal cost-effective strategy and consideration should be made to providing insurance coverage for this treatment option.

**MAIN TEXT:**

**Introduction:**

Genitourinary syndrome of menopause (GSM), previously described incompletely as vulvovaginal atrophy (VVA), is a chronic progressive condition associated with postmenopausal estrogen deficiency[1]. GSM is characterized by thinning and atrophy of the poorly unestrogenized vaginal epithelium causing genital dryness, decreased lubrication with sexual activity, discomfort or pain related to sexual activity, irritation of the vulva or vagina, dysuria and urinary frequency and urgency. Unlike menopausal vasomotor symptoms, GSM typically worsens without treatment and can significantly impact a patient's quality of life. Up to 60% of postmenopausal women may be affected by GSM, but many women do not seek treatment due to embarrassment or misconception that these vaginal symptoms are a "normal part of aging.[2,3]"

Due to the chronicity of this condition, a long-term therapy is required for symptom regression[4,5]. Topical vaginal estrogen is currently considered the gold standard therapy for GSM. Administration of exogenous estrogen restores normal vaginal pH levels, thickens and revascularizes the epithelium, and increases vaginal lubrication. The reported one-year efficacy of vaginal estrogen cream for GSM is approximately 80% to 90% based on observational data[6-10]. The recommended regimen for vaginal estrogen cream is vaginal administration daily for two weeks and then twice weekly. Although efficacy for vaginal estrogen cream is high, vaginal estrogen cream has been documented to have low adherence rates between 15-54%[11-16]. This lack of compliance may be attributed to vaginal estrogen cream being inconvenient and difficult to apply, especially in patients with limited dexterity. Although vaginal estrogen cream has few side effects and has not been shown to markedly increase blood estrogen levels, many patients are still concerned about the potential for postmenopausal bleeding and increased endometrial

thickening. Additionally, patients with a history of thromboembolism, endometrial hyperplasia or cancer, breast cancer or estrogen-dependent cancers may not feel comfortable using vaginal estrogens.

Nonhormonal therapies have been developed for these patients including selective estrogen receptor modulators (SERMs) and energy-based devices (EBDs) for vaginal therapy. SERMs, like ospemifene, exert estrogen agonist effects on vaginal epithelium. Ospemifene treatment consists of daily oral therapy and clinical trials have shown that ospemifene is generally well tolerated, has minimal effects on the endometrium, and neutral effects on the breast. Most of the ospemifene safety and efficacy data have been reported in clinical trials, where efficacy ranges from 75-80% after one-year follow-up. In general, adherence to an oral therapy is higher than adherence to a vaginal cream which can be inconvenient and messy. Previously, ospemifene adherence in the general population was difficult to approximate as most adherence data was extracted from randomized clinical trials (RCTs), where it is estimated to be 80-90%[16-23]. Faught et al. recently reviewed the medical and pharmacy claims data for 86,946 patients who were prescribed a dyspareunia-related medication. In this retrospective study, ospemifene adherence was 40% compared with vaginal estrogen cream adherence which was 21%[16].

Energy-based devices have gained momentum as minimally invasive procedures to treat both medical and cosmetic pelvic floor disorders (PFDs) including GSM, vaginal laxity, stress urinary incontinence, dyspareunia and vulvar disorders such as lichen diseases and vestibulitis[24-31]. Vaginal EBDs remodel connective tissue and rebuild stratified squamous epithelium with increased glycogen and fibroblasts[32]. While the FDA has cleared energy-based devices for the treatment of pre-cancerous cervical or vaginal tissue and condylomas, the FDA has not cleared

energy-based devices for the treatment of GSM, urinary incontinence, sexual dysfunction or vaginal rejuvenation[33,34]. However, early investigations of EBDs show good promise for the treatment of these PFDs and many physicians offer vaginal energy-based treatment for patients with contraindications or who are refractory to vaginal estrogen cream. There are multiple devices on the market and the most commonly used device in the United States is the Mona Lisa Touch® vaginal fractional $CO_2$ laser. Standard therapy consists of one laser treatment session every four to six weeks for a total of three sessions annually. After the first year, expert opinion recommends one laser treatment session annually for maintenance therapy. Long-term outcome studies on EBDs for GSM are lacking, but multiple one-year observational studies have shown efficacy approaching that of estrogen therapy. Published adherence rates of close to 100% are from observational and nonrandomized controlled trials[35-43].

In light of a recent FDA safety communication regarding EBDs for "vaginal rejuvenation," prospective RCTs are underway or currently being designed to further evaluate the efficacy and safety of these therapies for GSM[33,34]. Evaluating safety, efficacy and long-term outcomes for novel technologies is critically important when new technologies become available to treat unmet healthcare needs. In the current healthcare climate, evaluation of the costs of new technologies compared to existing therapies is also critically important, but often understudied.

The objective of this study was to perform a cost-effectiveness analysis of three therapies for GSM-associated dyspareunia including vaginal estrogen, oral ospemifene and vaginal $CO_2$ laser therapy and determine if vaginal laser therapy is a cost-effective treatment for this condition.

**Materials and Methods:**

An IRB-exempt cost-effectiveness analysis was performed on three therapies for GSM-associated dyspareunia including vaginal estrogen, oral ospemifene and vaginal $CO_2$ laser therapy. We constructed a decision tree using decision analysis software (TreeAge Pro; TreeAge Software, Inc., Williamstown, MA) using integrated empirical data from the published literature. The input parameters of the model and assumptions are discussed below and listed in Table 1.

*Treatments modeled*

We modeled a population of women with symptomatic GSM with dyspareunia without contraindication for any therapy. Our model time horizon was 1 year, consistent with reported outcomes of vaginal $CO_2$ laser therapy in the literature.

*Model Design and Parameters*

We did not allow crossover from vaginal estrogen cream to ospemifene to vaginal $CO_2$ laser or vice versa in order to focus on a single treatment effect. For example, patients who failed vaginal estrogen cream or SERMs were not allowed vaginal $CO_2$ laser in this model. With efficacy < 100%, there may be individuals using multiple treatment strategies, making it challenging to distinguish differential cost-effectiveness for each specific treatment arm.

Adherence and side effects were modeled for the three treatment options. Vaginal estrogen cream adherence in the general population is variable. To account for this variability, the average vaginal estrogen cream adherence of four large studies was calculated and then weighted by the number of patients in each study[11,12,14,16]. This estimated average adherence for vaginal estrogen cream was 24% which was used as the base case adherence rate. The base case adherence rate for ospemifene was 40% , derived from the retrospective study by Faught et al[16]. In order to more closely model real-world adherence rates for the vaginal $CO_2$ laser, we used adherence rates for other in-office procedures that require multiple visits. In-office procedures

such as intravesical Botox injections and percutaneous tibial nerve stimulation have adherence rates varying from 75-85% in the literature. As most RCTs have shown adherence close to 100% with the vaginal $CO_2$ laser, we used the upper limit of 85% as the base case adherence rate for the vaginal $CO_2$ laser[44-46].

*Data sources*

We derived all probabilities from literature searches in PubMed to find probabilities for each of the relevant outcomes. We used search terms to identify articles specific to all treatment arms, including relevant review articles. Table 1 shows the base case scenario treatment outcome probabilities.

The efficacy of vaginal estrogen was assumed to be 90% for those with twice weekly treatment for 1 year and the efficacy of ospemifene was assumed to be 80% for those with daily treatment for 1 year. The reported efficacy at one year after vaginal $CO_2$ laser therapy is 90%. As symptom resolution of GSM-associated dyspareunia requires persistent use of vaginal estrogen cream or ospemifene, non-adherent patients were assumed to have no efficacy of the treatment. We similarly assumed that patients who were nonadherent to vaginal CO2 laser therapy did not have any efficacy of treatment, as there is limited data on symptom resolution in patients who receive on one or two laser sessions.

Complications or side effects associated with treatment were modeled with noted relative probabilities based upon prior research. For vaginal estrogen, the probability of experiencing a side effect within one year was 42%. The most common side effects included in the model were vaginitis, headache, breast tenderness, endometrial hyperplasia/cancer, and vaginal discharge. For ospemifene, the probability of experiencing a side effect within one year was 29% and the most common side effects included in the model were muscle spasms, hot flashes, vaginitis,

vaginal bleeding and endometrial hyperplasia/cancer. The probability of experiencing a side effect with vaginal laser therapy was 6%, and the side effects included were dysuria, vaginal bleeding, and vaginitis. The relative probabilities of each side effect and the relative health utility scores are listed in Table 1 and Table 2.

*Health State Utility Values*

Health state utility values were obtained from the literature in a similar fashion for treatment efficacy, dyspareunia health states and side effects. Utility scores ranges from 0 to 1, with 0 representing a health state equivalent to death and 1 representing perfect health. We calculated the expected number of QALYs for each strategy by taking a weighted average of the utility of each pathway in the tree and the proportion of the patient cohort who followed that pathway. We then calculated the QALYs over a 1-year period because costs and health benefits were calculated over a 1-year time horizon. Based on published estimates, we estimated the relative health utility score of postmenopausal women with severe dyspareunia (0.5), moderate dyspareunia (0.65), and effective treatment without dyspareunia (0.9).

*Costs*

Drug costs were obtained from the 2017 Medicare database. This is a recognized source of available drug costs in the US. One vaginal estrogen cream tube lasts three months and costs $200. If the patient was adherent to the treatment regimen, a one-year supply of vaginal estrogen cream was equivalent to four tubes for a total of $800. If the patient was not adherent to the vaginal estrogen treatment regimen, then the cost was assumed to be $200 for the initial tube. A three-month supply of ospemifene costs $210. If the patient was adherent to ospemifene treatment, a one-year supply costs $840. If the patient was not adherent to the ospemifene treatment, then the cost was assumed to be $210 for the initial three-month supply. The vaginal

fractional $CO_2$ laser costs were $911 per treatment session which is the out-of-pocket cost at our institution. A one-year treatment regimen of vaginal laser therapy costs $2,733 which is equivalent to three treatment sessions. If the patient was not adherent to the vaginal fractional $CO_2$ laser, then the cost was assumed to be $911. Costs are listed in Table 3. Only patient costs were modeled in this cost-effectiveness analysis. Physician and hospital costs including physicians' and nurses' time and equipment, as well as indirect costs like transportation and productivity losses were not modeled. Side effects did not accrue additional costs.

*Cost-effectiveness analysis (CEA)*

Cost-effectiveness was determined using the incremental cost-effectiveness ratio (ICER). ICERs were calculated by first ranking strategies by increasing cost and then calculating ΔCost/Δ Effectiveness for adjacent strategies. The willingness-to-pay (WTP) threshold was set a priori at $50,000 per QALY. Strategies were considered "dominated" if they were both less effective and more expensive than another strategy. No ICER was reported for dominated strategies as they are not cost-effective.

*Sensitivity analysis*

The sensitivity analyses determined whether changes in the model's input parameters altered the overall outcome of the cost-effectiveness model. We conducted Tornado plots and multiple one-way and two-way sensitivity analyses. Probability values were varied across the ranges listed in Table 1and Table 2 to determine if a threshold existed where the preferred strategy would change. Costs were varied from 20 to 200% of the base case value.

**Results:**

*Cost-effectiveness analysis:*

All three treatment methods were found to be cost-effective at a WTP threshold of <$50,000 per QALY for moderate dyspareunia in the base case scenario. The ICER for vaginal $CO_2$ laser treatment of moderate dyspareunia was $16,372.01 and the ICER for ospemifene was $5,711.14. Although all three treatment strategies were on the efficient frontier, vaginal $CO_2$ laser treatment was the optimal strategy with the highest effectiveness (Table 4).

*One-way sensitivity analysis:*

Tornado plots and univariate sensitivity analyses were performed on all variables. The variables that most influenced the results were the adherence rates of vaginal estrogen cream, adherence rates of the vaginal $CO_2$ laser and the treated dyspareunia health utility scores (Figure 1).

A. Dyspareunia health utility score

In a one-way sensitivity analysis, all strategies were cost-effective when the health utility value of untreated dyspareunia was varied between 0.2 and 0.8. When using 0.5 as the health utility score of severe dyspareunia, all three strategies were cost effective with the vaginal $CO_2$ laser as the optimal treatment strategy (Table 4). All strategies were cost-effective when the health utility score of treated dyspareunia was above 0.75, but when the score fell below 0.65, ospemifene and the vaginal $CO_2$ laser were no longer cost-effective.

B. Adherence

In a one-way sensitivity analysis of treatment adherence, the vaginal $CO_2$ laser was no longer cost effective when the adherence fell below 38.8%. Vaginal estrogen cream and ospemifene remained cost-effective strategies at all ranges of adherence. The vaginal $CO_2$ laser was no longer a cost-effective strategy when adherence of vaginal estrogen cream increased to 90% and when the adherence of ospemifene increased to 100%.

C. Cost

All three treatment methods were cost effective when varying the annual cost from 20% to 200% of the base case cost of all three strategies.

D. Complications

When the probability of complications for each of the three strategies was varied from 0% to 100%, both vaginal estrogen cream and the vaginal $CO_2$ laser remained cost effective. When the probability of complications after vaginal $CO_2$ laser treatment exceeded 98%, then ospemifene became the optimal strategy. Ospemifene became a "dominated" strategy when the probability of complications with ospemifene treatment exceeded 85%.

*Two-way sensitivity analysis:*

A. Adherence of Different Treatment Strategies

When adherence was assumed to be 100% for all treatment strategies, then oral ospemifene was "dominated" by both vaginal $CO_2$ laser therapy and vaginal estrogen cream. Vaginal $CO_2$ laser remained the optimal strategy with the highest effectiveness and an ICER of $39,508.3 (Table 5). In a two-way sensitivity analysis of vaginal estrogen cream adherence and vaginal $CO_2$ laser adherence, ospemifene was the optimal treatment strategy if vaginal estrogen cream adherence was less than 36% and vaginal $CO_2$ laser adherence was less than 38%. Otherwise the relationship between vaginal estrogen cream adherence and vaginal $CO_2$ laser adherence was linear such that vaginal estrogen cream was the optimal strategy if adherence was 3-5% more than the vaginal $CO_2$ laser (Figure 2).

B. Adherence and Cost

In a two-way sensitivity analysis of vaginal $CO_2$ laser adherence and vaginal $CO_2$ laser cost, vaginal $CO_2$ laser therapy still remained the optimal strategy at 200% of its current cost

($5,554.00) if the adherence was greater than 55%. If the cost fell to 20% of its current cost ($555.40), it was the optimal strategy at all adherence values above 29% (Figure 3). In a two-way sensitivity analysis, even at 20% of its current cost ($160.00), vaginal estrogen cream only became the preferred strategy when vaginal estrogen cream adherence exceeded 83% (Figure 3). Similarly, in a two-way sensitivity analysis, ospemifene became the optimal strategy when ospemifene adherence exceeded 91% at 20% of its current cost ($168.00) (Figure 4).

**Discussion/Comment:**

1. **Principal Findings:**

The present study showed that the vaginal fractional $CO_2$ laser is a cost-effective strategy for the treatment of dyspareunia associated with GSM, as are vaginal estrogen and oral ospemifene.

2. **Results:**

Our model demonstrated that although all three strategies were cost-effective, the vaginal $CO_2$ laser was the optimal strategy with the highest effectiveness. We were surprised by this finding given the higher up-front costs of vaginal laser therapy. Currently, vaginal fractional $CO_2$ laser therapy for non-FDA approved indications is not covered by any private or government insurance and patients pay out-of-pocket for treatment. The results of our research could support coverage of vaginal laser therapy, as many insurance companies and Medicaid/Medicare provide coverage for vaginal estrogen cream and ospemifene. Our research suggests that the vaginal $CO_2$ laser is actually the preferred cost-effective strategy and consideration should be made to providing insurance coverage for this treatment option once the FDA has approved the use of the vaginal laser for the treatment of GSM-associated dyspareunia.

3. **Clinical Findings:**

At all ranges of adherence, both vaginal estrogen cream and ospemifene were cost-effective strategies. However, the vaginal $CO_2$ laser was always the optimal cost-effective strategy until adherence fell below 38.8%. Although adherence did not considerably affect cost-effectiveness in our model, vaginal estrogen cream and ospemifene were not optimal strategies at lower ranges of adherence. Our base case scenario models real-world situations where adherence rates of vaginal estrogen cream have been historically low in the general population. Weissman-Brenner at el retrospectively reviewed 1,782 Israeli patients who were using continuous monotherapy with estrogen-containing vaginal creams or gels. They found that after 6 months of treatment, only 54% of patients had asked for another prescription[12]. Similarly, in a recent study on 23,761 postmenopausal women who were using vaginal estrogen cream, Portman et al demonstrated that during 12 months of follow-up more than 86.2% to 89.4% of estrogen cream users had discontinued treatment after the first prescription[11].

Current observational cohort studies and randomized controlled trials of vaginal laser therapy have high compliance rates. While patient's out-of-pocket payment may confound this data, other in-office procedures such as intravesical Botox injections and percutaneous tibial nerve stimulation also have high adherence rates (75%-85%)[44-46]. If vaginal $CO_2$ laser therapy is as cost-effective for the patient as other treatment options, then a strategy with higher compliance rates may overcome suboptimal treatment of GSM due to low adherence.

Long-term efficacy, safety and complications of vaginal laser therapy for the treatment of GSM is limited. However, one-year and two-year studies seem to highlight the mild and transient nature of most side-effects of vaginal laser therapy[38-40]. Gasper et al published an 18-month prospective study comparing patients who received vaginal laser therapy with vaginal estrogen cream to those patients who received vaginal estrogen cream alone[55]. In the vaginal laser group,

4% of patients experienced side effects including mild-to-moderate pain, transient edema and vaginal spotting. This was less than the side effects of the vaginal estrogen group, 8% of whom experienced vaginal spotting, 4% mastodynia and 12% abdominal pain.

Although vaginal estrogen cream and ospemifene have a higher risk of side-effects in the literature, most of these are short-term and quickly treated. In our model, the health utility scores related to side-effects of the three treatment options were small. Sensitivity analyses show that they had minimal effect on the overall cost-effectiveness of the treatment strategies.

**4. Research Implications:**

At our institution, we try to systematically evaluate efficacy, safety, mechanisms of action, complications and cost-effectiveness of novel technologies to provide a complete picture. Recent controversies surrounding medical devices in the women's health space highlight the critical role of such a model before wide-spread adoption of these technologies. Our analysis should encourage hospital systems, private insurance companies and government insurers to consider coverage of vaginal laser treatments for patients if they are shown to be safe and effective, as required by FDA.

**5. Strength and Limitations:**

The major strength of this study was our use of published national data and data from randomized controlled trials where outcomes measures are collected with careful regular follow-up. Our results are also generalizable given that the vast majority of probabilities, costs, and utilities came from nationally representative studies and publicly available cost data from Medicare. Furthermore, our sensitivity analyses varied parameters including adherence across reasonable ranges of values to investigate factors that could affect the cost-effectiveness of our model.

As with any model, we are limited by the availability of data and the accuracy of our assumptions. This is further limited in the case of more novel therapies with less long-term data, such as ospemifene and vaginal $CO_2$ laser therapy. We chose to model the reported complications from recent randomized controlled trials of vaginal laser therapy. Anecdotal reports and some case series suggest that there may be additional rare complications of the vaginal laser such as post-treatment burning and scarring.[56] With more long-term outcome data on the horizon from randomized-controlled trials and prospective studies, the vaginal laser therapy complication profile may have to be updated.

As more efficacy data was available for vaginal laser treatment as mono-therapy for GSM, we chose not to allow concurrent treatment or crossover between treatment arms. In practice, many providers may use a multimodal treatment strategy for GSM with vaginal laser therapy in addition to estrogen or SERM therapy. More complex CEA models may model real-world situations more accurately, but models should also be simple enough to be reproducible and transparent. Inherent to the nature of modeling, this balance can be complicated when designing a model to garner meaningful results. Once more data is available on the outcomes of vaginal laser therapy plus estrogen or SERM treatment, an additional CEA of multimodal therapy may be warranted.

Our results should only be used as a guide in the context of existing clinical guidelines. Clinical decision-making for individual patients should also account for other factors, such as medical history, comorbidities, and patient preference. Future research on treatment efficacy, probabilities and costs will help decrease the uncertainty in the model input parameters and improve the precision of the finding. A unique limitation is that $CO_2$ laser therapy is the only non-covered treatment modality included in this study, so the costs may be artificially elevated

compared to vaginal estrogen and ospemifene, which are covered by Medicare. As costs of treatment evolve over time and more long-term data become available, this research may need to be replicated to account for these changes.

## 6. Conclusions:

In conclusion, we found that vaginal fractional $CO_2$ laser therapy is a cost-effective strategy for the treatment of menopausal dyspareunia, as are vaginal estrogen cream and oral ospemifene. Our research suggests that the vaginal $CO_2$ laser is actually the preferred cost-effective strategy and consideration should be made to providing insurance coverage for this treatment option if it is proven to be safe and effective in FDA trials.

References:


1. Shifren JL. Genitourinary Syndrome of Menopause. Clin Obstet Gynecol. 2018; 61(3):508-16.
2. Portman DJ, Gass MLS. Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause. 2014; 21(10):1063–8.
3. Parish SJ, Nappi RE, Krychman ML, et al. Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. Int J Womens Health. 2013; 5:437-47.
4. Gandhi J, Chen A, Dagur G, et al. Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. Am J Obstet Gynecol. 2016; 215(6):704-11.
5. North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause. 2013; 20(9):888-902.
6. Rioux JE, Devlin MC, Gelfand MM, et al. 17β-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. Menopause. 2018; 25(11):1208-13.
7. Biehl C, Plotsker O, Mirkin S. A systematic review of the efficacy and safety of vaginal estrogen products for the treatment of genitourinary syndrome of menopause. Menopause. 2019; 26(4):431-53.

8. Bachmann G, Bouchard C, Hoppe D, et al. Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. Menopause. 2009; 16(4):719-27.
9. Santen RJ. Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. Climacteric. 2015; 18(2):121-34.
10. Rahn D, Carberry C, Sanses T et al. Society of Gynecologic Surgeons Systematic Review Group. Vaginal Estrogen for Genitourinary Syndrome of Menopause A Systematic Review. Obstet Gynecol. 2014; 124(6): 1147-56.
11. Portman D, Shulman L, Yeaw J, et al. One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy. Menopause. 2015; 22(11):1197-203.
12. Weissmann-Brenner A, Bayevsky T, Yoles I. Compliance to vaginal treatment—tablets versus cream: a retrospective 9 years study. 2016; 24(1):73-6.
13. Minkin MJ, Maamari R, Reiter S. Improved compliance and patient satisfaction with estradiol vaginal tablets in postmenopausal women previously treated with another local estrogen therapy. Int J Womens Health. 2013; 5:133-9.
14. Shulman LP, Portman DJ, Lee WC, et al. A retrospective managed care claims data analysis of medication adherence to vaginal estrogen therapy: implications for clinical practice. J Womens Health (Larchmt). 2008; 17(4):569-78.
15. Krause M, Wheeler TL, Snyder TE, Richter HE. Local Effects of Vaginally Administered Estrogen Therapy: A Review. J Pelvic Med Surg. 2009; 15(3): 105-14.
16. Faught BM, Soulban G, Yeaw J. Ospemifene versus local estrogen: adherence and costs in postmenopausal dyspareunia. J Comp Eff Res. 2019; 8(13):1111-23.

17. Goldstein SR, Bachmann GA, Koninckx PR, et al. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. Climacteric. 2014; 17:173-82.

18. Constantine G, Graham S, Portman DJ, et al. Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. Climacteric. 2015; 18(2):226-32.

19. Bachmann GA, Komi JO. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause. 2010;17(3):480-6.

20. Portman D, Palacios S, Nappi RE, Mueck AO. Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: a randomized, placebo-controlled, phase III trial. Maturitas, 2014; 78(2): 91-8.

21. Wurtz GT, Kao CJ, DeGregorio MW. Safety and efficacy of ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy due to menopause. Clin Interv Aging. 2014; 9:1939-50.

22. Nappi RE, Panay N, Bruyniks N, et al. The clinical relevance of the effect of ospemifene on symptoms of vulvar and vaginal atrophy. Climacteric. 2015; 18(2):233-40.

23. Cui Y, Zong H, Yan H, et al. The Efficacy and Safety of Ospemifene in Treating Dyspareunia Associated with Postmenopausal Vulvar and Vaginal Atrophy: A Systematic Review and Meta□Analysis. J Sex Med. 2014; 11(2):487-97.

24. Gaspar A, Addamo G, Brandi H. Vaginal fractional $CO_2$ laser: A minimally invasive option for vaginal rejuvenation. Am J Cosmetic Surg. 2011*;* 28*(*3*):*156–62.

480 25. Tadir Y, Gaspar A, Lev-Sagie A, et al. Light and energy based therapeutics for
481 genitourinary syndrome of menopause: consensus and controversies. Lasers Surg Med.
482 2017; 49:137-59.
483 26. Sipos AG, Kozma B, Poka R, et al. The Effect of Fractional $CO_2$ laser Treatment on the
484 Symptoms of Pelvic Floor Dysfunctions: Pelvic Floor Distress Inventory-20
485 Questionnaire. Lasers Surg Med. 2019; 1-5.
486 27. Pergialiotis V, Prodromidou A, Perrea DN, et al. A systematic review on vaginal laser
487 therapy for treating stress urinary incontinence: do we have enough evidence? Int
488 Urogynecol J. 2017; 28(10):1445-51.
489 28. Krychman M, Rowan CG, Allan BB, et al. Effect of single-treatment, surface-cooled
490 radiofrequency therapy on vaginal laxity and female sexual function: The VIVEVE I
491 randomized controlled trial. J Sex Med. 2017; 14:215-25.
492 29. Salvatore S, Nappi RE, Parma M, et al. Sexual function after fractional microablative
493 $CO_2$ laser in women with vulvovaginal atrophy. Climacteric. 2015; 18:219-25.
494 30. Faubion SS, Larkin LC, Stuenkel CA, et al. Management of genitourinary syndrome of
495 menopause in women with or at high risk for breast cancer: consensus recommendations
496 from The North American Menopause Society and The International Society for the
497 Study of Women's Sexual Health. Menopause. 2018; 25(6):596–608.
498 31. Shobeiri SA, Kerkhof MH, Minassian VA, et al. IUGA Research and Development
499 Committee. IUGA committee opinion: laser-based vaginal devices for treatment of stress
500 urinary incontinence, genitourinary syndrome of menopause, and vaginal laxity. Int
501 Urogynecol J. 2019; 30(3):371-6.

32. Lang P, Karram M. Lasers for pelvic floor dysfunctions: is there evidence? Curr Opin Obstet Gynecol. 2017; 29(5):354-8

33. Statement from FDA Commissioner Scott Gottlieb, M.D., on efforts to safeguard women's health from deceptive health claims and significant risks related to devices marketed for use in medical procedures for "vaginal rejuvenation." https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-efforts-safeguard-womens-health-deceptive-health-claims

34. FDA Warns Against Use of Energy-Based Devices to Perform Vaginal "Rejuvenation" or Vaginal Cosmetic Procedures: FDA Safety Communication. https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-energy-based-devices-perform-vaginal-rejuvenation-or-vaginal-cosmetic

35. Pitsouni E, Grigoriadis T, Falagas ME, et al. Laser therapy for the genitourinary syndrome of menopause. A systematic review and meta-analysis. Maturitas. 2017; 103:78-88.

36. Siliquini GP, Tuninetti V, Bounous VE, et al. Fractional $CO_2$ laser therapy: a new challenge for vulvovaginal atrophy in postmenopausal women. Climacteric. 2017; 20(4):379–84.

37. Salvatore S, Nappi RE, Zerbinati N, et al. A 12-week treatment with fractional $CO_2$ laser for vulvovaginal atrophy: a pilot study. Climacteric. 2014; 17:363-9.

38. Salvatore S, Leone Roberti Maggiore U, Origoni M, et al. Microablative fractional $CO_2$ laser improves dyspareunia related to vulvovaginal atrophy: a pilot study. J Endometr. 2014; 6:150-6.

524 39. Sokol ER, Karram MM. Use of a novel fractional $CO_2$ laser for the treatment of
525 genitourinary syndrome of menopause: 1-year outcomes. Menopause. 2017; 24(7):810-4.
526 40. Sokol ER, Karram MM. An assessment of the safety and efficacy of a fractional $CO_2$
527 laser system for the treatment of vulvovaginal atrophy. Menopause. 2016; 23(10):1102-7.
528 41. Samuels JB, Garcia MA. Treatment to External Labia and Vaginal Canal with $CO_2$ Laser
529 for Symptoms of Vulvovaginal Atrophy in Postmenopausal Women. Aesthet Surg J.
530 2019; 39(1):83-93.
531 42. Cruz VL, Steiner ML, Pompei LM, et al. Randomized, double-blind, placebo-controlled
532 clinical trial for evaluating the efficacy of fractional $CO_2$ laser compared with topical
533 estriol in the treatment of vaginal atrophy in postmenopausal women. Menopause. 2018;
534 25(1):21-8.
535 43. Paraiso MFR, Ferrando CA, Sokol ER, et al. A randomized clinical trial comparing
536 vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome
537 of menopause: The VeLVET Trial. Menopause. 2019; 27. PMID: 31574047.
538 44. Sirls ER, Killinger KA, Boura J, Peters KM. Percutaneous Tibial Nerve Stimulation in
539 the Office Setting: Real-world Experience of Over 100 Patients. Urology. 2018; 113:34-
540 9.
541 45. Te Dorsthorst MJ, Heesakkers JPFA, van Balken MR. Long-term real-life adherence of
542 percutaneous tibial nerve stimulation in over 400 patients. Neurourol Urodyn. 2019; 1-5.
543 46. Nitti VW. Ginsberg D, Sievert KD, et al. Durable Efficacy and Safety of Long-Term
544 OnabotulinumtoxinA Treatment in Patients with Overactive Bladder Syndrome: Final
545 Results of a 3.5-Year Study. J Urol. 2016; 196(3):791-800.

546 47. DiBonaventura M, Luo X, Moffatt M, et al. The Association Between Vulvovaginal
547 Atrophy Symptoms and Quality of Life Among Postmenopausal Women in the United
548 States and Western Europe. J Womens Health (Larchmt). 2015; 24(9):713-22.
549 48. Craig BM, Mitchell SA. Examining the Value of Menopausal Symptom Relief among US
550 Women. Value in Health. 2016; 19(2):158-66.
551 49. Mittmann N, Trakas K, Risebrough N, Liu BA. Utility Scores for Chronic Conditions in a
552 Community-Dwelling Population. Pharmaceconomics. 1999; 15(4):396-76.
553 50. Hux M, Ng C, Ortega GL, et al. Utility values for pre-menopausal women suffering from
554 symptomatic uterine fibroids. Expert Rev. Pharmacoecon. Outcomes Res. 2015;
555 15(1):181-9.
556 51. Jewell EL, Smrtka M, Broadwater G, et al. Utility Scores and Treatment Preferences for
557 Clinical Early-Stage Cervical Cancer. Value in Health. 2011; 14(4):582-6.
558 52. Bermingham SL, Ashe JF. Systematic review of the impact of urinary tract infections on
559 health-related quality of life. BJUI. 2012; 110; 830-6.
560 53. WebMD. Prescription Drug Prices. [cited 2019 12/9/19]; Available from:
561 http://www.webmd.com/rx
562 54. Medicare Prescription Drug Coverage. [cited 2019 12/9/19]; Available from:
563 https://www.medicare.gov/drug-coverage-part-d
564 55. Gaspar A, Brandi H, Gomez V, et al. Efficacy of Erbium:YAG laser treatment compared
565 to topical estriol treatment for symptoms of genitourinary syndrome of menopause.
566 Lasers Surg Med. 2017; 49(2):160-8.

56. Gordon C, Gonzales S, Krychman ML. Rethinking the techno vagina: a case series of patient complications following vaginal laser treatment for atrophy. Menopause. 2019; 26(4):423-7.

591 Tables:

592 Table 1: Model Outcome Percentage

| Model Outcome Percentages | | | |
|---|---|---|---|
| **Variable** | **Probability** | **Source** | **Range** |
| One year adherence to vaginal estrogen cream | 28.0% | [11, 12] | 0%-100% |
| Symptom improvement with 1 year vaginal estrogen cream | 90.0% | [7, 8] | |
| Complications with 1 year vaginal estrogen cream | 42.0% | [7, 8, 9, 15] | 0%-100% |
| *If complications: | | | |
| Vaginitis with 1 year vaginal estrogen cream | 14.5% | [7, 8, 9, 15] | |
| Headache with 1 year vaginal estrogen cream | 34.3% | [7, 8, 9, 15] | |
| Breast tenderness with 1 year vaginal estrogen cream | 3.6% | [7, 8, 9, 15] | |
| Vaginal bleeding with 1 year vaginal estrogen cream | 21.0% | [7, 8, 9, 15] | |
| Endometrial hyperplasia/cancer with 1 year vaginal estrogen cream | 2.9% | [7, 8, 9, 15] | |
| Vaginal discharge with 1 year vaginal estrogen cream | 23.8% | [7, 8, 9, 15] | |
| One year adherence to ospemifene | 88.0% | [15, 16, 17] | 0%-100% |
| Symptom improvement with 1 year ospemifene | 70.0% | [16, 17, 20] | |
| Complications with 1 year ospemifene | 29.0% | [20, 21, 22] | 0%-100% |
| *If complications: | | | |
| Hot flashes with 1 year ospemifene | 24.3% | [20, 21, 22] | |
| Vaginitis with 1 year ospemifene | 26.7% | [20, 21, 22] | |
| Muscle spasms with 1 year ospemifene | 28.0% | [20, 21, 22] | |
| Vaginal bleeding with 1 year ospemifene | 19.0% | [20, 21, 22] | |
| Endometrial hyperplasia/cancer with with 1 year ospemifene | 2.1% | [20, 21, 22] | |
| One year adherence to $CO_2$ vaginal laser | 88.0% | [44, 45, 46, 55] | 0%-100% |
| Symptom improvement with $CO_2$ vaginal laser | 90.0% | [39, 40, 43] | |
| Complications after $CO_2$ vaginal laser | 6.6% | [39, 40, 43] | 0%-100% |
| *If complications: | | | |
| Vaginitis after $CO_2$ vaginal laser | 14.5% | [39, 40, 43] | |
| Dysuria after $CO_2$ vaginal laser | 45.5% | [39, 40, 43] | |
| Vaginal bleeding after $CO_2$ vaginal laser | 21.0% | [39, 40, 43] | |

* Indicates conditional probabilities

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600 Table 2: Model Utility Values

| Model Utility Values | | | |
|---|---|---|---|
| **Variable** | **Utility value** | **Source** | **Range** |
| Dyspareunia | 0.65 | [47, 48] | 0.2 -0.85 |
| Improved dyspareunia after treatment | 0.90 | [47, 48] | 0.65-0.95 |
| Headache | 0.79 | [49] | 0.3-0.95 |
| Breast tenderness | 0.83 | [48] | 0.4-0.98 |
| Postmenopausal vaginal bleeding | 0.83 | [50] | 0.4-0.98 |
| Endometrial hyperplasia/cancer | 0.76 | [51] | 0.3-0.95 |
| Vaginal discharge | 0.96 | [48] | 0.5-1.0 |
| Vaginitis | 0.96 | [48] | 0.5-1.0 |
| Dysuria | 0.90 | [52] | 0.45-1.0 |
| Hot flashes | 0.85 | [48] | 0.4-0.98 |
| Muscle spasms | 0.71 | [48] | 0.3-0.95 |

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602 Table 3: Model Cost Estimates

| Model Cost Estimates | | | |
|---|---|---|---|
| **Variable** | **Cost** | **Source** | **Range** |
| 3 months of vaginal estrogen cream | $200.00 | [53, 54] | $40-$400 |
| 1 year of vaginal estrogen cream | $800.00 | [53, 54] | $160-$1600 |
| 3 months of ospemifene | $210.00 | [53, 54] | $42-$420 |
| 1 year ospemifene | $840.00 | [53, 54] | $168-$1680 |
| 1 session of $CO_2$ vaginal laser treatement | $911.00 | [53, 54] | $182.20-$1822 |
| 3 sessions of $CO_2$ vaginal laser treatment | $2,733.00 | [53, 54] | $546.60-$5466 |

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612 Table 4: Base case one-year cost, effectiveness, and incremental cost-effectiveness ratio for
613 GSM-associated dyspareunia treatment options ranks by cost

| Model | Strategy | Cost (2017 Medicare $US) | Incremental cost | Effectiveness (QALY) | Incremental effectiveness (QALY) | ICER (2017 US$/QALY) |
|---|---|---|---|---|---|---|
| Base case adherence | | | | | | |
| Moderate Dyspareunia | Vaginal estrogen | $344.00 | - | 0.69 | - | - |
| | Ospemifene | $462.00 | $118.00 | 0.71 | 0.02 | $5,711.14 |
| | $CO_2$ vaginal laser | $2,497.10 | $2,035.10 | 0.84 | 0.12 | $16,372.01 |
| Base case adherence | | | | | | |
| Severe Dyspareunia | Vaginal estrogen | $344.00 | - | 0.57 | - | - |
| | Ospemifene | $462.00 | $118.00 | 0.61 | 0.02 | $3,254.15 |
| | $CO_2$ vaginal laser | $2,497.10 | $2,035.10 | 0.80 | 0.19 | $10,651.98 |

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615 Table 5: One-year cost, effectiveness, and incremental cost-effectiveness ratio for GSM-
616 associated dyspareunia treatment options ranks by cost assuming 100% adherence for all
617 strategies

| Model | Strategy | Cost (2017 Medicare $US) | Incremental cost | Effectiveness (QALY) | Incremental effectiveness (QALY) | ICER (2017 US$/QALY) |
|---|---|---|---|---|---|---|
| 100% adherence | | | | | | |
| Moderate Dyspareunia | Vaginal estrogen | $800.00 | - | 0.82 | - | - |
| | $CO_2$ vaginal laser | $2,777.00 | $1,977.00 | 0.87 | 0.05 | $39,508.31 |
| | Ospemifene | $840.00 | $40.00 | 0.8 | -0.02 | Dominated |
| 100% adherence | | | | | | |
| Severe Dyspareunia | Vaginal estrogen | $800.00 | - | 0.80 | - | - |
| | $CO_2$ vaginal laser | $2,777.00 | $1,977.00 | 0.85 | 0.05 | $39,508.31 |
| | Ospemifene | $840.00 | $40.00 | 77 | -0.03 | Dominated |

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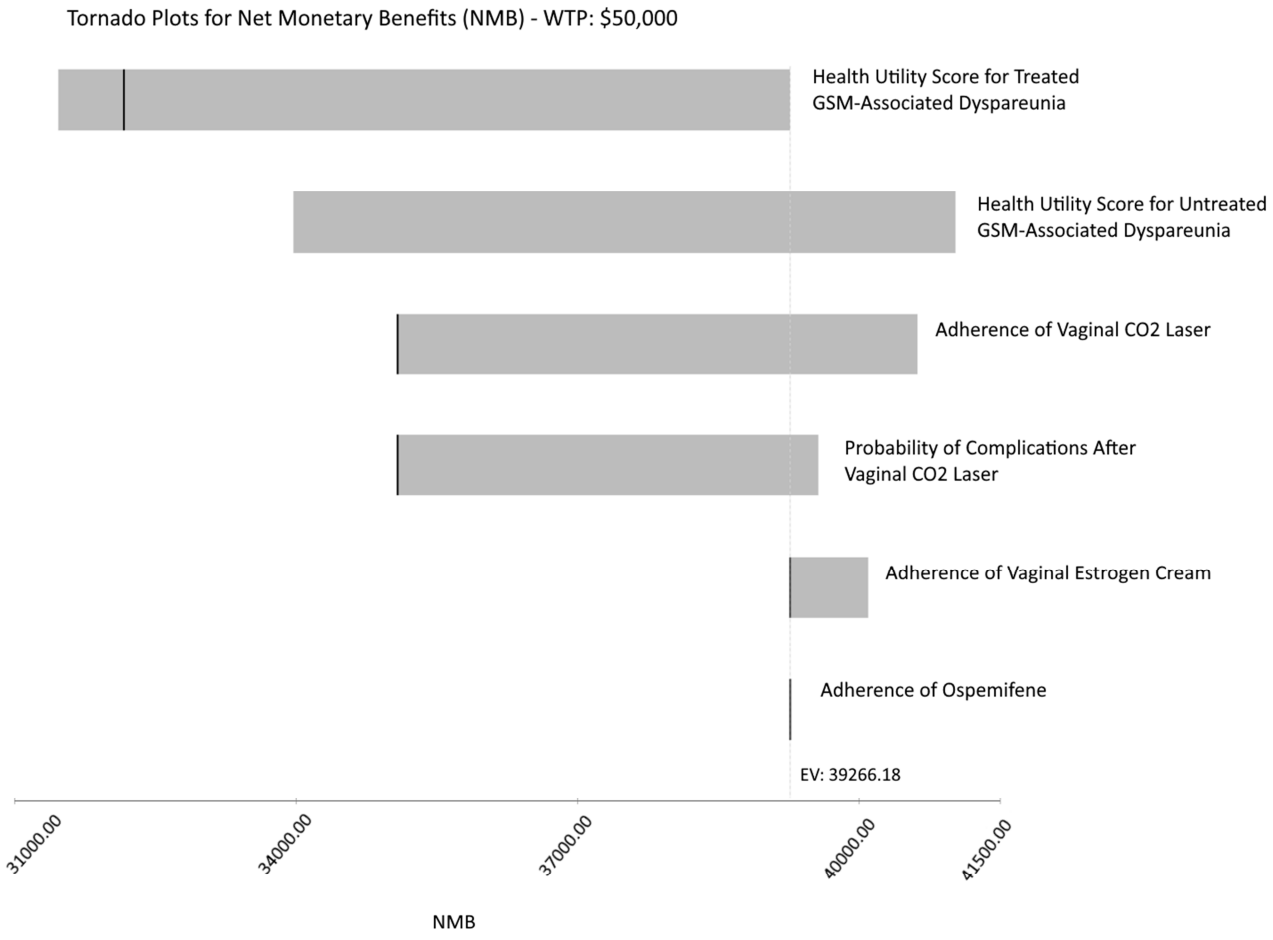
624 Figure 1: Tornado Plots

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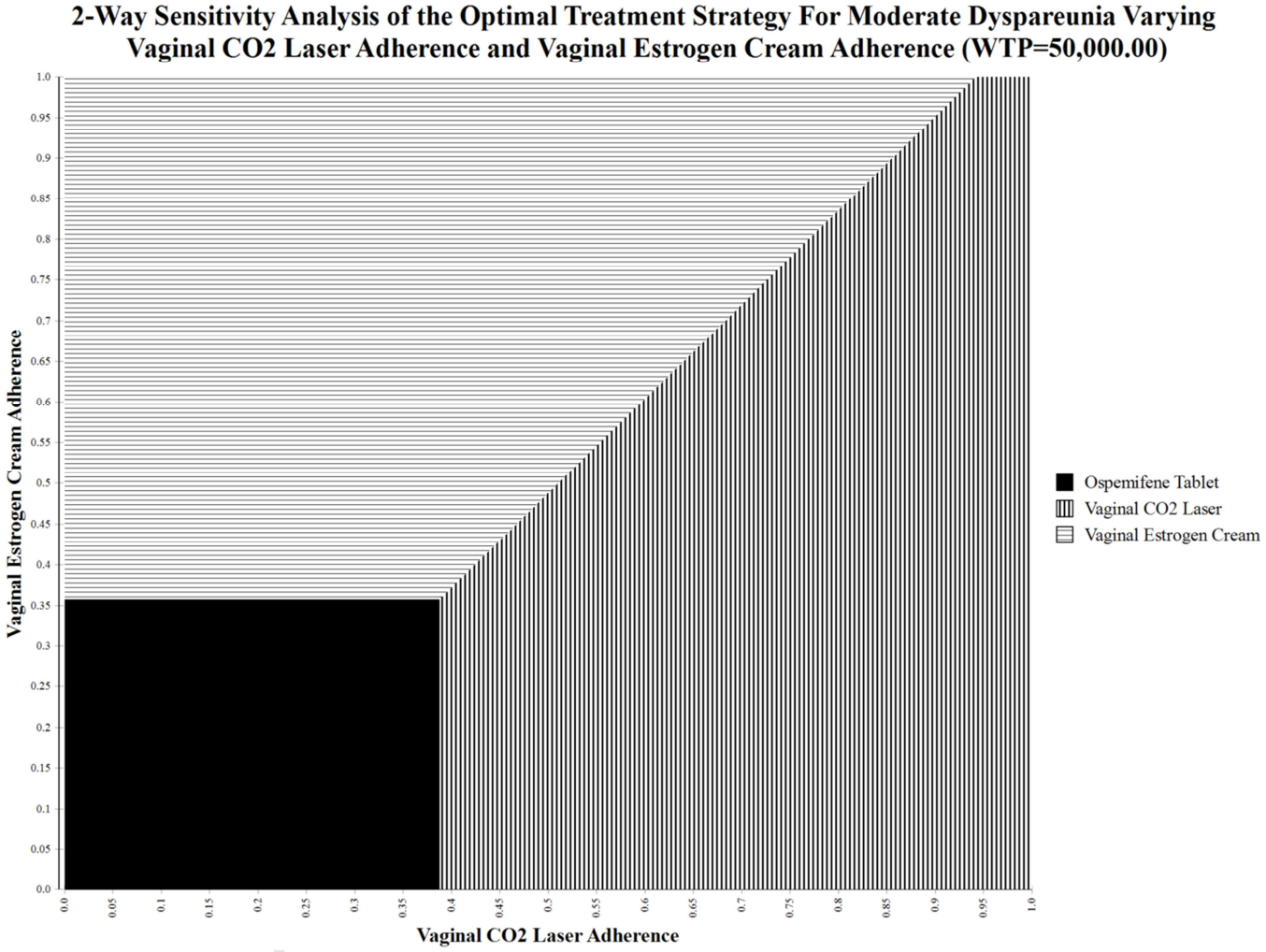
634 Figure 2

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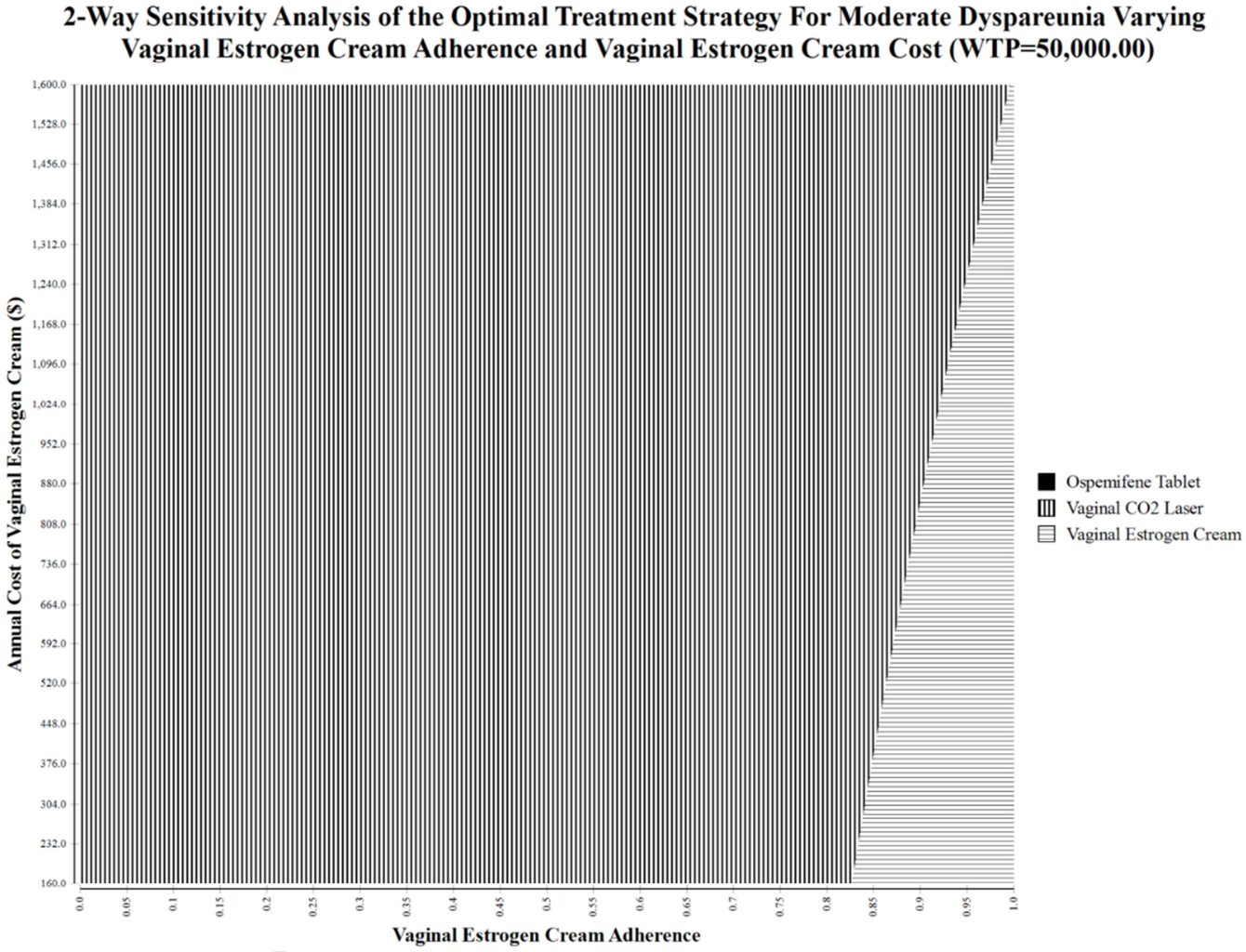
645 Figure 3

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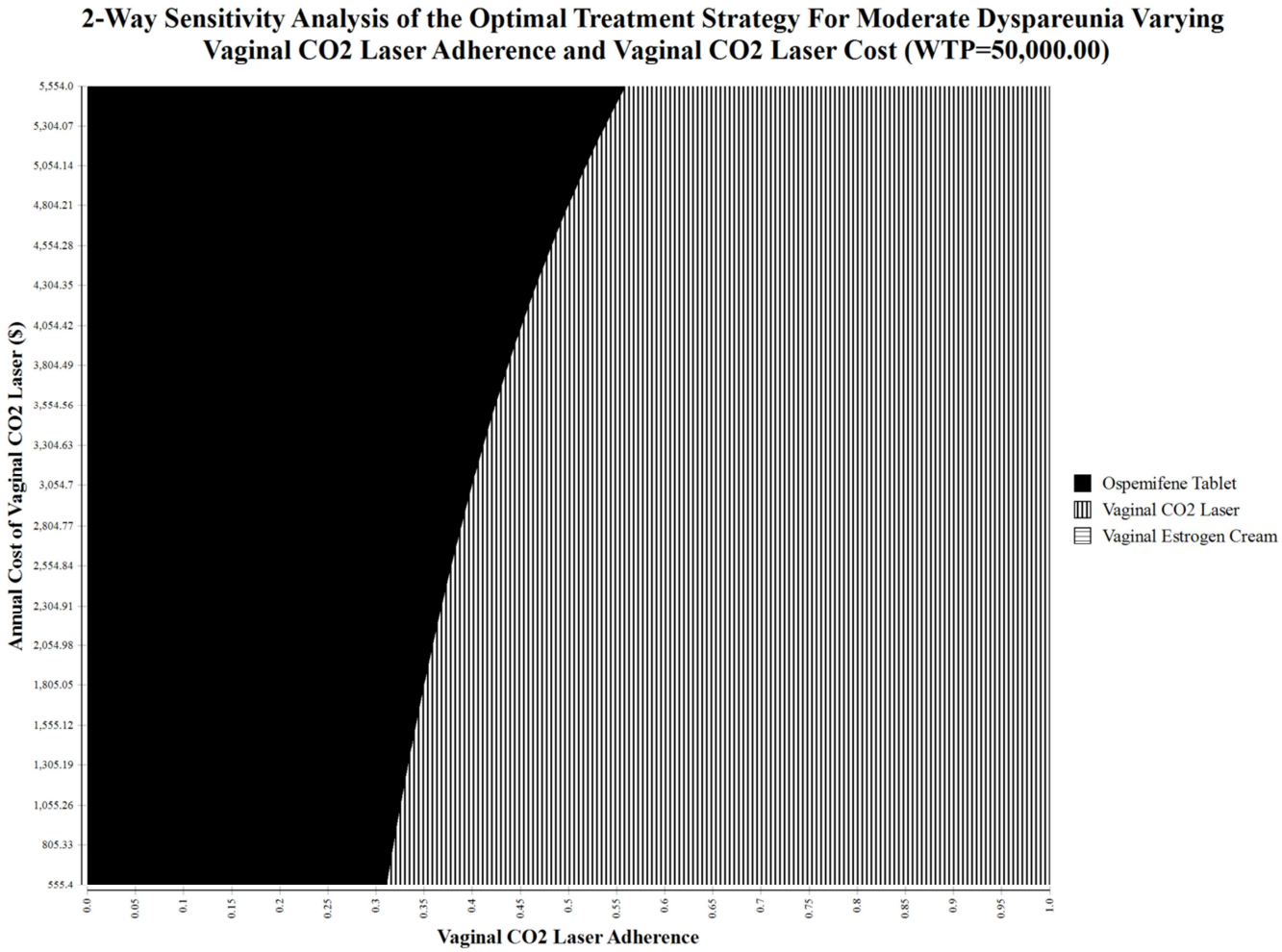
657 Figure 4

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