

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

### Interventional procedure overview of transvaginal laser therapy for urogenital atrophy

Urogenital atrophy is thinning, drying and inflammation of the tissues around the vaginal area. It most often happens after the menopause and can cause itching, burning and painful sexual intercourse. In this procedure, a device containing a laser is inserted into the vagina (transvaginal). The laser heats the tissue of the vaginal wall, causing changes that are thought to increase the strength and elasticity of the vagina. The aim is to improve the symptoms of urogenital atrophy.

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## Abbreviations

Word or phrase	Abbreviation
Confidence interval	CI
Day-to-day impact of vaginal ageing	DIVA
Female sexual function index	FSFI
Interquartile range	IQR
International Consultation on Incontinence Modular Questionnaire-Vaginal Symptoms	ICIQ-VS
ICIQ-UI SF, International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form	ICIQ-SF
Manufacturer and User Facility Device Experience	MAUDE
Standard deviation	SD
Urogenital distress	UDI
Vaginal health index	VHI
Vaginal health index score	VHIS
Vaginal maturation index	VMI
Visual analogue scale	VAS

## Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

## Date prepared

This overview was prepared in July 2020 and updated in March 2021.

## Procedure name

- Transvaginal laser therapy for urogenital atrophy.

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## Professional societies

- British Society of Urogynaecology
- British Association of Urological Surgeons
- British Menopause Society
- Royal College of Obstetrics and Gynaecology.

## Description of the procedure

### Indications and current treatment

Urogenital atrophy most often happens during or after the menopause when the lack of the hormone oestrogen affects the vagina, urethra and bladder trigone. The lack of oestrogen leads to a thinning of the tissues around the vaginal area and a reduction in the number of the mucus producing glands. The most common symptoms affecting the vulva and vagina include dryness, pain on sexual intercourse, vaginal itching and vaginal discharge. There is increased vulnerability to inflammation, trauma and infection. Urogenital atrophy can also result in urinary symptoms, such as urgency to urinate and urinary tract infections.

[NICE's guideline on diagnosis and management of menopause](#) describes the management of menopausal symptoms. The main treatments for urogenital atrophy are vaginal oestrogen, and non-hormonal lubricants and moisturisers.

### What the procedure involves

Transvaginal laser therapy for urogenital atrophy is done as an outpatient procedure and can be done without anaesthetic. A laser-probe device is inserted into the vagina to apply laser energy to the vaginal wall. The laser causes controlled thermal injury, which is claimed to make the tissue remodel and stimulate the production of new collagen. Treatment typically consists of 3 sessions at 4 to 6 weeks apart. The aim is to reduce the symptoms associated with urogenital atrophy.

There are different types of lasers used for this procedure, including CO<sub>2</sub> and erbium-doped yttrium aluminium garnet (Er:YAG) lasers. The type of laser and the energy level used have different tissue penetration and can cause different types of thermal injury.

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## Outcome measures

### Vaginal Health Index

The Vaginal Health Index assesses 5 components on a scale of 1 to 5: elasticity, fluid volume, pH, epithelial integrity and moisture. The minimum total score of 5 points indicates severe vulvovaginal atrophy and the maximum total score of 25 points indicates no clinical signs of vulvovaginal atrophy.

### Female Sexual Function Index

The Female Sexual Function Index (FSFI) is a multidimensional measure of female sexual functioning with 19 items that are scored from 0 (or 1) to 5. There are 6 domains: desire, arousal, lubrication, orgasm, satisfaction and pain. The scoring algorithm sums items on each domain and then scales the sums so that the maximum score is 6, with higher scores indicating better functioning. The FSFI total score is the sum of the 6 domain scores and has a maximum score of 36. A total score of 26 or less has been validated as a cutoff score for diagnosing female sexual dysfunction.

## Efficacy summary

### Dryness or atrophy

In a systematic review of 542 patients (14 studies), there was a statistically significant improvement in the dryness visual analogue scale (VAS) score at 1-month follow up (pooled mean difference -5.5, 95% confidence interval [CI] - 6.7 to -4.4, 7 studies,  $I^2=0%$ ,  $n=298$ ) (Pitsouni, 2017). In a systematic review of 522 women with a history of breast cancer treatment (10 studies), there was a statistically significant improvement in the dryness VAS score after laser therapy (mean difference 2.7, 95% CI 2.5 to 2.9, 5 studies,  $I^2=97%$ ,  $n=208$ ) (Jha, 2019).

In a randomised controlled trial (RCT) of 88 patients, the median score for vaginal dryness (measured on the International Consultation on Incontinence Modular Questionnaire, Vaginal Symptoms) reduced from 5.00 at baseline to 3.24 at 12-week follow up ( $p=0.02$ ) in the laser group and from 4.00 to 2.00

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( $p=0.07$ ) in the sham treatment group. The difference between the groups was not statistically significant. The vaginal atrophy symptom score reduced from 2.27 at baseline to 1.83 at 12-week follow up ( $p<0.001$ ) in the laser group and increased from 2.02 to 2.06 ( $p=0.59$ ) in the sham group. The difference between the groups was statistically significant 12 weeks after treatment ( $p=0.03$ ) (Ruanphoo, 2020).

In an RCT of 45 patients who had laser therapy, vaginal oestrogen cream or both, there was a statistically significant reduction in the VAS score for dryness in all 3 groups from baseline to week 20 (from 8.0 to 1.4 in the laser group, from 5.6 to 0.5 in the oestrogen cream group and from 7.9 to 0.3 in the group who had both,  $p<0.001$  for all 3 groups). There was no statistically significant difference between the groups (Cruz, 2018). In an RCT of 69 patients who had laser therapy or vaginal oestrogen cream, there were similar reductions in dryness between the groups at 6-month follow up (mean difference in VAS score -5.48 and -5.76 respectively,  $p=0.67$ ) (Paraiso, 2020). In an RCT of 72 patients who had laser therapy, vaginal oestrogen cream or vaginal lubricant, there was a statistically significant increase in moisture from baseline to week 14 in the laser and oestrogen groups (moisture domain of Vaginal Health Index score increased from 2.17 to 3.98 and from 1.83 to 3.11 respectively,  $p<0.05$  for both). The mean difference in scores between baseline and week 14 were 1.45, 1.16 and -0.06 for laser, oestrogen and lubricant respectively ( $p<0.001$  between groups) (Politano, 2019). In an RCT of 58 patients who had laser therapy or sham, the change in VAS score for dryness was 5.6 in the active group ( $p<0.001$ ) and 1.9 in the sham group ( $p=0.006$ ) (Salvatore, 2020).

In a non-randomised comparative study of 254 patients who had laser therapy or local treatment (hormonal or non-hormonal topical treatments), the VAS score for atrophy improved from 8.3 and 8.0 at baseline to 3.5 ( $p<0.01$ ) and 6.0 (not statistically significant) respectively at 6-month follow up ( $p<0.05$  between groups). At 12, 18 and 24-month follow up, the scores in the laser group were 5.6 ( $p<0.01$ ), 6.2 (not statistically significant) and 7.0 (not statistically significant) (Gambacciani, 2018).

## Dyspareunia

In the systematic review of 542 patients there was a statistically significant improvement in the dyspareunia visual analogue scale (VAS) score at 1-month follow up (pooled mean difference -5.6, 95% CI -6.8 to -4.5, 7 studies,  $I^2=0\%$ ,  $n=270$ ) (Pitsouni, 2017). In the systematic review of 522 women with a history of breast cancer treatment, there was a statistically significant improvement in the dyspareunia VAS score after laser therapy (mean difference 2.2, 95% CI 2.0 to 2.5, 4 studies,  $I^2=96\%$ ,  $n=183$ ) (Jha, 2019).

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In the RCT of 45 patients who had laser therapy, vaginal oestrogen cream or both, there was a statistically significant reduction in the VAS score for dyspareunia in the laser therapy and combined-treatment groups from baseline to week 20 (from 4.9 to 0.7 in the laser group [ $p=0.01$ ], from 3.2 to 0.2 in the oestrogen cream group [ $p=0.058$ ] and from 6.5 to 0.9 in the group who had both [ $p=0.009$ ]). There was no statistically significant difference between the groups (Cruz, 2018).

In the RCT of 58 patients who had laser therapy or sham, the change in VAS score for dyspareunia was 6 in the active group ( $p<0.001$ ) and 1.1 in the sham group ( $p=0.176$ ) (Salvatore, 2020).

In the non-randomised comparative study of 254 patients who had laser therapy or local treatment (hormonal or non-hormonal topical treatments), the VAS score for dyspareunia improved from 8.5 and 8.0 at baseline to 4.2 ( $p<0.01$ ) and 7.7 (not statistically significant) respectively at 6-month follow up ( $p<0.05$  between groups). At 12, 18 and 24-month follow up, the scores in the laser group were 5.3 ( $p<0.01$ ), 7.5 (not statistically significant) and 8.2 (not statistically significant) (Gambacciani, 2018).

### **Itching or burning**

In the systematic review of 542 patients there was a statistically significant improvement in the VAS score for itching and for burning at 1-month follow up (pooled mean difference -4.0, 95% CI -5.7 to -2.2, 6 studies,  $I^2=79%$ ,  $n=272$  and -3.9, 95% CI -5.9 to -2.0, 6 studies,  $I^2=87%$ ,  $n=281$ ) (Pitsouni, 2017).

In the RCT of 45 patients who had laser therapy, vaginal oestrogen cream or both, there was a statistically significant reduction in the VAS score for burning in the laser therapy and combined-treatment groups from baseline to week 20 (from 3.9 to 0.5 in the laser group [ $p=0.02$ ], from 0.9 to 0.1 in the oestrogen cream group [ $p=0.51$ ] and from 4.9 to 0.4 in the group who had both [ $p=0.002$ ]). This symptom was statistically significantly milder at baseline in the oestrogen cream group compared with the other 2 groups ( $p=0.017$ ), but there were no statistically significant differences between the groups at follow up (Cruz, 2018). In the RCT of 69 patients who had laser therapy or vaginal oestrogen cream, there were similar reductions in itching between the groups at 6-month follow-up (mean difference in VAS score -1.84 and -1.24 respectively,  $p=0.45$ ) (Paraiso, 2020).

### **Female Sexual Function Index**

In the systematic review of 542 patients there was a statistically significant improvement in the Female Sexual Function Index (FSFI) at 1-month follow up

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(pooled mean difference 13.2, 95% CI 9.1 to 17.3, 3 studies,  $I^2=0\%$ ,  $n=143$ ) (Pitsouni, 2017).

In the RCT of 45 patients who had laser therapy, vaginal oestrogen cream or both, there was a statistically significant improvement in total FSFI score only in the combined-treatment group (from 18.7 at baseline to 23.6 at week 20 [ $p=0.02$ ]). The score decreased in the laser group, from 18.6 to 14.4 ( $p=0.26$ ) and increased in the oestrogen cream group from 23.6 to 25.4 ( $p=0.56$ ) (Cruz, 2018). In the RCT of 69 patients who had laser therapy or vaginal oestrogen cream, there were no statistically significant differences between the groups at 6-month follow up (mean difference in FSFI 1.7 and 4.9 respectively,  $p=0.1$ ) (Paraiso, 2020). In the RCT of 72 patients who had laser therapy, vaginal oestrogen cream or vaginal lubricant, there was no statistically significant difference in FSFI score improvements between the groups at 14 weeks (score differences were 2.95, 1.99 and 3.05 respectively,  $p=0.577$ ) (Politano, 2019). In the RCT of 58 patients who had laser therapy or sham, the change in FSFI total score was 12.3 in the active group ( $p<0.001$ ) and 2.4 in the sham group ( $p=0.065$ ) (Salvatore, 2020).

In a case series of 1,081 patients, the FSFI scores improved from 15.5 at baseline to 27.0 at 24-week follow up ( $n=569$ ) (Gambacciani, 2020a).

### **Vaginal Health Index**

In the systematic review of 542 patients there was a statistically significant improvement in the Vaginal Health Index (VHI) score at 1-month follow up (pooled mean difference 10.7, 95% CI 8.7 to 12.7, 7 studies,  $I^2=0\%$ ,  $n=274$ ) (Pitsouni, 2017). In the systematic review of 522 women with a history of breast cancer treatment the mean difference in the VHI score after laser therapy was -11.4, 95% CI -11.8 to -10.9, 5 studies,  $I^2=98\%$ ,  $n=130$ ) (Jha, 2019).

In the RCT of 88 patients the VHI score improved from 14.18 at baseline to 17.45 at 12 weeks ( $p<0.001$ ) in the laser group and from 14.66 to 16.08 in the sham group ( $p=0.06$ ). The difference in the 2 groups at 12 weeks after treatment was statistically significant ( $p<0.001$ ) (Ruanphoo, 2020).

In the RCT of 45 patients who had laser therapy, vaginal oestrogen cream or both, there was a statistically significant improvement in mean VHI score in all 3 treatment groups from baseline to week 20 (from 11.7 to 18.5 in the laser group [ $p<0.01$ ], from 12.6 to 22.0 in the oestrogen cream group [ $p<0.01$ ] and from 12.6 to 23.0 in the group who had both [ $p<0.01$ ]). The difference between the groups was statistically significant ( $p<0.05$ ) (Cruz, 2018). In the RCT of 69 patients who had laser therapy or vaginal oestrogen cream, there were similar differences in the VHI score after treatment between the groups at 6-month follow up (mean difference 0.9 and 1.2 respectively,  $p=0.07$ ) (Paraiso, 2020). In the RCT of

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72 patients who had laser therapy, vaginal oestrogen cream or vaginal lubricant, there was a statistically significant increase in total VHI score from baseline to week 14 in the laser and oestrogen cream groups (from 9.50 to 18.68 and from 9.00 to 15.11 respectively,  $p < 0.001$  for both). The mean difference in scores between baseline and week 14 were 9.36, 5.89 and 0.06 for laser, oestrogen cream and lubricant respectively ( $p < 0.001$  between groups) (Politano, 2019).

In a randomised controlled trial of 237 patients who had laser treatment, radiofrequency treatment or placebo, there was a statistically significant improvement in VHI score in the laser group (from 10.9 at baseline to 12.7 after treatment,  $p = 0.002$ ) and the radiofrequency group (from 10.1 at baseline to 20.9 after treatment,  $p < 0.001$ ). There was no statistically significant change in the placebo group (10.6 at baseline compared with 10.5 after treatment,  $p = 0.636$ ) (Eftekhari, 2021).

In the non-randomised comparative study of 254 patients who had laser therapy or local treatment (hormonal or non-hormonal topical treatments), the VHI score improved from 10.6 and 10.8 at baseline to 18.7 ( $p < 0.01$ ) and 12.0 ( $p < 0.01$ ) respectively at 6-month follow up. At 12, 18 and 24-month follow-up the scores in the laser group were 16.5 ( $p < 0.01$ ), 15.3 ( $p < 0.01$ ) and 12.7 (not statistically significant) (Gambacciani, 2018).

### **Patient satisfaction**

In the systematic review of 522 women with a history of breast cancer treatment the proportion of patients with improvement in symptoms or satisfaction after laser treatment ranged from 59% to 96% (mean 84%, 6 studies) (Jha, 2019).

In the RCT of 88 patients who had laser therapy or sham treatment, the proportion of patients who were satisfied or very satisfied was 79.5% (31/39) and 44.7% (17/38) respectively ( $p = 0.002$ ) (Ruanphoo, 2020).

In the RCT of 69 patients who had laser therapy or vaginal oestrogen cream, the proportion of patients who were satisfied or very satisfied was 76% in both groups (Paraiso, 2020).

In the non-randomised comparative study of 254 patients who had laser therapy or local treatment (hormonal or non-hormonal topical treatments), 4% (8/205) of patients who had laser therapy stated it was not effective in reducing symptoms. Laser therapy was defined as effective up to 3 months by 23 patients (11%), up to 6 months by 18 patients (9%) and 74% (151/205) of patients stated it was effective for 12 to 18 months. Only 5 patients (2%) were still satisfied 24 months after the last laser treatment session (Gambacciani, 2018).

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In a case series of 184 patients, patient satisfaction was 92% (170/184), 72% (118/162), 63% (60/94) and 25% (4/16) at 6, 12, 18 and 24-month follow up respectively (Pieralli, 2017).

## Safety summary

### Persistent and worsening dyspareunia

Persistent painful intercourse was reported by 3 patients in a case series of 4 patients who had complications after laser therapy for genitourinary syndrome of menopause (Gordon, 2019). The first patient had mild dyspareunia before the laser treatment but the pain became progressively worse afterwards. On examination 10 months after finishing 3 courses of laser therapy this patient had moderate vaginal dryness, a vaginal pH of 6.5, a positive Q-tip test with vestibular inflammation, and pelvic floor hypertonus with spasm of both levator and vaginal muscles. Treatment involved vaginal rehabilitation with topical hormones to the vestibule, intravaginal Valium and intravaginal sex steroid for moderate to severe dyspareunia.

The second patient had persistent and worsening painful intercourse after completing 3 courses of laser treatment. She had severe vaginal dryness, with burning and itching and associated coital pain. On examination, there was a crescent shaped fibrous band mid vagina, which impinged on the diameter of the vaginal canal, creating a partial obstruction and vaginal canal stricture. The vaginal pH was 6.5 and there was decreased rugae, pale, frail and inelastic tissues. Treatment involved vaginal rehabilitation with nightly intravaginal local prasterone, vaginal moisturisers and a home vaginal dilator programme. At 1-month follow up she reported improvement in vaginal dryness but was concerned about resuming intercourse.

The third patient also had persistent and progressively worsening painful intercourse after 3 laser treatments. She had a history of hysterectomy with a bladder sling, mesh erosion surgery with removal and fascial sling placement and a third operation to loosen the sling because of overtightening. Before the laser procedure, she had vaginal dryness and mild to moderate dyspareunia. After the laser treatments, sexual intercourse was severely painful, with increased pain on penile insertion. On examination, she had a moderate amount of pelvic floor hypertonus, and a moderate amount of levator ani spasms with minimal anterior and lateral wall scarring. Treatment involved vaginal moisturiser and nightly off-label use of intravaginal Valium, and self-dilation exercises.

### Vaginal lacerations after resumption of intercourse

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Vaginal lacerations were reported in 1 patient after resumption of intercourse a few weeks after laser therapy (Gordon, 2019). These were repaired but the patient presented several months later with severe vaginal pain, dryness and inability to engage in penetrative intercourse. On examination, she had a foreshortened vaginal canal (about 2.5 cm in length) and fibrotic tissue was noted at the apex and within the canal of the vagina. She was offered intravaginal dehydroepiandrosterone, genitopelvic physical therapy and a vaginal dilator programme. At 3-month follow up she reported being able to engage in intercourse using alternative sexual positions, copious amounts of silicone-based lubricant and use of dilators before coitus.

### **Discomfort during treatment**

Discomfort or a burning sensation that made it necessary to discontinue treatment was reported in less than 1% of patients (2/542) in the systematic review of 542 patients and 4% (3/82) of patients in 1 study included in the systematic review of 522 patients (Pitsouni, 2017; Jha, 2019).

### **Pain**

Pain after the procedure was reported in 1% (3/41) of patients who had laser therapy and 1% (4/38) of patients who had sham treatment in the RCT of 88 patients (Ruanphoo, 2020). Vaginal pain was reported in 1 patient who had laser therapy in the RCT of 69 patients (Paraiso, 2020).

### **Bleeding**

Vaginal bleeding was reported in 7% (2/30) of patients who had laser therapy and 6% (2/32) of patients who had oestrogen cream in the RCT of 69 patients (Paraiso, 2020).

### **Infection**

Vaginitis was reported in 1 patient who had laser therapy in the RCT of 88 patients (Ruanphoo, 2020). Urinary tract infection was reported in 1 patient who had laser therapy in the RCT of 69 patients (Paraiso, 2020).

### **Vaginal discharge**

Vaginal discharge was reported in 1% (3/41) of patients who had laser therapy and less than 1% (1/38) of patients who had sham treatment in the RCT of 88 patients (Ruanphoo, 2020). Vaginal discharge was reported in 1 patient who had laser therapy in the RCT of 69 patients (Paraiso, 2020).

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## Adverse events reported to the US Food and Drug Administration

There were 30 events on the MAUDE database that detailed potential complications or adverse events associated with vaginal laser treatment. These included reports of pain, burn, lack of effect, dryness, dyspareunia, numbness, urinary tract infection, itchiness, bleeding, dysuria, infection, urinary frequency, hyperpigmentation, 'customer service dissatisfaction', and other unspecified complaints. The most common of these side effects were pain (n=13) and burning (n=10) (Guo, 2020).

## Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts did not describe any additional anecdotal or theoretical adverse events.

## The evidence assessed

### Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transvaginal laser therapy for urogenital atrophy. The following databases were searched, covering the period from their start to 12 January 2021: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the [literature search strategy](#)). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The [inclusion criteria](#) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

## Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	<p>Clinical studies were included. Emphasis was placed on identifying good quality studies.</p> <p>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.</p> <p>Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.</p>
Patient	Patients with urogenital atrophy.
Intervention/test	Transvaginal laser therapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

## List of studies included in the IP overview

This IP overview is based on about 3,000 patients from 3 systematic reviews, 6 randomised controlled trials, 1 non-randomised comparative study and 3 case series. In addition, there are data from a survey of 535 sites with 113,174 patients (Pitsouni, 2017; Jha, 2019; Ruanphoo, 2020; Cruz, 2018; Paraiso, 2020; Politano, 2019; Gambacciani, 2018; Gambacciani, 2020a; Guo, 2020; Eftekhar, 2021; Salvatore, 2020; Gambacciani, 2020b).

Other studies that were considered to be relevant to the procedure but were not included in the main [summary of the key evidence](#) are listed in the [appendix](#).

## Summary of key evidence on transvaginal laser therapy for urogenital atrophy

### Study 1 Pitsouni E (2017)

#### Study details

<b>Study type</b>	Systematic review
<b>Country</b>	Not reported for individual studies
<b>Recruitment period</b>	Search date: October 2016
<b>Study population and number</b>	n=542 (14 studies) Postmenopausal women with symptoms and clinical signs of genitourinary syndrome of menopause, with or without urinary incontinence
<b>Age and sex</b>	Mean age range 53 to 63 years
<b>Patient selection criteria</b>	The search strategy included the following combinations of keywords: 'laser genitourinary syndrome of menopause' or 'laser vulvovaginal atrophy' or 'laser vaginal atrophy' or 'laser women incontinence'. No limits were used. Articles were full-text, peer-reviewed and English language.
<b>Technique</b>	10 studies used CO <sub>2</sub> laser (SmartXide <sup>2</sup> V <sup>2</sup> LR, Monalisa Touch, DEKA, Italy) and 4 studies used Er:YAG laser (Fotona Smooth XS, Fotona, Slovenia). In all studies, the treatment protocol involved 3 laser sessions.
<b>Follow-up</b>	Range 1 to 25 months (8 studies had 1-month follow-up)
<b>Conflict of interest/source of funding</b>	One author has had financial relations (expert testimonies and lectures) with DEKA laser. No funding was received for the review.

#### Analysis

Study design issues: All authors independently evaluated the studies design for quality of reporting, risk of bias and quality of evidence. Quality of reporting was assessed using Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist. Risk of bias assessment was done using the methodological index for non-randomised studies (MINORS) checklist. A study with score 50% or less of maximum score was considered to be at 'high risk of bias'; none of the studies were in this category. Quality of the body of evidence was assessed by the GRADE system of rating for the outcomes that could be meta-analysed; it was described as 'low' or 'very low'.

Of the 14 studies, 12 were prospective uncontrolled before- and after-studies and 2 were prospective controlled before- and after-studies, using estriol as a control group. The 2 controlled studies were not included in the meta-analysis.

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Dyspareunia and dryness were measured on a visual analogue scale (VAS) from 0 to 10 (2 studies that used a different scale were excluded from the meta-analysis). Itching, burning, and dysuria were also assessed by VAS 0 to 10.

## Key efficacy findings

Number of patients analysed: 542

All genitourinary syndrome of menopause symptoms (dryness, dyspareunia, itching, burning, dysuria, urgency, frequency) and urinary incontinence decreased significantly and consistently in all available publications.

### Primary outcomes - pooled mean differences at 1-month follow-up:

- Dryness=-5.5 (95% CI -6.7 to -4.4; 7 studies;  $I^2=0%$ , n=298)
- Dyspareunia=-5.6 (95% CI -6.8 to -4.5; 7 studies;  $I^2=0%$ , n=270)
- Itching=-4.0 (95% CI -5.7 to -2.2; 6 studies;  $I^2=79%$ , n=272)
- Burning=-3.9 (95% CI -5.9 to -2.0; 6 studies;  $I^2=87%$ , n=281)
- Dysuria=-2.9 (95% CI -5.1 to -0.7; 4 studies;  $I^2=90%$ , n=185)
- Urinary incontinence=-4.9% (95% CI -6.4 to -3.4; 2 studies;  $I^2=0%$ , n=54)

### Subgroup analysis – pooled mean differences in CO<sub>2</sub> laser group (6 studies)

- Dryness=-5.5 (95% CI -6.6 to -4.4,  $p<0.00001$ ,  $I^2=0%$ , n=255)
- Dyspareunia=-5.5 (95% -6.6 to -4.4,  $p<0.00001$ ,  $I^2=0%$ , n=229)

### Secondary outcomes - pooled mean differences at 1-month follow-up:

- Female Sexual Function Index=13.2 (95% CI 9.1 to 17.3; 3 studies;  $I^2=0%$ , n=143)
- Mental Component Summary-12=4.5 (95% CI 1.9 to 7.0; 3 studies;  $I^2=59%$ , n=139)
- Physical Component Summary-12=6.2 (95% CI 0.8 to 11.5; 3 studies;  $I^2=91%$ , n=139)
- Vaginal Health Index Score (above 15 is considered the threshold of non-atrophic values)=10.7 (95% CI 8.7 to 12.7; 7 studies;  $I^2=0%$ , n=274)
- Vaginal Maturation Value=20.6 (95% CI 1.4 to 39.9; 2 studies;  $I^2=76%$ , n=78)

## Key safety findings

6 studies (n=230) reported that there were no adverse events.

In other studies, adverse events included:

- Pain during probe insertion
- Discomfort related to first application
- Mild irritation of the introitus that started immediately after laser therapy and resolved spontaneously in about 2 hours
- Mild or moderate pain lasting 2 to 3 days

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- Minor bleeding or spotting
- Sensation of warmth and slight oedema

0.4% (2/542) of patients discontinued therapy because of discomfort related to the first application or a burning sensation that started 36 hours after laser treatment and lasted for 2 days. Both women had Er:YAG laser therapy.

## Study 2 Jha S (2019)

### Study details

<b>Study type</b>	Systematic review
<b>Country</b>	Italy, US, Belgium, Germany, Australia
<b>Recruitment period</b>	2014 to 2017
<b>Study population and number</b>	n=522 (10 studies) Women with genitourinary syndrome of menopause after breast cancer treatment
<b>Age and sex</b>	Mean age range 44 to 71 years
<b>Patient selection criteria</b>	The study population included women with breast cancer who had completed preliminary treatment for their cancer and subsequently had genitourinary syndrome of menopause. Conference abstracts were included if data could be extracted. Unpublished work was excluded. No language restrictions were applied.
<b>Technique</b>	7 studies used a CO <sub>2</sub> laser and 3 used an Erbium YAG laser. The treatment protocol varied in the different studies, ranging from 3 to 5 treatment sessions in the CO <sub>2</sub> laser studies and 1 to 3 in the Erbium YAG laser studies.
<b>Follow-up</b>	4 weeks to 24 months (1 study reported 24-month outcomes)
<b>Conflict of interest/source of funding</b>	The authors of the review stated that they have no conflicts of interest.

### Analysis

Study design issues: The review followed the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines for the reporting of meta-analysis of observational studies. When data were incomplete, the authors were contacted by email, and if no response was received after 2 weeks, a further email was sent. The risk of bias assessment based on the quality of the studies was done using the Modified Newcastle Ottawa Scale. Meta-analysis was done if more than 3 studies reported data.

All included studies were observational cohort studies reporting on the effects of laser treatment before and after completion of treatment on the same cohort of patients. There were no randomised controlled trials. There was significant heterogeneity of the studies with respect to women having the laser treatment. The time elapsed since the completion of active treatment for breast cancer varied, as did the age of patients and time elapsed since menopause. Most studies did not comment on the type of endocrine therapies the patients were on. Of the 10 studies, 5 were conference abstracts with limited data available. None of the studies reported a formal sample size calculation.

Study population issues: Most women in the studies were on some form of antioestrogen therapy, either tamoxifen or an aromatase inhibitor.

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## Key efficacy findings

Number of patients analysed: 522

### Vaginal Health Index

Mean difference=-11.4 (95% CI -11.8 to -10.9; 5 studies,  $I^2=98%$ ; n=130)

2 further studies reported a statistically significant improvement ( $p<0.01$ ) but were not included in the meta-analysis because individual scores before and after treatment were not reported.

### Dyspareunia (VAS)

Mean difference=2.2 (95% CI 2.0 to 2.5; 4 studies,  $I^2=96%$ , n=183)

### Dryness (VAS)

Mean difference=2.7 (95% CI 2.5 to 2.9; 5 studies,  $I^2=97%$ , n=208)

### Sexual Function (measured using Female Sexual Function Index)

3 studies reported this outcome and all 3 showed an improvement in sexual function (no further details given)

### Improvement or satisfaction after treatment

The percentage of patients with improvement in symptoms or satisfaction after laser treatment ranged from 58.9% to 96.1% (mean 83.5%; 6 studies).

## Key safety findings

### Adverse events

9 studies reported no adverse effects from treatment.

In 1 study, 3.7% (3/82) of patients discontinued treatment after 2 cycles because of discomfort.

## Study 3 Ruanphoo P (2020)

### Study details

<b>Study type</b>	Randomised controlled trial
<b>Country</b>	Thailand
<b>Recruitment period</b>	2016 to 2017
<b>Study population and number</b>	n=88 (44 laser therapy, 44 sham) Postmenopausal women with any vaginal atrophy symptom of moderate to severe intensity
<b>Age and sex</b>	Mean 61 years
<b>Patient selection criteria</b>	Inclusion criteria: postmenopausal women (aged at least 50 years and had their last menstruation at least 1 year ago) with any vaginal atrophy symptom (burning, dryness or dyspareunia) of moderate to severe intensity. Exclusion criteria: history of hormonal therapy within the last 6 months, vaginal moisturiser or lubricant applications within the past 30 days, acute or recurrent urinary tract infection, active genital infection, genital hiatus diameter of less than 2 cm or pelvic organ prolapse stage 2 or higher according to pelvic organ prolapse quantification system classification.
<b>Technique</b>	Laser therapy: Laser treatment was done with a CO <sub>2</sub> laser (SmartXide <sup>2</sup> , V <sup>2</sup> LR, DEKA, Italy). In the lithotomy position, the vaginal laser probe was inserted into the total length of the vagina and subsequently withdrawn 0.5 cm following each laser beam application until the distal end of the vaginal probe reached the introitus. Sham: the vaginal probe was inserted and withdrawn in the same manner as the laser treatment but without using the laser. Treatment was done on an outpatient basis without local anaesthesia. There were 3 treatment sessions, 4 weeks apart. All patients were advised to avoid sexual intercourse or intravaginal devices for at least 3 days after the procedure.
<b>Follow-up</b>	12 weeks
<b>Conflict of interest/source of funding</b>	No funding or support was reported. A laser machine was supported by Lasermed Co. Ltd without involvement in the study protocol, data collection or manuscript development.

### Analysis

Follow-up issues: 10% (9/88) of patients were lost to follow-up (3 in the laser treatment group and 6 in the sham group). All patients were scheduled for 4 visits with a 4-week interval. One patient in the laser group withdrew from the study because she could not tolerate the pain when the vaginal probe was inserted into the vagina. The remaining 8 patients withdrew because it was inconvenient for them to attend the clinic.

Study design issues: Prospective randomised controlled trial. Simple randomisation was generated by a computer and allocation concealment was done using opaque, sealed envelopes. The envelopes were opened by a research assistant at the first visit before starting treatment. Signs of vaginal atrophy were evaluated by

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an investigator who was blinded to the treatment allocation. Treatment was done by an investigator who did not know the clinical outcomes of the treatment. The primary outcome was vaginal health index (VHI) score. Secondary outcomes were vaginal atrophy symptoms score, score for vaginal dryness from the International Consultation on Incontinence Modular Questionnaire-Vaginal Symptoms (ICIQ-VS) questionnaire, patient satisfaction, and adverse events. Intention-to-treat analysis was used for the primary outcome. The sample size calculation was based on the primary efficacy variable, a 5% level of significance (2-sided) and a power of 80%. A sample size of 44 women per group was needed, assuming a 20% dropout rate.

Study population issues: In the laser group, 23% (10/44) of women were sexually active compared with 55% (24/44) in the sham group. At baseline, the VHI score, vaginal atrophy symptoms score and ICIQ-VS score for vaginal dryness were comparable between the groups.

## Key efficacy findings

Number of patients analysed: 88 (44 laser, 44 sham)

### Vaginal signs and symptoms at baseline and 12 weeks after treatment

Outcome measure	Baseline	12-week follow up	p value
VHI score (mean±SD)			
Laser group	14.18±3.39	17.45±2.61	<0.001
Sham group	14.66±2.91	16.08±3.27	0.06
p value	0.48	<0.001	
Vaginal atrophy symptoms score (mean±SD)			
Laser group	2.27±0.42	1.83±0.51	<0.001
Sham group	2.02±0.40	2.06±0.49	0.59
p value	0.06	0.03	
ICIQ-VS vaginal dryness (median [IQR])			
Laser group	5.00 (2.00 to 6.00)	3.24 (0 to 4.00)	0.02
Sham group	4.00 (2.00 to 6.00)	2.00 (0.26 to 4.00)	0.07
p value	0.09	0.56	

The results of the per protocol analysis were similar to the intention-to-treat analysis.

**Patient satisfaction, n (%)**

Level of satisfaction	Laser group (n=39)	Sham group (n=38)	P value
Very satisfied or satisfied	31 (79.5%)	17 (44.7%)	0.002
Neither satisfied or dissatisfied or lower	8 (20.5%)	21 (55.3%)	

**Key safety findings****Complications, n (%)**

Complication	Laser group (n=39)	Sham group (n=38)	P value
Vaginal bleeding	0 (0)	1 (0.26)	0.30
Vaginal discharge	3 (0.73)	1 (0.26)	0.34
Vaginitis	1 (0.24)	0 (0)	0.33
Pain after procedure	3 (0.73)	4 (1.05)	0.34
De novo dyspareunia	0 (0)	0 (0)	-

## Study 4 Cruz V (2018)

### Study details

<b>Study type</b>	Randomised controlled trial
<b>Country</b>	Brazil
<b>Recruitment period</b>	2015
<b>Study population and number</b>	n=45 (15 laser therapy, 15 estriol, 15 laser plus estriol) Postmenopausal women with vulvovaginal atrophy
<b>Age and sex</b>	Mean 56 years (laser therapy and laser plus estriol), 57 years (estriol)
<b>Patient selection criteria</b>	Women aged between 45 and 70 years who presented with amenorrhoea for 24 months or longer and at least 1 moderate symptom (score of 4 or more on visual analogue scale from 0 to 10) of vulvovaginal atrophy (dyspareunia, dryness or burning). Exclusion criteria: Body mass index 35 kg/m <sup>2</sup> or above, chronic kidney or liver disease, drug-induced menopause, history of any form of cancer, previous vaginal radiotherapy, pap smear consistent with atypical squamous cells of undetermined significance, low-grade intraepithelial lesion or high-grade intraepithelial lesion in the previous 12 months, current use of vaginal lubricants or moisturisers, use of anabolic steroids, ospemifene or systemic oestrogen therapy in the past 6 months or diagnosis of vulvovaginitis within previous 30 days.
<b>Technique</b>	Laser treatment was done using a fractional microablative CO <sub>2</sub> laser (Monalisa Touch, DEKA laser, Italy). Patients had 2 sessions, 4 weeks apart. Estriol therapy consisted of 1 mg vaginal estriol therapy 3 times a week for 20 consecutive weeks. Patients in the laser therapy group also had placebo vaginal cream treatment (similar in appearance, odour, consistency and packaging to the estriol cream) and patients in the estriol group also had sham laser treatment (power adjusted to 0 W).
<b>Follow-up</b>	16 weeks
<b>Conflict of interest/source of funding</b>	None

### Analysis

Follow-up issues: Of the 45 randomised patients, 3 (7%) were lost to follow-up (2 in the laser group and 1 in the estriol group).

Study design issues: Randomised, double-blind, placebo-controlled clinical trial. Patients were block randomised into the 3 treatment groups using a computer-generated randomisation list. An unblinded nurse programmed the laser parameters before the doctor and patient entered the room. Once programmed, a cover was placed over the screen to maintain blinding. The same nurse was responsible for selecting the appropriate topical cream of either placebo or estriol for each patient. The same physician conducted all appointments and

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laser sessions. The main outcomes included improvement in Vaginal Health Index (VHI) and in vulvovaginal symptoms using a visual analogue scale from 0 to 10. Secondary outcome measures included analysis of vaginal smear samples and the assessment of sexual function using the validated Portuguese version of the Female Sexual Function Index (FSFI). The sample size of 45 was calculated to detect a 3-point difference in the VHI with  $p < 0.05$  and power  $\geq 0.8$ , allowing for a potential loss of 20% of patients throughout the study. Intention-to-treat analysis and per-protocol analysis were used for the main outcomes.

Study population issues: There were no statistically significant differences in demographic characteristics between the groups at baseline. Clinical characteristics were similar except for burning, which was statistically significantly milder in the estriol group.

## Key efficacy findings

Number of patients analysed: 45 (15 laser, 15 estriol, 15 laser plus estriol)

### Vaginal Health Index mean score (per protocol analysis)

Timepoint	Laser	estriol	Laser plus estriol	p
Baseline	11.7	12.6	12.6	0.76
8 weeks*	19.0 <sup>^</sup>	21.0 <sup>^</sup>	20.0 <sup>^</sup>	-
20 weeks*	18.5 <sup>**</sup>	22.0 <sup>**</sup>	23.0 <sup>**</sup>	<0.05 <sup>#</sup>

\* estimated from chart; <sup>^</sup> $p < 0.05$ , <sup>\*\*</sup> $p < 0.01$  compared with baseline; <sup>#</sup> laser compared with other study arms

### Mean differences between groups at week 20

- Laser and estriol groups = -2.87 (95% CI -5.99 to 0.26)
- Laser and laser plus estriol = 4.73 (95% CI 2.42 to 7.07)
- Estriol and laser plus estriol = 1.87 (95% CI -0.59 to 4.31)

**Visual analogue scale symptom scores (intention-to-treat analysis), mean±sd**

Symptom	Laser	estriol	Laser plus estriol	p
Dyspareunia				
Baseline	4.9±3.7	3.2±3.4	6.5±3.9	0.09
Week 8	2.9±2.9	0.6±1.7	2.5±3.8	0.16
Week 20	0.7±1.5	0.2±0.6	0.9±1.8	0.95
p	0.01	0.058	0.009	
Dryness				
Baseline	8.0±2.6	5.6±2.9	7.9±3.0	0.07
Week 8	3.6±2.6	2.4±2.0	3.3±2.9	0.57
Week 20	1.4±2.0	0.5±1.4	0.3±0.7	0.35
p	<0.001	<0.001	<0.001	
Burning				
Baseline	3.9±4.5	0.9±1.6	4.9±3.8	0.017
Week 8	1.0±2.0	0.1±0.5	1.2±2.7	0.33
Week 20	0.5±1.5	0.1±0.3	0.4±1.1	0.95
p	0.02	0.51	0.002	

**Total FSFI score, median (interquartile range); higher scores better**

Timepoint	Laser	estriol	Laser plus estriol	p
Baseline	18.6 (16.4, 24.6)	23.6 (17.5, 29.8)	18.7 (7.2, 22.6)	0.21
8 weeks	18.0 (11.4, 20.7)	22.9 (8.4, 29.7)	22.6 (11.3, 26.3)	0.39
20 weeks	14.4 (7.8, 22.4)	25.4 (16.8, 29.3)	23.6 (14.9, 28.6)	0.10
p (week 20 vs baseline)	0.26	0.56	0.02	

**Pain domain of FSFI score, median (interquartile range)**

Timepoint	Laser	estriol	Laser plus estriol	p
Baseline	4.4 (1.6, 5.6)	4.8 (2.2, 5.7)	2.4 (1.2, 3.6)	0.04
8 weeks	2.0 (0.0, 4.4)	5.2 (0.0, 6.0)	3.6 (1.2, 4.8)	0.39
20 weeks	2.0 (0.0, 3.6)	6.0 (3.9, 6.0)	2.8 (1.6, 5.6)	0.006
p (week 20 vs baseline)	0.04	0.16	0.02	

No statistically significant difference was observed in vaginal smear samples between the groups.

**Key safety findings**

No adverse effects of laser treatment or pain during laser application were observed during the study.



## Study 5 Paraiso MFR (2020)

### Study details

<b>Study type</b>	Randomised controlled trial (VeLVET trial)
<b>Country</b>	US (6 centres)
<b>Recruitment period</b>	2016 to 2017
<b>Study population and number</b>	n=69 (34 laser treatment, 35 vaginal oestrogen cream) Women with vulvovaginal atrophy/genitourinary syndrome of menopause
<b>Age and sex</b>	Mean 61 years
<b>Patient selection criteria</b>	<p>Inclusion criteria: menopausal women with absence of menstruation for 12 months and bothersome vaginal dryness of 7 cm or more on visual analogue scale (VAS).</p> <p>Exclusion criteria: contraindication to vaginal oestrogen therapy, history of vulvovaginal condyloma, vaginal intraepithelial neoplasia, vaginal carcinoma, lichen sclerosus, lichen planus, history of vaginal radiation, history of cervical cancer, other gynaecological cancer or pelvic radiation, acute or recurrent urinary tract infection, or genital infection. Women were also excluded if they had a personal history of thrombophlebitis, heart failure or myocardial infarction within 12 months, scleroderma, or any chronic condition that could interfere with study compliance. They were also excluded if they had pelvic organ prolapse higher than stage 2, if they had had pelvic surgery within 6 months or if they previously had reconstructive pelvic surgery with transvaginal mesh kits. Previous midurethral sling and sacrocolpopexy with synthetic mesh for prolapse were not excluded. Patients were excluded if they had used vaginal oestrogen cream, ring or tablet within 1 month before entering the study, or vaginal moisturisers, lubricants, or homeopathic preparations within 2 weeks of therapy.</p>
<b>Technique</b>	<p>Laser group: laser treatment was done using a fractional microablative CO<sub>2</sub> laser (Monalisa Touch, DEKA laser, Italy). Patients had 3 sessions, at least 6 weeks apart.</p> <p>The laser beam was applied using a 90° vaginal probe gently inserted up to the top of the vaginal canal and subsequently withdrawn at centimetre intervals while rotated to 6 positions in an alternating clockwise and counter clockwise fashion to provide complete circumferential treatment of the vagina. At the investigator's discretion, a flat probe was used to treat the introital area and vestibule. EMLA cream was applied to the introitus for 10 minutes beforehand, if desired.</p> <p>Patients were advised to avoid coital sexual activity for at least 3 days after each laser application and topical lidocaine 5% ointment was prescribed for vulvar pain after the procedure for those patients who wanted it.</p> <p>Vaginal oestrogen cream group: conjugated oestrogen cream 0.5 g intravaginally daily was prescribed for 14 days followed by 0.5 g twice weekly for 24 weeks.</p>
<b>Follow-up</b>	6 months
<b>Conflict of interest/source of funding</b>	The study was supported by an unrestricted research grant from the Foundation of Female Health Awareness.

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	<p>6 authors declared research support from companies including NICHHD, Coloplast, Caldera, Acell, FFHA, NIH, Solace, Pelvalon, Boston Scientific, Pelvalon, National Vulvodynia Association, International Society for the Study of Women's Sexual Health.</p> <p>3 authors are consultants for companies including Pelvalon, Eximis, Boston Scientific, Hologic, Coloplast.</p>
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## Analysis

**Follow-up issues:** Of the 69 randomised patients, 4 withdrew before they had treatment (2 in each group) and 3 were lost to follow-up (2 in the laser group and 1 in the vaginal oestrogen group).

**Study design issues:** Multicentre randomised controlled trial comparing laser treatment with vaginal oestrogen cream. Patients were not blinded to their treatment allocation. A computer-generated randomisation schedule with random block sizes was used. All follow-up questionnaires and examinations were done by study personnel blinded to treatment allocation. The primary outcome of the study was to compare subjective improvement of vaginal dryness using a VAS 6 months after treatment between groups. Secondary outcomes included comparisons between groups of the vaginal health index and vaginal maturation index scores, the effect of genitourinary syndrome of menopause on quality of life, the effect of treatment on sexual function, the effect of treatment on urinary symptoms, and comparison of patient satisfaction. A sample size of 85 patients in each group was calculated to provide 90% power to reject the null hypothesis that the true difference in vaginal dryness VAS score is less than or equal to 1.0 in favour of the alternative hypothesis that the true difference is greater than 1.0 using a 1-sided 2-sample t test. A 15% loss to follow-up or dropout rate was accounted for. The study was closed early because of a request from the US Federal Drug Administration to obtain an Investigational Device Exemption, so the planned sample size was not reached. The study therefore lacked power. An intention-to-treat analysis was done, but it showed no changes from the per protocol analysis and the results were not included in the paper.

**Study population issues:** The 2 treatment groups were similar with regard to baseline characteristics. According to the body of the text in the paper, patients in the laser group were less parous than those in the oestrogen group (0 [0 to 4] compared with 2 [0 to 6],  $p=0.04$ ), but the table in the paper shows similar parity between the groups.

Most patients (80%) had previously taken exogenous hormones and 78% had previously used vaginal oestrogen.

## Key efficacy findings

Number of patients analysed: 62 (30 laser, 32 oestrogen cream)

**Outcome measures at 6-month follow-up**

Outcome	Laser, n=30	Oestrogen cream, n=32	p
Mean difference VAS score - dryness	-5.48±2.68	-5.76±2.48	0.67
Mean difference VAS score - itching	-1.84±3.01	-1.24±2.96	0.45
Mean difference VAS score - irritation	-3.29±3.73	-3.49±3.19	0.87
Mean difference VAS score - dysuria	-1.4±2.89	-2.11±2.85	0.36
Mean difference VHI	0.9±0.7	1.2±0.9	0.07
Mean difference DIVA	-3.3±3.2	-4.4±3.1	0.18
Mean difference VMI*	3.9±30.6	25±22.6	0.04 <sup>^</sup>
Mean difference FSFI	1.7±6.7	4.9±8.3	0.1
Mean difference UDI	-9.4±15.7	-6.2±12	0.37
% sexually active	45.5 (15)	48.3 (14)	0.82

\* remained statistically significant after controlling for confounding factors

<sup>^</sup> baseline and follow-up data were only available for 55% of patients

**FSFI subgroup outcomes at 6 months (mean differences)**

Subgroup	Laser, n=30	Oestrogen cream, n=32	p
Desire*	0.32±1.3	1.02±1.4	0.05
Arousal*	0.62±1.6	1.63±1.9	0.03
Lubrication	0.11±1.2	0.35±1.4	0.50
Orgasm	0.37±1.3	0.9±1.6	0.17
Satisfaction	0.88±2.1	1.7±1.7	0.50
Pain	-0.59±2.8	-0.04±3.3	0.81

\* No longer statistically significant after controlling for confounding factors

**Proportion of patients who rated improvement as 'better or much better'**

- Laser=71.9%
- Oestrogen cream=82.8%, p=not significant

**Proportion of patients who were 'satisfied or very satisfied'**

- Laser=75.8%

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- Oestrogen cream=75.9%, p=not significant

## Key safety findings

### Adverse events, n (%)

Subgroup	Laser, n=30	Oestrogen cream, n=32
Vaginal bleeding	2 (6.7)	2 (6.3)
Vaginal pain	1 (3.3)	0 (0)
Vaginal discharge	1 (3.3)	0 (0)
Urinary tract infection	1 (3.3)	0 (0)
Breast tenderness	0 (0)	1 (3.1)
Migraine	0 (0)	1 (3.1)
Abdominal cramping	0 (0)	1 (3.1)

## Study 6 Politano CA (2019)

### Study details

<b>Study type</b>	Randomised controlled trial
<b>Country</b>	Brazil
<b>Recruitment period</b>	2017 to 2018
<b>Study population and number</b>	n=72 (24 laser treatment, 24 vaginal oestrogen cream, 24 vaginal lubricant) Postmenopausal women with genitourinary syndrome of menopause
<b>Age and sex</b>	<ul style="list-style-type: none"> <li>• Laser treatment group: mean age 58 years</li> <li>• Vaginal oestrogen group: mean age 57 years</li> <li>• Vaginal lubricant group: mean age 57 years</li> </ul>
<b>Patient selection criteria</b>	<p>Inclusion criteria: women aged 50 to 70 years; physiological amenorrhoea for at least 12 months; symptoms of vaginal dryness with or without dyspareunia, vaginal burning or pruritis; no use of hormonal medications to treat vaginal symptoms in the previous 6 months.</p> <p>Exclusion criteria: previous bilateral oophorectomy; body mass index less than 18.5 or greater than 30 kg/m<sup>2</sup>; contraindications to local oestrogen use, including recent myocardial infarction, severe hypertension, diabetes mellitus, thromboembolic disorders, previous breast or endometrial cancer, or abnormal postmenopausal bleeding. Women having behavioural treatment for depression or taking antidepressant medications, those with any other psychiatric disorders, HIV-positive women on antiretroviral therapy, women with a history of previous radiation therapy, and women with previous surgery for stress urinary incontinence were also excluded.</p>
<b>Technique</b>	<p>Laser treatment was done with a fractional CO<sub>2</sub> laser (SmartXide<sup>2</sup>, V<sup>2</sup>LR, Monalisa Touch, DEKA laser, Italy). Three sessions were done at 30-day intervals. A 360° cylindrical probe was introduced into the vaginal and rotated and slowly withdrawn, with continuous use of the pedal according to precalibrated marks on the probe. Patients were advised to abstain from sexual activity for 10 days before treatment.</p> <p>Vaginal oestrogen cream treatment consisted of 1 vaginal applicator containing 1 g of cream and 10 mg of promestriene administered 3 times a week.</p> <p>Vaginal lubricant treatment consisted of water-based lubricant applied with sexual activity.</p>
<b>Follow-up</b>	14 weeks
<b>Conflict of interest/source of funding</b>	None

### Analysis

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Follow-up issues: Of the 72 randomised patients, 15 (21%) were lost to follow-up (2 in the laser group, 5 in the oestrogen group and 8 in the lubricant group). One patient in the lubricant group discontinued treatment because of allergic vaginitis.

Study design issues: Single centre randomised controlled trial. Randomisation was done using a computer-generated list that was prepared by a statistician. The primary outcome was improvement in vaginal atrophy, measured by the Vaginal Health Index (VHI) and vaginal maturation. The Frost index was used to determine the degree of atrophy. This index evaluates the differential count of each cell group (parabasal, intermediate and superficial) expressed as a percentage. A deep cell percentage between 30% and 49% indicated moderate hypoestrogenism and a more than 50% deep cell percentage indicated hypoestrogenism. The secondary outcome was sexual function, measured using the FSFI. A cut-off score of 26.55 was used to differentiate the presence or absence of sexual dysfunction. A sample size of 20 for each group was calculated based on a standard deviation of 2.5, a difference of 2 points in the VHI, a significance level of 5% and a power of 80%.

Study population issues: The 3 treatment groups were similar with regard to age, years since menopause and menopause age. There was a statistically significantly higher proportion of patients in the laser group (96%) who declared themselves to be white compared with those in the oestrogen group (67%) and the lubricant group (71%),  $p=0.032$ .

Other issues: A total of 267 women were recruited to take part in the study, but only 27% (72) met the inclusion criteria.

## Key efficacy findings

Number of patients analysed: 72 (24 laser, 24 vaginal oestrogen, 24 vaginal lubricant)

**VHI score at baseline and 14 weeks according to treatment group, mean (SD)**

<b>VHI domain</b>	<b>Laser</b>	<b>Oestrogen</b>	<b>Lubricant</b>	<b>p</b>
Elasticity at baseline	2.04 (0.55)	1.96 (0.55)	2.08 (0.65)	0.817
Elasticity at week 14	3.41 (0.91)	2.58 (0.81)	2.19 (0.54)	<b>&lt;0.001</b>
p	<b>0.006</b>	<b>0.025</b>	0.970	
Difference	1.36 (0.79)	0.58 (0.69)	0.00 (0.63)	<b>&lt;0.001</b>
Fluid volume at baseline	1.92 (0.58)	1.79 (0.66)	1.92 (0.72)	0.736
Fluid volume at week 14	3.41 (0.73)	2.79 (0.99)	2.00 (0.63)	<b>&lt;0.001</b>
p	<b>0.029</b>	<b>0.03</b>	0.572	
Difference	1.50 (0.91)	1.05 (0.85)	-0.13 (0.62)	<b>&lt;0.001</b>
pH at baseline	6.33 (0.64)	6.21 (0.66)	6.17 (0.70)	0.799
pH at week 14	3.98 (0.59)	4.89 (0.94)	5.75 (0.58)	<b>&lt;0.001</b>
p	<b>0.001</b>	<b>0.043</b>	0.262	
difference	-2.38 (0.93)	-1.32 (1.34)	-0.31 (0.87)	<b>&lt;0.001</b>
Moisture at baseline	2.17 (0.92)	1.83 (0.70)	2.04 (0.75)	0.799
Moisture at week 14	3.98 (0.59)	3.11 (0.88)	2.13 (0.89)	<b>&lt;0.001</b>
p	<b>0.036</b>	<b>0.03</b>	0.392	
Difference	1.45 (1.26)	1.16 (0.76)	-0.06 (0.57)	<b>&lt;0.001</b>
Epithelial integrity at baseline	2.00 (0.66)	1.92 (0.50)	2.00 (0.66)	0.868
Epithelial integrity at week 14	3.68 (0.99)	3.00 (0.88)	2.13 (0.72)	<b>&lt;0.001</b>
p	<b>&lt;0.001</b>	<b>&lt;0.001</b>	1.00	
Difference	1.73 (1.03)	1.05 (0.78)	0.19 (0.40)	<b>&lt;0.001</b>
Total at baseline	9.50 (2.59)	9.00 (2.52)	9.79 (3.09)	0.836
Total at week 14	18.68 (3.20)	15.11 (3.98)	10.44 (2.78)	<b>&lt;0.001</b>
p	<b>&lt;0.001</b>	<b>&lt;0.001</b>	1.00	
Difference	9.36 (3.40)	5.89 (3.68)	0.06 (1.65)	<b>&lt;0.001</b>

## Frost index at baseline and 14 weeks according to treatment group, mean (SD)

Cells	Laser	Oestrogen	Lubricant	p
Basal at baseline	27.23 (17.20)	27.84 (22.62)	37.00 (21.69)	<b>0.044</b>
Basal at week 14	5.82 (4.23)	20.84 (23.39)	40.19 (18.10)	<b>&lt;0.001</b>
p	<b>&lt;0.001</b>	0.080	0.537	
Difference	-21.41 (16.50)	-7.00 (10.36)	3.19 (23.26)	<b>&lt;0.001</b>
Intermediary at baseline	73.45 (16.72)	71.89 (22.67)	61.50 (24.15)	<b>0.027</b>
Intermediary at week 14	88.73 (5.81)	77.68 (22.66)	58.88 (18.24)	<b>&lt;0.001</b>
p	<b>&lt;0.001</b>	<b>0.042</b>	0.715	
Difference	15.27 (14.98)	5.79 (10.86)	-2.63 (26.75)	<b>&lt;0.001</b>
Superficial at baseline	0.50 (1.74)	0.26 (1.15)	0.25 (0.77)	0.877
Superficial at week 14	5.00 (3.83)	2.00 (2.62)	0.31 (1.25)	<b>&lt;0.001</b>
p	<b>&lt;0.001</b>	<b>0.004</b>	1.00	
difference	4.50 (4.27)	1.74 (2.56)	0.06 (1.53)	<b>&lt;0.001</b>



## FSFI score at baseline and 14 weeks according to treatment group, mean (SD)

FSFI domain	Laser	Oestrogen	Lubricant	p
Desire at baseline	2.80 (1.20)	2.83 (1.24)	2.98 (1.45)	0.643
Desire at 14 weeks	3.16 (1.19)	2.97 (0.93)	2.89 (1.09)	
p	<b>0.047</b>	0.910	0.406	
Difference	0.41 (0.86)	-0.03 (1.07)	0.28 (0.93)	0.071
Arousal at baseline	2.95 (1.80)	2.64 (1.87)	2.63 (1.77)	0.628
Arousal at 14 weeks	3.22 (1.61)	2.87 (1.83)	2.93 (1.52)	
p	0.533	0.417	0.399	
Difference	0.23 (1.60)	0.19 (1.54)	0.42 (1.54)	0.0823
Lubrication at baseline	2.46 (1.74)	2.00 (1.46)	2.44 (1.65)	0.234
Lubrication at 14 weeks	3.59 (1.94)	2.75 (2.02)	2.86 (1.44)	
p	<b>0.011</b>	0.139	0.051	
difference	1.02 (1.94)	0.69 (1.82)	0.58 (1.09)	0.295
Orgasm at baseline	2.93 (1.96)	2.85 (1.89)	2.67 (1.93)	0.404
Orgasm at 14 weeks	3.64 (1.96)	2.86 (2.14)	3.39 (1.74)	
p	0.061	0.808	<b>0.014</b>	
Difference	0.62 (2.14)	-0.13 (1.88)	0.89 (1.31)	0.175
Satisfaction at baseline	3.58 (1.55)	3.30 (1.62)	3.13 (1.48)	0.918
Satisfaction at 14 weeks	3.76 (1.53)	3.96 (1.58)	4.00 (1.37)	
p	0.351	0.098	<b>0.038</b>	
Difference	0.20 (2.06)	0.67 (1.50)	0.92 (1.52)	0.562
Pain at baseline	2.55 (1.85)	1.73 (1.50)	2.00 (1.80)	0.202
Pain at 14 weeks	3.18 (2.39)	2.63 (2.09)	1.72 (1.07)	
p	0.456	0.188	0.969	
Difference	0.47 (2.36)	0.59 (1.95)	-0.05 (1.16)	0.978
Total at baseline	17.28 (8.46)	15.35 (7.57)	15.84 (7.66)	0.396
Total at 14 weeks	20.55 (8.68)	18.04 (9.46)	17.79 (7.13)	
p	0.134	0.182	<b>0.038</b>	
Difference	2.95 (8.92)	1.99 (7.74)	3.05 (5.59)	0.577

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## Key safety findings

One woman assigned to the lubricant group discontinued the study because she developed allergic vaginitis in week 4. No other adverse effects were reported in any of the treatment groups.

## Study 7 Gambacciani M (2018)

### Study details

<b>Study type</b>	Non-randomised comparative study
<b>Country</b>	Italy
<b>Recruitment period</b>	Not reported
<b>Study population and number</b>	n=254 (205 laser treatment, 49 local treatment) Postmenopausal women with genitourinary syndrome of menopause
<b>Age and sex</b>	Mean 61 years (laser group); 62 years (local treatment group)
<b>Patient selection criteria</b>	Inclusion criteria: presence of genitourinary syndrome of menopause in women with plasma levels of gonadotropin and oestradiol in the postmenopausal range and negative Pap smear. Exclusion criteria: use of lubricants, local preparations, hormones or other medications to relieve menopausal symptoms in the previous 3 months before inclusion to the study; lesions, scars or infection, active or recent (30 days) of the genitourinary tract; abnormal uterine bleeding; history of photosensitivity disorder or use of photosensitising drugs; genital prolapse (grade 2 to 3 classification POP-Q); and serious or chronic illness that could interfere with the study.
<b>Technique</b>	Laser treatment device: non-ablative 2940 nm Er:YAG laser (XS Fotona Smooth, Fotona, Slovenia). Patients had 3 treatment sessions at 30-day intervals. The procedures were done in an outpatient clinical setting without any preparation, anaesthesia or post-treatment medications. Before the procedure, the vagina was cleaned with disinfectant solution and dried with a swab. All patients had circular treatment of the vaginal wall followed by treatment of the vestibule and introitus. Patients with stress urinary incontinence had additional laser treatment of the anterior vaginal wall. After treatment, all patients were advised to abstain from sexual intercourse for 1 week. Control group: local treatments consisted of hormonal (estriol gel twice weekly) or non-hormonal therapies such as hyaluronic acid-based preparations or different moisturisers and lubricants for 3 months.
<b>Follow-up</b>	24 months
<b>Conflict of interest/source of funding</b>	None

### Analysis

Follow-up issues: A total of 235 women were treated by laser but only 205 completed the study; 11 patients left the study for personal reasons, 13 because of other pharmacological or surgical interventions, and 1 patient who complained of discomfort after the first application. The follow-up period in the control group ended at 6 months because most patients started a new local or systemic treatment. The paper states that 23 (16.6%)

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patients were lost to follow-up, but it is unclear whether this refers to the whole cohort or just those women with stress urinary incontinence.

Study design issues: Prospective longitudinal single centre study. The study does not describe how patients were allocated to each treatment group. The aim of the study was to evaluate the long-term efficacy of vaginal laser treatment for the management of genitourinary syndrome of menopause. Subjective symptoms (vaginal dryness and dyspareunia) were evaluated by a VAS (range 0 to 10, where 0=total absence of the symptom and 10=the worst possible symptom). The Vaginal Health Index Score (VHIS) was evaluated at every visit and the general acceptability and efficacy of laser therapy was assessed as excellent, good, acceptable, bad, or unacceptable. Patients were excluded from the analysis after they had a repeat procedure.

Study population issues: There were no statistically significant differences in age, age at menopause, years since menopause and body mass index between the 2 groups at baseline. The basal VAS scores were also similar in the 2 groups. The mean number of years since menopause was 13 in both groups.

## **Key efficacy findings**

Number of patients analysed: 254 (205 laser treatment, 49 control)

## Symptom scores before, during and after treatment, mean±standard error

Time period	n (laser group)	Atrophy (VAS)		Dyspareunia (VAS)		VHIS	
		Laser	Control	Laser	Control	Laser	Control
Basal	205	8.3±1.5	8.0±2.7	8.5±1.3	8.0±2.7	10.6±2.7	10.8±1.7
First laser treatment	205	5.2±1.7*	3.1±1.5	5.1±1.8*	4.5±1.5*	16.2±1.5*	18±2.5*
Second laser treatment	205	4.3±2.0*	3.0±2.0*	4.0±1.9*	4.2±2.0*	18.1±2.0*	19±2.4*
Third laser treatment	205	3.0±1.3*	4.0±2.1*	4.1±1.9*	3.8±2.1*	19.5±1.2*	18±2.6*
1 month after last laser treatment	204	3.0±1.1*	3.0±1.5*	3.5±1.0*	4.0±1.5*	20.1±1.3*	18±2.8*
3 months after last laser treatment	203	3.0±0.9* <sup>^</sup>	5.0±2.9	3.8±1.5*	6.8±1.5 <sup>^</sup>	19.5±1.5*	16±2.7*
6 months after last laser treatment	163	3.5±1.2*	6.0±3.2 <sup>^</sup>	4.2±2.0*	7.7±2.7 <sup>^</sup>	18.7±1.5*	12±2.9*
12 months after last laser treatment	152	5.6±1.5*	-	5.3±2.2*	-	16.5±2.0*	-
18 months after last laser treatment	119	6.2±1.3	-	7.5±2.3	-	15.3±2.0*	-
24 after last laser treatment	66	7.0±1.0	-	8.2±2.4	-	12.7±2.7	-

\* p<0.01 compared with baseline; <sup>^</sup>p<0.05 compared with laser group

In the laser group, 3.9% (8/205) of patients stated that the treatment was not effective in reducing symptoms. Treatment was defined as effective up to 3 months by 23 patients (11.2%), up to 6 months by 18 patients (8.8%) and 73.6% (151/205) of patients stated that laser treatment was effective for 12 to 18 months.

Only 5 patients (2.4%) were still satisfied after 24 months from the last laser treatment session.

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**Proportion of patients who had a repeat procedure by follow-up period after last laser treatment**

- 3 months=1.0% (2/205)
- 6 months=9.8% (20/205)
- 12 months=30.2% (62/205)
- 18 months=26.8% (55/205)
- 24 months=16.6% (34/205)
- Total=84.9% (174/205)

**Key safety findings**

The paper states 'No adverse events related to the procedure were recorded throughout the study period' but it also states 'Less than 3% of patients discontinued treatment due to adverse events.'

## Study 8 Gambacciani M (2020a)

### Study details

<b>Study type</b>	Case series
<b>Country</b>	Italy (4 centres)
<b>Recruitment period</b>	Not reported
<b>Study population and number</b>	n=1,081 Sexually active postmenopausal women with genitourinary syndrome of menopause
<b>Age and sex</b>	mean 54.3 years
<b>Patient selection criteria</b>	Inclusion criteria: the presence of genitourinary syndrome of menopause diagnosed on the basis of subjective symptoms and signs, the presence of a concomitant jeopardised sexual life in otherwise healthy, sexually active postmenopausal women; all patients included in the study were referred to the study centre for the laser treatment. All patients were at least 12 months since their last menstrual period or bilateral oophorectomy, presenting a negative Papanicolaou smear.  Exclusion criteria: vaginal lesions, scars, active or recent (30 days) infections of the genitourinary tract; abnormal uterine bleeding; use of vaginal preparations within 30 days of the study; history of photosensitivity disorder or use of photosensitising drugs; genital prolapse; serious or chronic condition that could interfere with study compliance; treatment with hormones to relieve menopausal symptoms in the 6 months before the study.
<b>Technique</b>	Device: erbium laser (XS Fotona SmoothVR, Fotona, Slovenia) Treatment sessions were offered at 4 weekly intervals (651 patients had 2 procedures and 221 patients had 3). No additional hormonal or non-hormonal treatment was allowed during the study.
<b>Follow-up</b>	24 weeks
<b>Conflict of interest/source of funding</b>	None

### Analysis

**Follow-up issues:** Of the 1,081 patients, 554 (51%) returned the Female Sexual Distress Scale-Revised (FSDS-R) questionnaire and 569 (53%) returned the Female Sexual Function Index (FSFI) at all time points. The remaining questionnaires were not completed at all given time points and therefore were not included in the statistical analysis.

**Study design issues:** Prospective multicentre case series. The study recruitment was stopped when the interim evaluation of the data, performed bi-annually, consistently showed the effects of the procedure on the selected parameters.

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## Key efficacy findings

Number of patients analysed: 569

### Female Sexual Distress Scale-Revised (FSDS-R) questionnaire scores (n=554)

- Baseline=25.5 ± 3.5,
- 4 weeks=11.5 ± 3.0, p<0.01
- 12 weeks=10.5 ± 3.5, p<0.01
- 24 weeks=11.5 ± 3.5, p<0.01

### Female Sexual Function Index (FSFI) questionnaire scores (n=569)

- Baseline=15.5 ± 1.5
- 4 weeks=27.5 ± 2.5, p<0.01
- 12 weeks=27.6 ± 2.7, p<0.01
- 24 weeks=27.0 ± 3.5, p<0.01

### Individual FSFI domain scores by follow up period, mean ± standard error

Domain	Baseline	4 weeks	12 weeks	24 weeks
Desire	3.0±0.5	4.0±1.5	4.5±1.5	4.7±1.5
Arousal	2.7±1.5	4.0±1.5	4.0±1.5	4.0±1.5
Lubrication	2.1±0.5	4.8±0.5	4.9±0.5	4.8±1.5
Orgasm	2.7±0.7	4.0±0.5	4.0±0.5	4.0±1.5
Satisfaction	2.5±1.5	4.9±1.5	4.9±1.5	4.9±1.5
Pain	2.5±0.5	4.8±0.5	4.9±0.5	4.7±1.5

## Key safety findings

No adverse events were recorded during the study.



## Study 9 Pieralli A (2017)

### Study details

<b>Study type</b>	Case series
<b>Country</b>	Italy
<b>Recruitment period</b>	2013 to 2016
<b>Study population and number</b>	n=184 Postmenopausal women with 1 or more symptom related to vulvovaginal atrophy
<b>Age and sex</b>	Mean 56 years (range 38 to 72)
<b>Patient selection criteria</b>	Inclusion criteria: menopause status (spontaneous menopause or menopause induced by chemotherapy or surgical adnexectomy), 1 or more vulvovaginal atrophy symptoms (itching, burning, reduced lubrication, postcoital bleeding or dyspareunia), negative Pap smear not older than a year or negative human papillomavirus test not older than 5 years.  Exclusion criteria: the use of vaginal moisturising agents and lubricants within 30 days of study inclusion, the presence of active genital infection during the enrolment visit, prolapse stage 2 or above according to pelvic organ prolapse quantification system, previous reconstructive pelvic surgery or topical radiotherapy, previous vulvar, vaginal or cervical cancer.
<b>Technique</b>	Device: fractional microablative CO <sub>2</sub> laser (Smart Xide2; V2LR Monalisa Touch system, Italy). Each patient had 3 treatment sessions, 4 weeks apart. No local anaesthesia was used. Laser energy was released by 2 single shots oriented at 45° to each other, to treat the entire circular vaginal surface.  Patients were not prohibited from having sexual activity before or after the treatment sessions.
<b>Follow-up</b>	6 to 24 months
<b>Conflict of interest/source of funding</b>	None

### Analysis

**Follow-up issues:** The final study group constituted 70% (184/262) of patients who were originally enrolled in the study: 12 patients were very dissatisfied with the treatment and decided to abandon the study and 66 patients were excluded from the study because they were unavailable for long-term follow-up. The paper states that 184 patients were available for long-term follow-up data but only reports patient satisfaction for 94 patients at 18 months and 16 patients at 24 months.

**Study design issues:** Prospective, single centre cohort study. The aim of the study was to evaluate long-term effects of the treatment. The main outcome was patient satisfaction measured on a 5-point Likert scale. All patients were called in September 2016 to evaluate treatment effects and the time of follow up was between 6 and 24 months after treatment.

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Study population issues: The mean time from onset of menopause was 8 years (range 1 to 25) at baseline. Of the 184 patients, 128 (70%) had spontaneous menopause and 56 (30%) had oncological menopause (women with current or previous breast cancer).

## Key efficacy findings

Number of patients analysed: 184

### Patient satisfaction by follow-up:

- 6 months=92% (170/184)
- 12 months=72% (118/162)
- 18 months=63% (60/94)
- 24 months=25% (4/16)

At the follow-up interview, 66.3% (122/184) of patients answered that they wanted to repeat the treatment; 17.4% (32/184) had decided to start or were making a new treatment cycle; 16.3% (30/184) did not want to repeat the treatment.

### Patient satisfaction in patients with spontaneous menopause:

- 6 months=92% (118/128)
- 12 months=69% (78/112)
- 18 months=44% (22/50)
- 24 months=0% (0/8)

### Patient satisfaction in patients with oncological menopause:

- 6 months=93% (52/56)
- 12 months=80% (40/50)
- 18 months=86% (38/44)
- 24 months=50% (4/8)

## Key safety findings

Safety data were not reported.

## Study 10 Gordon C (2019)

### Study details

<b>Study type</b>	Case series
<b>Country</b>	US
<b>Recruitment period</b>	Not reported
<b>Study population and number</b>	n=4 Patients with complications after laser treatment for genitourinary syndrome of menopause
<b>Age and sex</b>	65, 61, 68 and 55 years
<b>Patient selection criteria</b>	Not applicable
<b>Technique</b>	All patients had 3 consecutive treatment sessions using a CO <sub>2</sub> laser.
<b>Follow-up</b>	Not reported
<b>Conflict of interest/source of funding</b>	One author is a paid consultant for Viveve Medical.

### Key safety findings

#### Case 1: vaginal lacerations after resumption of intercourse

65-year old postmenopausal woman with history of breast cancer presented with symptoms of severe vaginal dryness and moderate vaginal stenosis. She had previously tried vaginal oestrogen cream but discontinued it because of headaches. She had 3 laser treatments and engaged in intercourse a few weeks after the last session. She had heavy vaginal bleeding immediately afterwards. An examination under anaesthesia revealed 2 vaginal wall lacerations, which were repaired. There were areas of adhesive agglutination noted in the vaginal canal. Several months later, the patient presented with complaints of severe vaginal pain, dryness and inability to engage in penetrative intercourse. She had a foreshortened vaginal canal (about 2.5 cm in length) and fibrotic tissue was noted at the apex and within the canal of the vagina. She was offered intravaginal dehydroepiandrosterone, genitopelvic physical therapy and a vaginal dilator programme. At the 3-month follow-up, she was able to engage in intercourse using alternative sexual positions, copious amounts of silicone-based lubricant and use of dilators before coitus.

#### Case 2: persistent dyspareunia

61-year old woman with persistent painful intercourse 10 months after finishing 3 courses of laser treatment. She had mild dyspareunia before the laser treatment but the pain became progressively worse afterwards. On examination, there was moderate vaginal dryness with a vaginal pH of 6.5; she had a positive Q-tip test with vestibular inflammation and pelvic floor hypertonus with spasm of both levator and vaginal muscles. Treatment

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involved vaginal rehabilitation with topical hormones to the vestibule, intravaginal Valium and intravaginal sex steroid for moderate to severe dyspareunia.

### **Case 3: worsening dyspareunia and fibrous band mid vagina**

68-year old woman with persistent and worsening painful intercourse after completing 3 courses of laser treatment. She had severe vaginal dryness, with burning and itching and associated coital pain. On examination, there was a crescent shaped fibrous band mid vagina, which impinged on the diameter of the vaginal canal, creating a partial obstruction and vaginal canal stricture. The vaginal pH was 6.5 and there was decreased rugae, pale, frail and inelastic tissues. Treatment involved vaginal rehabilitation with nightly intravaginal local prasterone coupled with vaginal moisturisers and a home vaginal dilator programme. At 1-month follow-up, she reported improvement in vaginal dryness but she was still concerned about resuming intercourse.

### **Case 4: dyspareunia and insertional pain**

55-year old woman with persistent and progressively worsening painful intercourse after 3 laser treatments. She had a history of hysterectomy with a bladder sling, mesh erosion surgery with removal and fascial sling placement and a third operation to loosen the sling because of overtightening. Before the laser procedure, she had vaginal dryness and mild to moderate dyspareunia. After the laser treatments, sexual intercourse was severely painful, with increased pain on penile insertion. On examination, she had a moderate amount of pelvic floor hypertonus, and a moderate amount of levator ani spasms with minimal anterior and lateral wall scarring. Treatment involved vaginal moisturiser and nightly off-label use of intravaginal Valium, and self-dilation exercises.

## Study 11 Guo J (2020)

### Study details

<b>Study type</b>	Systematic review
<b>Country</b>	Not reported for individual studies
<b>Recruitment period</b>	Search date: September 2019
<b>Study population and number</b>	Adverse events after vaginal laser treatment. literature review: 3 publications with 29 presumptive laser-associated complications MAUDE database review: 30 detailed potential adverse patient events
<b>Age and sex</b>	not reported
<b>Patient selection criteria</b>	Possible adverse events attributed to vaginal laser treatment of GSM were identified. Inclusion criteria for literature review: peer-reviewed articles, case reports, and conference abstracts. Search terms included “vaginal laser,” “vaginal rejuvenation,” “genitourinary syndrome of menopause” and “laser,” or “atrophy” and “laser”. Basic science articles and animal studies were excluded; remaining articles were examined for documentation of adverse events, side effects, or discomfort after treatment. Non-English articles were translated using Google translate. The references from each pertinent article were searched to identify articles missed in the original search. The MAUDE database was searched using vaginal laser devices and manufacturers. Data on product liability claims in the Bloomberg Law database from 2010 to June 2019 were reviewed by a law librarian.
<b>Technique</b>	erbium:YAG laser and fractionated CO <sub>2</sub> laser
<b>Follow-up</b>	Not reported
<b>Conflict of interest/source of funding</b>	One author is an expert witness for Boston Scientific, 1 author is an investigator and expert witness for Boston Scientific, an investigator for Aquinox, and a consultant for Boston Scientific and Allergan, and 1 author is an expert witness for Cynosure.

### Analysis

Study design issues: Review of the medical literature assessing the safety of vaginal laser treatments, survey of adverse events detailed in the Manufacturer and User Facility Device Experience (MAUDE) database, and comprehensive search of the Bloomberg Law database. It was not possible to distinguish whether complications or potential adverse events were related to vaginal therapy or vestibular treatment. The literature review identified 2 case series and 1 conference presentation detailing adverse events.

Study population issues: the indications for treatment were often not reported in the MAUDE database.

Other issues: Reports from the MAUDE database are subject to reporting and verification biases. Reports from the database cannot be used to determine the incidence of adverse events. The authors noted that there are insufficient data to understand whether the adverse event represents a lack of efficacy, natural progression of disease, inappropriate device use, or true device-related harm, especially as the majority of the post-treatment complaints are the symptoms of GSM for which these patients likely sought treatment. The Bloomberg

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database also has data capture limitations and some case filings related to vaginal laser treatments may have been missed. If a patient filed a claim directly against the physician and did not name the manufacturer as a defendant, these claims would not have been captured.

## Key safety findings

Literature review: 2 case series and 1 conference presentation described 29 adverse events or complications. Of these, 12 described persistence of the initial symptoms for which the patient sought treatment. These instances were classified by the authors as “no treatment effect” and were not considered to be adverse events.

Of the 17 patients with adverse events, 5 patients had increased symptoms after laser treatments, typically exhibiting worsening of the initial symptoms of vaginal pain or dyspareunia. In 12 patients, there was not enough information to determine the effects of laser treatment.

## Reported adverse events after vaginal laser treatments (n=17)

Patient	Indication	Laser type	Adverse events
1	Vaginal stenosis, dryness	CO <sub>2</sub>	Postcoital vaginal bleeding, vaginal pain, dryness, tissue fibrosis and shortened vaginal canal
2	Mild painful intercourse	CO <sub>2</sub>	Delayed worsening painful intercourse, vaginal dryness, pelvic floor hypertonus with spasm
3	No information	CO <sub>2</sub>	Persistent and worsening painful intercourse, vaginal dryness, burning, itchiness, crescent shaped fibrous band, decreased rugae, pale, frail, inelastic tissues
4	Vaginal dryness, dyspareunia	CO <sub>2</sub>	Worsening painful intercourse, pelvic floor hypertonus, levator ani spasms, vaginal scarring
5	Vaginal rejuvenation	CO <sub>2</sub>	Bladder pain, urethral pain
6	No information	CO <sub>2</sub>	Unspecified pain
7	Vaginal rejuvenation	CO <sub>2</sub>	Dyspareunia
8	Vaginal rejuvenation	CO <sub>2</sub>	Bartholin's cyst
9	Dyspareunia	CO <sub>2</sub>	Dyspareunia, urinary frequency, vaginal pain, lichen sclerosis, yeast infection
10	No information	CO <sub>2</sub>	Vaginal pain, bladder pain
11	No information	Er:YAG	Bladder pain, dysuria, urinary tract infection, bacterial vaginosis
12	No information	Er:YAG	Third-degree burns, vaginal pain
13	No information	Er:YAG	Third-degree burns, vaginal pain
14	Vaginal rejuvenation	Er:YAG	Dyspareunia, vaginal pain
15	No information	CO <sub>2</sub>	No information
16	Urinary incontinence	CO <sub>2</sub>	Vaginal pain, vaginal bleeding, dyspareunia, urinary incontinence, vaginal bleeding, yeast infection

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17	Vaginal rejuvenation	CO <sub>2</sub>	Blurry vision, eye irritation, facial pain
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Review of the MAUDE database revealed 120 cases, 78 (65%) of which were complaints detailing equipment malfunction, which includes error messages on machine display and inability to perform procedures. Review of the event description confirmed that no patients were harmed in those malfunction events. Five cases (4%) were reported after improper handling of the devices by the operators, and 7 cases (6%) documented injury to the operator. There were 30 events that detailed potential complications or adverse events, which included reports of pain, burn, lack of effect, dryness, dyspareunia, numbness, urinary tract infection, itchiness, bleeding, dysuria, infection, urinary frequency, hyperpigmentation, 'customer service dissatisfaction', and other unspecified complaints.

The most common of these side effects were pain (n=13) and burning (n=10).

In the Bloomberg Law database, no claims for the specific laser devices marketed for the treatment of vaginal complaints associated with GSM were identified and manually reviewed. None of the identified filings were found to pertain to the use of laser treatment for vaginal indications.

## Study 12 Eftekhari T (2021)

### Study details

<b>Study type</b>	Randomised controlled trial
<b>Country</b>	Iran
<b>Recruitment period</b>	2018
<b>Study population and number</b>	n=237 (78 laser treatment, 80 radiofrequency treatment, 79 placebo) Menopausal women with mixed urinary incontinence and vulvovaginal atrophy
<b>Age</b>	Mean 56.3 ± 7.2 (laser treatment), 57.7 ± 7.3 (radiofrequency treatment, 54.8 ± 11.5 (placebo)
<b>Patient selection criteria</b>	Inclusion criteria: history of urinary incontinence symptoms, sexual intercourse, sexual problems because of vulvovaginal atrophy, at least 1 year after the termination of menstruation, the presence of vulvovaginal atrophy symptoms, and sexual dysfunction. Exclusion criteria included: urinary infection, haematuria, pelvic organ prolapse, Pelvic Organ Prolapse Quantification (POP-Q) greater than 2, pregnancy, childbirth in less than a year, abnormal vaginal bleeding, damaged vaginal tissue, history of damage to spinal nerves, radical hysterectomy with neuropathy, epilepsy, autoimmune diseases, and more than 50 g of urine leakage per hour.
<b>Technique</b>	Laser treatment: fractional CO <sub>2</sub> laser system (Monalisa Touch). Patients had 3 treatment sessions 4 weeks apart. Radiofrequency treatment: Physio Vag Device, which has monopolar and bipolar modes, 4 working frequencies (500 Hz was used in this study) and both continuous and pulsed modes of operation. Patients had 3 treatment sessions 4 to 6 weeks apart. Placebo group: treatment not described
<b>Follow-up</b>	End of treatment
<b>Conflict of interest/source of funding</b>	None

### Analysis

Follow-up issues: An additional 9 patients were randomised but were unwilling to continue with the study so were excluded.

Study design issues: Randomised controlled trial. The method of randomisation, blinding and the treatment offered to patients in the placebo group is not described. The sample size was estimated as 71 patients per group for a power of 80% and a 95% confidence interval. Finally, 82 people were included in each group, allowing for a 10% fallout. Outcomes were measured using the PISQ-12 (self-administered questionnaire for evaluating sexual function in women with urinary incontinence or pelvic organ prolapse), ICIQ-SF (a brief measure to assess the impact of urinary incontinence symptoms on the quality of life and the outcome of

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treatment), VHI to assess vaginal health, and a visual analogue score to assess the severity of vulvovaginal atrophy symptoms (4-point scale from asymptomatic to severe).

## Key efficacy findings

- Number of patients analysed: 237 (78 laser, 80 radiofrequency, 79 placebo)

### Comparison of study variables before and after the intervention, mean $\pm$ standard deviation

Outcome	Treatment group	Before	After	p
VAS	Laser	23.3 $\pm$ 12.6	17.6 $\pm$ 12.2	<0.001
	RF	26.5 $\pm$ 12.6	13.5 $\pm$ 9.9	<0.001
	Placebo	24.5 $\pm$ 15.8	23.3 $\pm$ 15.3	0.006
VHI	Laser	10.9 $\pm$ 3.4	12.7 $\pm$ 4.8	0.002
	RF	10.1 $\pm$ 2.1	20.9 $\pm$ 1.5	<0.001
	Placebo	10.6 $\pm$ 4.6	10.5 $\pm$ 4.0	0.636
Mixed urinary incontinence	Laser	6.5 $\pm$ 3.3	4.9 $\pm$ 3.6	<0.001
	RF	7.6 $\pm$ 5.1	4.1 $\pm$ 3.6	<0.001
	Placebo	6.7 $\pm$ 4.0	6.1 $\pm$ 3.9	0.067
Emotional behaviour	Laser	6.3 $\pm$ 3.2	7.9 $\pm$ 3.2	<0.001
	RF	6.7 $\pm$ 3.3	10.0 $\pm$ 2.6	<0.001
	Placebo	8.8 $\pm$ 3.8	8.8 $\pm$ 3.8	0.1
Physical behaviour	Laser	11.1 $\pm$ 4.1	10.5 $\pm$ 4.2	0.029
	RF	11.4 $\pm$ 4.0	16.3 $\pm$ 2.9	<0.001
	Placebo	14.0 $\pm$ 2.5	14.5 $\pm$ 2.7	0.197
Partner related	Laser	6.8 $\pm$ 2.2	6.9 $\pm$ 2.1	0.566
	RF	6.7 $\pm$ 2.2	8.1 $\pm$ 2.7	0.002
	Placebo	7.0 $\pm$ 2.1	7.3 $\pm$ 2.9	0.159

**Results of Tukey's test for vulvovaginal atrophy symptoms**

Treatment group	Comparator	Mean difference	standard error	p
RF	Laser	-5.738	1.713	0.003
	Placebo	-15.813	1.713	<0.001
Laser	Placebo	-10.075	1.73	<0.001

**Results of Tukey's test for VHI**

Treatment group	Comparator	Mean difference	standard error	p
RF	Laser	8.194	0.593	<0.001
	Placebo	10.425	0.589	<0.001
Laser	Placebo	2.231	0.589	<0.001

**Results of Tukey's test for mixed urinary incontinence**

Treatment group	Comparator	Mean difference	standard error	p
RF	Laser	-0.871	0.633	0.355
	Placebo	-2.025	0.591	0.002
Laser	Placebo	-1.154	0.616	0.149

**Key safety findings**

No safety data were reported.

## Study 13 Salvatore S (2020)

### Study details

<b>Study type</b>	Randomised controlled trial (NCT03754205)
<b>Country</b>	Greece and Italy
<b>Recruitment period</b>	2018 to 2020
<b>Study population and number</b>	n=58 (28 laser treatment, 30 sham) Postmenopausal women with genitourinary syndrome of menopause
<b>Age</b>	Mean 57.0 (laser), 58.4 (sham)
<b>Patient selection criteria</b>	Inclusion criteria: postmenopausal women with genitourinary syndrome of menopause diagnosis according to the definition by the International Society for the Study of Women's Sexual Health and The North American Menopause Society. Dryness and dyspareunia related to GSM had to be the 2 most bothersome symptoms in all women. Exclusion criteria: vulvodynia, vulvovaginitis, any vulvovaginal pathology, dryness, and dyspareunia induced for reasons other than GSM (such as previous pelvic radiotherapy or Sjögren's Syndrome), prior treatment with intravaginal energy-based devices, use of non-hormonal/hormonal local therapies (3 and 6 months before the screening process, respectively), other pathologies that could interfere with participants' compliance to the protocol, pelvic organ prolapse higher than stage 2 according to the Pelvic Organ Prolapse Quantification (POP-Q) staging system and a history of gynaecological or breast cancer.
<b>Technique</b>	All laser treatments (active or sham) were done using the microablative fractional CO <sub>2</sub> laser (SmartXide2 V2LR Monalisa Touch; DEKA, Italy). Patients had 3 treatment sessions at monthly intervals. Laser energy was released only in the active treatment group. Patients were not allowed to use any moisturisers or lubricants or hormonal treatments until the end of the study protocol.
<b>Follow-up</b>	4 months (1 month after third treatment session)
<b>Conflict of interest/source of funding</b>	None

### Analysis

Follow-up issues: There were no losses to follow up. Two patients allocated to active laser treatment dropped out for personal reasons irrelevant to the study.

Study design issues: Multicentre, randomised, placebo-controlled, double-blind trial. The laser parameters were manually inserted by authorised nurses and remained hidden to the participants. They were the only people with access to the patient's allocation. Patients were allocated to a treatment group by 1:1 block randomisation using an online program. The block sizes were 4, 6, and 8. Allocation concealment was done using sealed opaque envelopes. The envelopes were locked in a safe place with limited access. A sample size

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of 27 per group was calculated to give a power of 0.85 for the between-subjects main effect at an effect size of 0.36, a power of 0.95 for the within-subjects main effect at an effect size of 0.25, and a power of 0.95 for the interaction effect at an effect size of 0.25. With the assumption of a possible drop-out rate of 10%, the sample size increased to 30 patients per group. Primary endpoints were changes in dryness and dyspareunia intensity, measured using a VAS on a scale of 0 to 10.

Study population issues: There were no statistically significant differences between the 2 groups at baseline.

## Key efficacy findings

- Number of patients analysed: 58 (28 laser, 30 sham)

### Changes in symptoms after treatment mean (standard deviation); VAS

Group	Baseline	4 months	change	within group p value	between group p value
Dryness					
sham	7.5 (1.9)	5.6 (2.9)	-1.9 (2)	0.006	<0.001
active	8.0 (1.7)	2.4 (2.9)	-5.6 (2.8)	<0.001	
p	0.327	<0.001			
Dyspareunia					
sham	8.7 (1.4)	7.6 (1.9)	-1.1 (1.8)	0.176	<0.001
active	8.6 (1.5)	2.6 (2.6)	-6 (2.6)	<0.001	
p	0.822	<0.001			
Itching					
sham	3.1 (3.2)	1.8 (2.6)	-1.4 (1.9)	0.004	0.015
active	3.9 (3.1)	1.0 (2.1)	-2.9 (2.8)	<0.001	
p	0.282	0.255			
Burning					
sham	4.6 (3.4)	3.7 (3.4)	-1 (1.9)	0.047	0.014
active	3.6 (3)	1.4 (2.4)	-2.3 (2.8)	<0.001	
p	0.440	0.007			
Dysuria					
sham	0.9 (1.6)	0.6 (1.2)	-0.3 (1.5)	0.534	0.181
active	1.6 (2.4)	0.6 (1.5)	-0.9 (2.1)	0.016	
p	0.343	0.793			

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### Changes in FSFI and UDI-6 after treatment, mean (standard deviation)

Group	Baseline	4 months	change	within group p value	between group p value
FSFI total score					
sham	9.7 (7.8)	12.1 (8.3)	2.4 (4.9)	0.065	0.001
active	11.4 (8.2)	23.8 (6.6)	12.3 (8.9)	<0.001	
p	0.416	<0.001			
Desire					
sham	2.4 (1.1)	2.6 (1.3)	0.2 (1.3)	0.552	0.001
active	2.1 (1.1)	3.2 (0.9)	1.1 (1.0)	<0.001	
p	0.173	0.019			
Arousal					
sham	1.7 (1.9)	2.0 (1.8)	0.3 (1.0)	0.075	0.002
active	1.8 (1.6)	3.6 (1.1)	1.8 (1.5)	<0.001	
p	0.490	<0.001			
Lubrication					
sham	1.3 (1.6)	2.0 (1.7)	0.7 (1.2)	0.022	0.005
active	1.8 (1.6)	4.3 (1.5)	2.5 (2.0)	<0.001	
p	0.216	<0.001			
Orgasm					
sham	1.4 (1.8)	1.9 (1.8)	0.5 (1.0)	0.023	0.008
active	1.7 (1.6)	3.7 (1.5)	2.0 (1.7)	<0.001	
p	0.323	<0.001			
Satisfaction					
sham	1.8 (1.4)	2.1 (1.6)	0.3 (1.1)	0.217	0.005
active	2.5 (1.5)	4.3 (1.2)	1.7 (1.7)	<0.001	
p	0.056	<0.001			
Pain					
sham	1.0 (1.2)	1.5 (1.2)	0.4 (1.1)	0.070	<0.001
active	1.4 (1.5)	4.5 (1.7)	3.1 (2.0)	<0.001	
p	0.403	<0.001			
UDI-6					
sham	17.4 (21.5)	14.7 (21.3)	-2.6 (9.6)	0.061	0.363
active	24.0 (22.1)	15.9 (17.4)	-8.0 (15.3)	0.003	
p	0.229	0.532			

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## Study 14 Gambacciani M (2020b)

### Study details

<b>Study type</b>	Case series (survey)
<b>Country</b>	International; 43 countries (Asia, Australia, Europe, Middle East, North America and South America)
<b>Recruitment period</b>	2012 to 2019
<b>Study population and number</b>	n=113,174 Patients treated by vaginal erbium:YAG laser
<b>Age</b>	Not reported
<b>Patient selection criteria</b>	Users of non-ablative vaginal erbium:YAG laser treatment were invited to provide the number of patients treated and the number of observed laser-related adverse events.
<b>Technique</b>	Device: FotonaSMOOTH non-ablative thermal-only Er:YAG laser (Fotona, Slovenia)
<b>Follow-up</b>	Not reported
<b>Conflict of interest/source of funding</b>	2 authors are employees of Fotona, manufacturer of the medical device used in the study. No potential conflict of interest was reported by other authors.

### Analysis

**Study design issues:** A survey was sent to practitioners using the non-ablative vaginal erbium:YAG laser across the world. Users were invited to provide the number of patients treated with the laser and the number of observed laser-related adverse events.

Responses were collected from 535 practitioners, with a total of 113,174 patients. Out of the 535 respondents, 160 (30%) shared detailed information about the indications they treated in a population of 62,727 patients and 188 (35%) respondents provided information on the frequency of adverse events observed in their treated population of 43,095 patients. 6% (33/535) of respondents provided only qualitative, descriptive information about adverse events observed in their practices and 35% (188/535) of respondents provided quantitative data. Overall frequency of adverse events was reported as a quotient of the absolute number of adverse event occurrences and the total number of patients included in the safety analysis (n=43,095). The bootstrapping method was used for calculating confidence intervals to compensate for the uncertainty of the normality of the data distribution and small sample sizes of some observed adverse events. A bias-corrected and accelerated bootstrap interval (based on 1,000 bootstrap samples) was used, which corrects for bias and skewness in the distribution of bootstrap estimates.

**Population issues:** According to the survey data, 46% of patients had treatment for vaginal laxity, 31% of patients had stress urinary incontinence, 9% had genitourinary syndrome of menopause, 7% had pelvic organ prolapse and 7% had concurrent symptoms of vaginal laxity and stress urinary incontinence.

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## Key safety findings

### Overview of data collected

Region/country	Total number of sites	Total number of patients	Number of sites reporting on adverse events	Number of patients from sites reporting on adverse events
Asia	209	71,159	76	27,452
Australia	8	418	6	269
Europe	88	9,687	20	2,515
Middle East	109	20,800	79	11,642
North America	84	2,683	6	667
South America	37	8,427	1	550
Total	535	113,174	188	43,095

### Reported adverse events, mean frequency of adverse event occurrence, range of reported frequencies and calculated overall frequency

Adverse event	Number of respondents reporting the adverse event (n)	Mean of frequencies (%)	Range of frequencies (%)	Bootstrap interval	Overall frequency (%)
Vaginal discharge	47	6.53	0 to 100	3.69 to 9.67	4.01
Oedema	23	3.72	0 to 100	1.80 to 5.86	3.45
Pain during treatment	30	1.92	0 to 50.0	1.09 to 2.92	1.44
Pinpoint bleeding	33	1.55	0 to 50.0	0.87 to 2.36	1.16
Dryness	14	0.22	0 to 7.37	0.10 to 0.36	0.48
<i>De novo</i> urinary incontinence	13	0.28	0 to 14.3	0.12 to 0.49	0.21
Burns	7	0.10	0 to 10.0	0.02 to 0.22	0.16
Postoperative pain	7	0.47	0 to 37.7	0.07 to 1.06	0.10
Mild irritation of the introitus	4	0.56	0 to 70.0	0.007 to 1.70	0.44
Discolouration	2	0.10	0 to 16.7	0.003 to 0.32	0.02

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Itching	2	0.06	0 to 10.0	0.001 to 0.24	0.01
Infection	4	0.03	0 to 3.33	0.001 to 0.07	0.01
Abnormal bleeding	1	0.04	0 to 6.67	0.04 to 0.16	0.005
Dyspareunia	1	0.004	0 to 0.69	0.04 to 0.17	0.002

Overall frequency was calculated as the number of adverse events per patients included in the safety analysis (n=43,095).



## Validity and generalisability of the studies

- Several small randomised controlled trials were identified.
- There were different types of lasers and different treatment regimens used in the studies.
- One systematic review only included women who had been treated for breast cancer (Jha, 2019).
- The report from the US Food and Drug Administration MAUDE database included adverse events associated with radiofrequency devices as well as those associated with lasers (Guo, 2020). Vaginal atrophy was the indication for treatment in a small proportion of the patients.
- None of the studies reported follow-up beyond 2 years.

## Existing assessments of this procedure

A technical bulletin on intravaginal laser for genitourinary syndrome of menopause and stress urinary incontinence was published by the Society of Obstetricians and Gynaecologists of Canada in 2018 (Walter, 2018). The report includes the following recommendations:

1. 'In patients declining or with apparent contraindications to local estrogen, intravaginal laser therapy may be considered for short-term relief of symptoms associated with genitourinary syndrome of menopause'.
2. 'There is insufficient evidence to offer intravaginal laser therapy as an equivalent modality to local oestrogen for the treatment of genitourinary syndrome of menopause (including vulvovaginal atrophy, lower urinary tract symptoms, and sexual dysfunction)'.
3. 'There is insufficient evidence to offer intravaginal laser therapy as an effective modality for the treatment of stress urinary incontinence over alternate managements such as pelvic floor physiotherapy, incontinence pessaries, or surgery'.
4. 'Long-term use of intravaginal laser therapy for the management of genitourinary syndrome of menopause remains experimental and should remain within the protocols of well-executed clinical trials in attempts to establish its safety and efficacy'.

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A best practice consensus document, developed by the International Society for the Study of Vulvovaginal Disease and the International Continence Society, was published in 2019 (Preti, 2019). With regard to urogenital atrophy, the report states: 'There is currently not enough scientific data demonstrating efficacy and safety of LASER for treating vulvovaginal atrophy (level of recommendation 2b/3b, grade of recommendation C).'

A committee opinion on laser-based vaginal devices for treatment of stress urinary incontinence, genitourinary syndrome of menopause, and vaginal laxity was published by the International Urogynecological Association in 2019 (Shobeiri, 2019). The report concluded: 'The therapeutic advantages of nonsurgical laser-based devices in urogynecology can only be recommended after robust clinical trials have demonstrated their long-term complication profile, safety, and efficacy.'

## Related NICE guidance

Below is a list of NICE guidance related to this procedure.

### NICE guidelines

- Menopause: diagnosis and management. NICE guideline 23 (2015). Available from <http://www.nice.org.uk/guidance/NG23>

## Additional information considered by IPAC

### Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One Professional expert questionnaires for transvaginal laser therapy for urogenital atrophy was submitted and can be found on the [NICE website](#).

### Patient commentators' opinions

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the professional experts.

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## Company engagement

A structured information request was sent to 4 companies who manufacture a potentially relevant device for use in this procedure. NICE received 3 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

## Issues for consideration by IPAC

Below is a list of ongoing trials:

- LASER and Radiofrequency as Alternative Treatment of Vaginal Vulvar Atrophy in Women Treated for Breast Cancer (NCT04081805); RCT; Brazil; n=195; estimated study completion date September 2023.
- The Use of Laser in the Treatment of Atrophic Vulvovaginitis (NCT04297319); RCT; Argentina; n=70; estimated study completion date December 2021.
- Laser Vaginal Treatment for GSM (NCT04042766); RCT; Canada; n=60; estimated study completion date April 2022.
- Effect of Hybrid Laser 10600+1540 nm on Vaginal Atrophy-genitourinary Syndrome of the Menopause (NCT03956563); RCT; Spain; n=30; estimated study completion date August 2020.
- Vaginal CO2 Laser and the Genitourinary Syndrome of Menopause (NCT03754205); RCT; Greece; n=60; estimated study completion date January 2021.
- Clinical Study to Compare the Efficacy of Erbium-Yag Laser or CO2RE Intimate Laser With Sham (COER) (NCT04039555); RCT; Spain; n=136; estimated study completion date May 2020.
- Randomized, Controlled Trial With Hybrid Fractional Laser (NCT03647189); RCT; US; n=25; estimated study completion date January 2020.
- Vaginal Laser Therapy in Breast Cancer Survivors (NCT03738605); RCT; Greece; n=50; estimated study completion date August 2020.

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- Hybrid Fractional Laser for Symptoms of Genitourinary Syndrome of Menopause (NCT03178825); single group assignment; US; n=60; estimated study completion date March 2020.
- Laser Treatment of Genito-urinary Syndrome in Women (NCT03238053); RCT; Denmark; n=160; estimated study completion date December 2021.

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12. Eftekhar T, Ghorbani L, Ghanbari Z et al. (2021) Comparison of the effect of radiofrequency and laser treatment on mixed urinary incontinence and vulvovaginal atrophy in Iranian menopausal women: A randomized controlled trial. *International Journal of Women's Health and Reproduction Sciences* 9: 61-68
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## Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	12/01/2021	Issue 1 of 12, January 2021
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	12/01/2021	Issue 1 of 12, January 2021
MEDLINE (Ovid)	12/01/2021	1946 to January 08, 2021
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	12/01/2021	January 08, 2021
EMBASE (Ovid)	12/01/2021	1974 to 2021 January 11

### Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

### Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

### Literature search strategy

Number	Search term
1	Laser Therapy/
2	Lasers/ or Lasers, Gas/ or Lasers, Solid-State/
3	VAGINAL DISEASES/ or Vagina/ or VULVA/
4	2 and 3

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5	((treatment* or device* or therap* or appl* or fractional or surg* or scapel* or carbon dioxide* or non-ablative or transvaginal* or vagina* or procedure*) adj4 (laser* or lazer*)).ti,ab.
6	(Alma Pixel CO2 laser* or FEMILIFT CO2 LASER* or SMARTXIDE* or IntimaLase* or RenovaLase* or Incontilase* or Fotana*).mp.
7	1 or 4 or 5 or 6
8	exp Urinary Incontinence, Stress/
9	(SUI or (incont* adj4 (urin* or stress*))).ti,ab.
10	(sphincter adj4 (defic* or dysfunct*)).tw.
11	exp Urethra/
12	(urethra* adj4 hypermob*).ti,ab.
13	or/8-12
14	7 and 13
15	VAGINA/ or VULVA/
16	Atrophy/
17	PRURITUS/ or PRURITUS VULVAE/
18	DEHYDRATION/
19	DYSPAREUNIA/
20	16 or 17 or 18 or 19
21	15 and 20
22	VULVOVAGINITIS/ or Atrophic Vaginitis/ or Vaginitis/
23	FEMALE UROGENITAL DISEASES/
24	exp VULVAR DISEASES/
25	VAGINAL DISEASES/
26	vulvovagini*.ti,ab.
27	((vagina* or vulvovagina* or urogenital or genitourinary or genito-urinary) adj4 (atroph* or dry* or pruritis or sore* or irrita* or itch* or pain* or dyspar?euni* or dysuri* or discharge* or discomfort* or erosion or dehydrat* or thin* or inflam* or burn*)).ti,ab.
28	(vaginitis adj4 atroph*).ti,ab.
29	(genitourinary syndrome of the menopause or genito-urinary syndrome of the menopause or GSM).ti,ab.

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30	or/21-29
31	7 and 30
32	Animals/ not Humans/
33	14 not 32
34	31 not 32

## Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the [summary of the key evidence](#). It is by no means an exhaustive list of potentially relevant studies.

### Additional papers identified

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Adabi K, Golshahi F, Niroomansh S et al. (2020) Effect of the fractional CO2 laser on the quality of life, general health, and genitourinary symptoms in postmenopausal women with vaginal atrophy: a prospective cohort. <i>Journal of Lasers in Medical Sciences</i> 11: 65–9	Case series n=140 FU=3 months	The fractional CO2 laser can be effective in treating vaginal atrophy and urinary symptoms. It improved the quality of life and the sexual function of post-menopausal women.	Case series with more patients or longer follow-up are included.
Alexiades MR (2020) Fractional CO2 laser treatment of the vulva and vagina and the effect of postmenopausal duration on efficacy. <i>Lasers in Surgery and Medicine</i> DOI 10.1002/lsm.23247	Case series n=18 FU=12 months	Fractional CO2 laser treatment of the vulva and vagina resulted in statistically significant improvements in VHI and FSFI compared with baseline in postmenopausal population that were sustained to 12-month follow-up. Restoration of normal VHI was observed in a statistically significant greater percentage in the recently postmenopausal cohort (1–3 years) as compared with postmenopausal cohort of >3 years, suggesting that early intervention is	Case series with more patients or longer follow-up are included.

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		correlated with improved outcomes.	
Angioli R, Stefano S, Filippini Maurizio et al. (2020) Effectiveness of CO2 laser on urogenital syndrome in women with a previous gynecological neoplasia: a multicentric study. International Journal of Gynecological Cancer: official journal of the International Gynecological Cancer Society 30: 590–95	Case series n=165 FU=4 weeks	Dryness improved by 66%, dyspareunia improved by 59%, burning improved by 66%, pain at introitus improved by 54%, and itching improved by 54%. No side effects were seen in any sessions.	Case series with more patients or longer follow-up are included.
Areas F, Valadares ALR, Conde DM et al. (2019) The effect of vaginal erbium laser treatment on sexual function and vaginal health in women with a history of breast cancer and symptoms of the genitourinary syndrome of menopause: A prospective study. Menopause 26: 1052–8	Case series n=24 FU=1 month	Vaginal health improved, as shown by an increased overall score ( $p<0.001$ ). The effect size was large for vaginal elasticity, fluid volume, epithelial integrity, and moisture. The effect size was also statistically significant for the overall sexual function score and for the score in the dyspareunia domain.	Case series with more patients or longer follow-up are included.
Arroyo C (2017) Fractional CO2 laser treatment for vulvovaginal atrophy symptoms and vaginal rejuvenation in perimenopausal women. International Journal of Women's Health 9: 591–5	Case series n=21 FU=6 to 8 months	82% of the patients showed a statistically significant improvement in VHI ( $p<0.05$ ). Additionally, 81% of patients reported improvement in sexual gratification, 94% reported improvement in vaginal rejuvenation, and 100% reported satisfaction with treatment. VHI improvement remained significant at 6-8 months after treatments	Case series with more patients or longer follow-up are included.

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		( $p < 0.01$ ). Most patients (97%) reported no to mild discomfort with treatment.	
Arunkalaivanan A, Kaur H, Onuma O (2017) Laser therapy as a treatment modality for genitourinary syndrome of menopause: a critical appraisal of evidence. International Urogynecology Journal 28: 681– 5	Systematic review 4 studies (n=220)	The collated data suggest that laser therapy may be valuable as a nonhormonal therapeutic modality in the management of GSM. Higher quality of evidence from randomized controlled trials is required to establish the efficacy of laser treatment in the management of GSM.	Another systematic review with a meta-analysis has been included, which includes all 4 studies described in this review.
Athanasίου S, Pitsouni E, Douskos A et al. (2020) Intravaginal energy-based devices and sexual health of female cancer survivors: a systematic review and meta-analysis. Lasers in Medical Science 35 (no. 1)	Systematic review 8 studies (n=274)	Serious adverse events were not observed in any of the studies. Intravaginal laser therapies appear to have a positive effect on dyspareunia, vaginal dryness, and FSFI of cancer survivors. However, the quality of evidence is "very low". Further research with high-quality RCTs and long-term follow-up is needed to evaluate the value of energy-based devices as a therapeutic option for cancer survivors with sexual problems.	Review focuses on patients who have had breast cancer or gynaecological cancer. A similar systematic review is already included (Jha et al., 2019).
Athanasίου S, Pitsouni E, Grigoriadis T et al. (2019) Microablative fractional CO2 laser for the genitourinary syndrome of menopause: Up to 12-month results. Menopause 26: 248– 55	Case series n=94 FU=12 months	Laser therapy may provide significant improvement and/or absence of GSM symptoms up to 12 months follow-up, irrespectively to the number of laser therapies applied. Symptoms intensity 1 month after last laser therapy may be indicative of GSM symptoms intensity at 12 months. One month after third laser therapy is the critical time to decide	Case series with more patients or longer follow-up are included.

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		whether treatment extension should be offered.	
Athanasίου S, Pitsouni E, Antonopoulou S et al. (2016) The effect of microablative fractional CO <sub>2</sub> laser on vaginal flora of postmenopausal women. <i>Climacteric: the journal of the International Menopause Society</i> 19: 512–8	Case series n=53 FU=1 month	Microablative fractional CO <sub>2</sub> -laser therapy is a promising treatment for improving the vaginal health of postmenopausal women by helping repopulate the vagina with normally existing <i>Lactobacillus</i> species and reconstituting the normal flora to premenopausal status.	Study focuses on the effect of laser therapy on the vaginal microenvironment of postmenopausal women. Study is included in Pitsouni et al. (2017).
Athanasίου S, Pitsouni E, Falagas ME et al. (2017) CO <sub>2</sub> -laser for the genitourinary syndrome of menopause. How many laser sessions? <i>Maturitas</i> 104: 24–28	Case series n=55 FU=end of treatment session	Results of this study indicate that CO <sub>2</sub> -laser therapy may contribute to complete regression of dyspareunia and dryness and reestablishment of normal sexual function in postmenopausal women, in a dose-response manner. An extra fourth or fifth session may further increase the GSM symptom-free rate.	Case series with more patients or longer follow-up are included.
Baggish MS (2016) Fractional CO <sub>2</sub> laser treatment for vaginal atrophy and vulvar lichen sclerosus. <i>Journal of Gynecologic Surgery</i> 32: 309–17	Case series n=23 (with vaginal atrophy)	22/23 women who previously complained of dryness and discomfort had these symptoms alleviated and vaginal microscopic exam showed significant changes in colour, elasticity, and wetness following 3 courses of CO <sub>2</sub> laser fractional treatment; additionally 20/23 women had elimination of urinary frequency and urgency, 18/21 women had alleviation of dyspareunia.	Case series with more patients or longer follow-up are included.
Barber MA, Eguluz I (2016) Patient satisfaction with vaginal erbium laser	Case series n=40	More than 80% of patients presenting with vaginal dryness experienced improvement after the	Case series with more patients or

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<p>treatment of stress urinary incontinence, vaginal relaxation syndrome and genitourinary syndrome of menopause. Journal of the Laser and Health Academy 1: 18–23</p>		<p>procedure and 85% of these achieved important improvement.</p>	<p>longer follow-up are included.</p>
<p>Beorpi A, Campisciano G, Zanotta N et al. (2018) Fractional CO<sub>2</sub> laser for genitourinary syndrome of menopause in breast cancer survivors: clinical, immunological, and microbiological aspects. Lasers in Medical Science 33: 1047–54</p>	<p>Case series n=20</p>	<p>The significant reduction of clinical symptoms related to GSM after the CO<sub>2</sub> laser treatment supports its efficacy as therapy in postmenopausal cancer survivors. The exact mechanism responsible for the clinical improvement is still to be elucidated and further studies are needed in this field to clarify its long-term efficacy and other effects.</p>	<p>Case series with more patients or longer follow-up are included.</p>
<p>Behnia-Willison F, Sarraf S, Miller J et al. (2017) Safety and long-term efficacy of fractional CO<sub>2</sub> laser treatment in women suffering from genitourinary syndrome of menopause. European Journal of Obstetrics, Gynecology, and Reproductive Biology 213: 39–44</p>	<p>Case series n=102 FU=12 months</p>	<p>84% of patients had statistically significant improvement in their symptoms after CO<sub>2</sub> laser treatment. Scores on measures of sexual function, dyspareunia, and bothersomeness of sexual issues were improved from pretreatment to long-term (12-24 month) follow-up. Furthermore, there were improvements on measures of bladder function (p=0.001), prolapse (p=0.001), vaginal sensation (p=0.001), vaginal lubrication (p&lt;0.001) and urge incontinence (p=0.003) from the pretreatment assessment to the second assessment.</p>	<p>Case series with more patients or longer follow-up are included.</p>

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<p>Bhide AA, Khullar V, Swift S et al. (2019) The use of laser in urogynaecology. International Urogynecology Journal 30: 683– 92</p>	<p>Review 25 studies</p>	<p>The use of lasers to treat these conditions may seem appealing; however, the lack of good-quality evidence in the form of multi-centre randomised placebo-controlled trials is concerning. The safety and effectiveness of these laser devices have not been established. Use of lasers may lead to serious adverse events such as vaginal burns, scarring, dyspareunia and chronic pain. Randomised placebo-controlled trials in addition to formal evaluation of the laser devices are required before this treatment modality can be recommended.</p>	<p>A systematic review that is more specific to the indication of urogenital atrophy has been included.</p>
<p>Bojanini JF (2016) Treatment of Genitourinary syndrome of menopause with Erbium:YAG laser: a prospective study of efficacy and safety of the treatment for women after menopause of natural origin and therapy-induced menopause in breast cancer survivors. Journal of the Laser and Health Academy 2016, No.1</p>	<p>Non-randomised comparative study n=40 FU=12 months</p>	<p>Statistically significant reduction of vaginal dryness and dyspareunia was observed in all 3 groups at all follow-ups up to 12 months posttreatment. Also improvement in patients' sexual life measured by patient evaluation of intercourse avoidance was statistically significant in all 3 groups at all follow-ups. There were no serious side effects noted. Patients were highly satisfied with the treatment.</p>	<p>Studies with more patients or longer follow-up are included.</p>
<p>Bojanini JF, Mejía AM (2014) Laser treatment of vaginal atrophy in post-menopause and post-gynecological cancer patients. Journal of</p>	<p>Non-randomised comparative study n=40 FU=3 months</p>	<p>Results were similar for all treatment groups, independent of whether the patient had gynaecological cancer. Before treatment, all patients reported severe vaginal dryness and severe dyspareunia, and 98% of</p>	<p>Studies with more patients or longer follow-up are included.</p>

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the Laser and Health Academy 2014, No.1		patients avoided having sex because of the symptoms. At 3 month follow-up, 70% of patients reported no vaginal dryness and 30% had only mild vaginal dryness; 90% of the patients said they did not have dyspareunia and no longer avoided sexual intercourse, while only 10% of the patients remained with mild dyspareunia and rare sex avoidance.	
Burton R (2019) Vaginal Health and Wellness: Vaginal Laser Therapy. Plastic Surgical Nursing: official journal of the American Society of Plastic and Reconstructive Surgical Nurses 39: 97–102	Review	The CO <sub>2</sub> fractional laser treatment of VVA has been shown to alleviate symptoms of VVA by remodelling the vaginal epithelium and offers an additional effective treatment. The author's experience has shown short-term relief but lacks the evidence of longstanding relief of symptoms. This treatment is directed not only at symptom relief but also at counteracting the urogenital atrophy that occurs with menopause as well as other conditions. More data are needed to assess the long-term effects of this treatment.	All relevant studies are included in table 2 or the appendix.
Di Donato V, D'Oria O, Scudo M et al. (2020) Safety evaluation of fractional CO <sub>2</sub> laser treatment in post-menopausal women with vaginal atrophy: A prospective observational study. Maturitas 135: 34–39	Case series n=53 FU=median 6 months	Fractional CO <sub>2</sub> laser for treatment of VVA seems a safe therapeutic option. No severe complications occurred. A minority of patients reported mild complications, but these resolved without the need for treatment. Most discomfort was related to probe introduction and rotation. Overall, patients	Case series with more patients or longer follow-up are included.

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		were highly satisfied, and they would repeat laser treatment.	
Eder SE (2018) Early effect of fractional CO2 laser treatment in post-menopausal women with vaginal atrophy. Laser Therapy 27: 41–47	Case series n=28 FU=6 months	The mean VHIS score improved at 1 month (13.89 compared with 11.93 at baseline, $p<0.05$ ), and improved further at 3 and 6 months following all 3 laser treatments (16.43 and 17.46 respectively). Almost all vulvovaginal atrophy symptoms were improved at 1 month after the first treatment. A further statistically significant improvement in symptoms was noted at 3 and 6 months after the third laser session. The FSFI score increased (22.36 compared with 13.78 at baseline, $p<0.05$ ), and remained statistically significantly higher than baseline at the 3- and 6-month follow-up visits.	Case series with more patients or longer follow-up are included.
Eder SE (2019) Long-term safety and efficacy of fractional CO2 laser treatment in post-menopausal women with vaginal atrophy. Laser Therapy 28: 103–9	Case series n=20 FU=18 months	Almost all vulvovaginal atrophy symptoms were statistically significantly improved at 12 months after the third treatment compared to baseline and this improvement was sustained at 15 and 18 months. At 12 months, the total FSFI score increased significantly ( $n=15$ , $24.4 \pm 6.9$ ; $p<0.05$ ), and at the 15- and 18-month follow-up visits, the total FSFI remained higher than baseline ( $22.2 \pm 6.7$ , $25.8 \pm 6.6$ ).	Case series with more patients or longer follow-up are included.
Elia D, Gambacciani M, Berreni N et al. (2019) Genitourinary	review	The vaginal Er:YAG laser (VEL) technology acts only by thermal effect and not by	A systematic review with a meta-analysis has been included.

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<p>syndrome of menopause (GSM) and laser VEL: a review. <i>Hormone Molecular Biology and Clinical Investigation</i> 20190024</p>		<p>ablation on tissue. It is a safe solution in terms of side effects and potential complications. Studies have been increasing since 2012 and all demonstrate improvement in the GSM signs and symptoms, as well as an improved sexual life after VEL treatment. Double-blind, placebo-controlled, randomised studies are needed, to ultimately confirm the safety and effectiveness of VEL.</p>	
<p>Filippini M, Luvero D, Salvatore S et al. (2020) Efficacy of fractional CO2 laser treatment in postmenopausal women with genitourinary syndrome: A multicenter study. <i>Menopause</i> 27: 43–49</p>	<p>Case series n=645 FU=1 month</p>	<p>No side effects were reported. In all the parameters examined there were statistically significant improvements; dryness: before=8.30, after=2.97 (p&lt;0.0001), dyspareunia: before=8.70, after=3.51 (p&lt;0.0001); burning: before=6.12, after=1.78 p&lt;0.0001); vaginal orifice pain: before=8.07, after=2.94 (p&lt;0.0001); itching: before=6.09, after=1.32 (p&lt;0.0001).</p>	<p>Studies with more patients or longer follow up are included.</p>
<p>Filippini M, Del Duca E, Negosanti F et al. (2017) Fractional CO2 laser: from skin rejuvenation to vulvo-vaginal reshaping. <i>Photomedicine and Laser Surgery</i> 35: 171–5</p>	<p>Case series n=386 FU=2 months</p>	<p>After 3 treatments, patients reported improvement of symptoms (60% dryness, 56% burn, sensation, 49% dyspareunia, 56% itch, 73% soreness, and 49% vaginal introitus pain).</p>	<p>A larger and more recent study from the same author is included.</p>
<p>Franic D, Fistic I (2019) Laser therapy in the treatment of female urinary incontinence and genitourinary syndrome of</p>	<p>review</p>	<p>Additional studies are needed to explore the long-term safety and efficacy of various laser therapies for genitourinary symptoms.</p>	<p>A systematic review with a meta-analysis has been included.</p>

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menopause: an update. BioMed Research International 1576359			
Gambacciani M, Levancini M (2015) Short-term effect of vaginal erbium laser on the genitourinary syndrome of menopause. Minerva Ginecologica 67: 97–102	Case series n=65	VEL treatment statistically significantly improved vaginal dryness, dyspareunia, and mild-moderate SUI. Larger and long-term studies are needed to investigate the role of laser treatments in the management of GSM.	Case series with more patients or longer follow-up are included. Study is included in Pitsouni et al. (2017).
Gambacciani M, Levancini M, Cervigni M (2015) Vaginal erbium laser: the second-generation thermotherapy for the genitourinary syndrome of menopause. Climacteric: the journal of the International Menopause Society 18: 757–63	Non-randomised comparative study n=70 (45 laser)	VEL treatment induced a significant decrease of VAS of both vaginal dryness and dyspareunia ( $p<0.01$ ), with a significant ( $p<0.01$ ) increase of VHIS.	A larger and more recent study from the same author is included. Study is included in Pitsouni et al. (2017).
Gambacciani M, Levancini M (2017) Vaginal erbium laser as second-generation thermotherapy for the genitourinary syndrome of menopause: a pilot study in breast cancer survivors. Menopause 24: 316–9	Case series n=43 FU=18 months	This study suggests that the vaginal erbium laser is effective and safe for the treatment of genitourinary syndrome of menopause in breast cancer survivors.	Case series with more patients or longer follow-up are included. Included in Jha S et al., 2019.
Gambacciani M, Palacios S (2017) Laser therapy for the restoration of vaginal function. Maturitas 99: 10–15	Review	Although large randomised trials have not been reported, the evidence suggests that VEL can be offered as a safe and efficacious alternative to hormone replacement therapy for GSM, as well as a first-line treatment for mild	A systematic review with a meta-analysis has been included.

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		to moderate SUI, before surgical procedures are resorted to. Randomised studies are needed to compare laser treatments with other therapies, as well as to assess the duration of the therapeutic effects and the safety of repeated applications.	
Gaspar A, Brandi H, Gomez V et al. (2017) Efficacy of Erbium:YAG laser treatment compared to topical estriol treatment for symptoms of genitourinary syndrome of menopause. <i>Lasers in Surgery and Medicine</i> 49: 160–8	Non-randomised comparative study n=50 FU= up to 18 months	Er:YAG laser treatment successfully relieved symptoms of genitourinary syndrome of menopause and the results were more pronounced and longer lasting than topical estriol treatment.	Larger studies are included. Study is included in Pitsouni et al. (2017).
Gittens P, Mullen G (2019) The effects of fractional microablative CO2 laser therapy on sexual function in postmenopausal women and women with a history of breast cancer treated with endocrine therapy. <i>Journal of Cosmetic and Laser Therapy: official publication of the European Society for Laser Dermatology</i> 21: 127–31	Case series n=25	There was a statistically significant improvement in every domain of FSFI, WBFS, and FSDS-R when comparing baseline symptom scores to after treatment 3 symptom scores for all patients. The secondary outcome was to evaluate the differences, if any, in outcomes of sexual function between postmenopausal women and women with a history of breast cancer treated with endocrine therapy. Both groups had statistically significant improvements in many domains studied.	Case series with more patients or longer follow-up are included.
Hersant B, Werkoff G, Sawan D et al. (2020) Carbon dioxide laser treatment for vulvovaginal atrophy	Case series n=20 FU=6 months	This pilot feasibility study showed that CO <sub>2</sub> laser treatment appears to be an effective and safe method to improve the trophicity and	Case series with more patients or longer follow-up are included.

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<p>in women treated for breast cancer: Preliminary results of the feasibility EPIONE trial. <i>Annales de Chirurgie Plastique et Esthetique</i> doi.org/10.1016/j.anplas.2020.05.002</p>		<p>decrease vaginal mucosal dryness in women with vulvovaginal atrophy that developed after systemic breast cancer therapy.</p>	
<p>Knight C, Logan V, Fenlon D (2019) A systematic review of laser therapy for vulvovaginal atrophy/genitourinary syndrome of menopause in breast cancer survivors. <i>ecancer</i> 13: 988</p>	<p>Systematic review n=163 (6 studies)</p>	<p>There are a number of small-scale studies which all suggest an improvement in vaginal health in women who have had breast cancer, both objectively and subjectively. However, there are no large-scale studies which discuss the acceptability of the intervention and which were randomised. There is a need to undertake large-scale prospective, randomised controlled trials to fully explore the benefits of vaginal laser as a therapy for vaginal atrophy and to gain a better understanding of whether this treatment can reduce symptom burden and improve QoL for postmenopausal women, particularly after breast cancer treatment.</p>	<p>A systematic review with a meta-analysis is included.</p>
<p>Lang P, Dell JR, Rosen L et al. (2017) Fractional CO2 laser of the vagina for genitourinary syndrome of menopause: Is the out-of-pocket cost worth the outcome of treatment? <i>Lasers in Surgery and Medicine</i> 49: 882–85</p>	<p>Case series n=122</p>	<p>Patients reported vaginal dryness significantly improved following treatment (<math>p &lt; 0.05</math>). The frequency of intercourse increased from "once a month" to "few times a month" (<math>p &lt; 0.001</math>). 86% of patients were satisfied with their treatment results.</p>	<p>Case series with more patients or longer follow-up are included.</p>

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Lang P, Karram M (2017) Lasers for pelvic floor dysfunctions: is there evidence? Current Opinion in Obstetrics & Gynecology 29: 354–8	Review	The existing data is limited to mostly observational studies with additional quality randomised controlled trials and sham studies needed to ensure that physicians are providing the optimum evidence-based treatments to their patients. At the present time there is insufficient data to promote these therapies for stress incontinence, vaginal tightening, or other pelvic floor abnormalities.	A systematic review with a meta-analysis is included.
Lekskulchai O, Mairaing K, Vinayanuvattikhun N (2016) Fractional CO2 laser for vulvovaginal atrophy. Journal of the Medical Association of Thailand 99: 54–8	Case series n=112 FU=3 months	Fractional CO2 laser could ameliorate the vulvovaginal atrophy symptoms with at least 3 months of long lasting improvement of vaginal health with safety.	Case series with more patients or longer follow-up are included.
Lugo Salcedo F, Estrada Blanco Z (2020) Experience with ospemifene in patients with vulvovaginal atrophy treated with laser therapy: case studies. Drugs in Context 9: 2020-3-7	Case reports n=2	Postmenopausal women with VVA and severe dyspareunia can benefit from combined treatment with laser therapy and ospemifene. As shown in the case studies, ospemifene appears to be useful in preparing and conditioning the vaginal epithelium for laser therapy, at minimum allowing laser therapy to be performed and potentially augmenting its beneficial effects.	Case reports focusing on the use of ospemifene with laser therapy.
Marin J, Lipa G, Dunet E (2019) The results of new low dose fractional CO2 Laser - A prospective clinical study in France. Journal of Gynecology	Case series n=50 FU=6 months	The new micro-fractionated laser device with low dose energy - 18W, demonstrated significant improvement of genitourinary syndrome in both non-menopausal and post-menopausal women	Case series with more patients or longer follow-up are included.

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Obstetrics and Human Reproduction 101614		with no important adverse events.	
Mendoza N, Carrion R, Mendoza-Huertas L et al. (2020) Efficacy and safety of treatments to improve dyspareunia in breast cancer survivors: a systematic review. Breast Care	Systematic review 3 studies on laser	In the 3 prospective observational studies of this review, which globally analysed 113 women, the efficacy and safety of laser therapy were observed even when applied only once. There are not enough RCTs to determine its effectiveness and safety, although some trials are already in progress.	All relevant studies are already included in table 2 or the appendix.
Mothes AR, Runnebaum M, Runnebaum IB (2018) Ablative dual-phase Erbium:YAG laser treatment of atrophy-related vaginal symptoms in post-menopausal breast cancer survivors omitting hormonal treatment. Journal of Cancer Research and Clinical Oncology 144: 955–60	Case series n=16 FU=8 weeks	Pre-laser vaginal health index (VHI) scored 16 (SD 4.6) and post-laser VHI 20 (SD 3) with p=0.01. 94% (15/16) of patients were satisfied regarding symptom relief.	Case series with more patients or longer follow-up are included. Included in Jha S et al., 2019.
Mothes AR, Runnebaum M, Runnebaum IB (2018) An innovative dual-phase protocol for pulsed ablative vaginal Erbium:YAG laser treatment of urogynecological symptoms. European Journal of Obstetrics, Gynecology, and Reproductive Biology 229: 167–71	Case series n=71 FU=6 weeks	In patients with genitourinary syndrome of menopause, pre- and post-treatment VHI and pH differed significantly [15.3 +/- 4.5 compared with 19.9 +/- 2.8 (p<0.001) and 5.2 +/- 0.6 compared with 4.8 +/- 0.4 (p=0.024), respectively]. Overall, 82% (n=58) of patients were satisfied with the treatment, 84% (47/56) post-menopausal patients were satisfied.	Case series with more patients or longer follow-up are included.
Pagano I, Gieri S, Nocera F et al. (2017) Evaluation of the CO2	Case series n=33	Fractionated CO2 laser therapy is a safe, effective and easy-to-perform	Case series with more patients or

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laser therapy on vulvo-vaginal atrophy (VVA) in oncological patients: preliminary results. <i>Journal of Cancer Therapy</i> 8: 452–63	FU=3 months	treatment modality for menopause-related vaginal atrophy and stress urinary incontinence.	longer follow-up are included.
Pagano T, De Rosa P, Vallone R et al. (2018) Fractional microablative CO <sub>2</sub> laser in breast cancer survivors affected by iatrogenic vulvovaginal atrophy after failure of nonestrogenic local treatments: a retrospective study. <i>Menopause</i> 25: 657–62	Case series n=82	This study shows that CO <sub>2</sub> laser treatment is effective and safe in breast cancer patients with iatrogenic menopause. However, the optimal number of cycles to administer and the need for retreatment remain to be defined. Prospective trials are needed to compare CO <sub>2</sub> laser therapy with therapeutic alternatives.	Case series with more patients or longer follow-up are included.
Pagano T, De Rosa P, Vallone R et al. (2016) Fractional microablative CO <sub>2</sub> laser for vulvovaginal atrophy in women treated with chemotherapy and/or hormonal therapy for breast cancer: a retrospective study. <i>Menopause</i> 23: 1108–13	Case series n=26	Treatment resulted in a significant regression of vulvovaginal atrophy symptoms compared with baseline ( $p < 0.001$ in almost all cases). No adverse reactions were observed or reported by women.	Case series with more patients or longer follow-up are included.
Pearson A, Booker A, Tio M et al. (2019) Vaginal CO <sub>2</sub> laser for the treatment of vulvovaginal atrophy in women with breast cancer: LAAVA pilot study. <i>Breast Cancer Research and Treatment</i> 178: 135–40	Case series n=26 FU=12 weeks	There was significant improvement in each of the vulvovaginal atrophy symptoms: dryness ( $p < 0.001$ ), itch ( $p < 0.001$ ), burning ( $p = 0.003$ ), dysuria ( $p < 0.001$ ) and dyspareunia ( $p < 0.001$ ). Patients also reported improvement in sexual function on the FSFI ( $p \leq 0.001$ ).	Case series with more patients or longer follow-up are included.
Perino A, Calligaro A, Forlani F et al. (2015)	Case series	There was a statistically significant improvement in	Case series with more patients or

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<p>Vulvo-vaginal atrophy: a new treatment modality using thermo-ablative fractional CO<sub>2</sub> laser. <i>Maturitas</i> 80: 296–301</p>	<p>n=48 FU=30 days</p>	<p>vulvovaginal symptoms (vaginal dryness, burning, itching and dyspareunia) (<math>p &lt; 0.0001</math>) in patients who had 3 sessions of vaginal fractional CO<sub>2</sub> laser treatment. Overall, 92% of patients were satisfied or very satisfied with the procedure and experienced considerable improvement in quality of life. There were no adverse events due to fractional CO<sub>2</sub> laser treatment.</p>	<p>longer follow-up are included. Study is included in Pitsouni et al. (2017).</p>
<p>Perrone AM, Tesei M, Ferioli M et al. (2020) Results of a phase I-II study on laser therapy for vaginal side effects after radiotherapy for cancer of uterine cervix or endometrium. <i>Cancers</i> 12, 1639; doi:10.3390/cancers12061639</p>	<p>Case series n=43 FU=6 months</p>	<p>Laser therapy improved vaginal length and VHI in women having pelvic radiotherapy; prospective studies are needed.</p>	<p>Case series with more patients or longer follow-up are included.</p>
<p>Phillips C, Hillard T, Salvatore S et al. (2020) Lasers in gynaecology. <i>European Journal of Obstetrics and Gynecology and Reproductive Biology</i> 251: 146–55</p>	<p>review</p>	<p>The authors recommend further independently or nationally funded, large multicentre randomised controlled trials are needed to assess efficacy and safety of each laser as well as any dose related effects. There are several studies underway and results should be available over the next few years. Best practice in treatments for incontinence and prolapse would also dictate that if used, a database of indication, assessment, treatment regimes: including energy settings, number of passes</p>	<p>A systematic review with a meta-analysis is included.</p>

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		and follow up outcomes should be mandatory.	
Photiou L, Lin MJ, Dubin DP et al. (2019) Review of non-invasive vulvovaginal rejuvenation. Journal of the European Academy of Dermatology and Venereology DOI:10.1111/jdv.16066	review	It appears that there is more evidence in favour of the CO <sub>2</sub> laser than the erbium:YAG laser. Both lasers have more evidence than radiofrequency (RF). In conclusion, microablative CO <sub>2</sub> laser, erbium:YAG laser and RF may be offered to patients with vulvovaginal atrophy/genitourinary syndrome of menopause as an alternative or adjunct to conventional therapies. Further well-conducted controlled studies are needed.	A systematic review with a meta-analysis is included.
Pieralli A, Fallani MG, Becorpi A et al. (2016) Fractional CO <sub>2</sub> laser for vulvovaginal atrophy (VVA) dyspareunia relief in breast cancer survivors. Archives of Gynecology and Obstetrics 294: 841–6	Case series n=50 FU=mean 11 months	The treatment with fractionated CO <sub>2</sub> laser appeared to be a feasible and effective treatment for VVA dyspareunia in breast cancer survivors with contraindications to hormonal treatments.	Case series with more patients or longer follow-up are included.  Included in Jha S et al., 2019 and Pitsouni E et al., 2017.
Pitsouni E, Grigoriadis T, Falagas M et al. (2017) Microablative fractional CO <sub>2</sub> laser for the genitourinary syndrome of menopause: power of 30 or 40 W? Lasers in Medical Science 32: 1865–72	Case series n=50 FU=1 month	Comparison between 30 and 40 W revealed that mean improvement or presence of all GSM symptoms and clinical signs was not statistically significant different. CO <sub>2</sub> laser therapy may improve GSM symptoms and clinical signs. This improvement did not seem to associate to power of 30 or 40 W.	Case series with more patients or longer follow-up are included.
Pitsouni E, Grigoriadis T, Tsiveleka A et al. (2016) Microablative fractional CO <sub>2</sub> -laser therapy and the	Case series n=53 FU=4 weeks	This study suggests that intravaginal CO <sub>2</sub> -laser therapy for postmenopausal women with clinical signs and symptoms of GSM may be effective in improving	Case series with more patients or longer follow-up are included.

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genitourinary syndrome of menopause: An observational study. <i>Maturitas</i> 94: 131–6		both vaginal pathophysiology and reported symptoms.	Study is included in Pitsouni et al. (2017).
Quick AM, Zvinovski F, Hudson C et al. (2019) Fractional CO <sub>2</sub> laser therapy for genitourinary syndrome of menopause for breast cancer survivors. <i>Supportive Care in Cancer: official journal of the Multinational Association of Supportive Care in Cancer</i> <a href="https://doi.org/10.1007/s00520-019-05211-3">https://doi.org/10.1007/s00520-019-05211-3</a>	Case series n=64 FU=1 month	Fractional CO <sub>2</sub> laser treatment for breast cancer survivors is feasible and appears to reduce GSM symptoms across treatment and follow-up.	Case series with more patients or longer follow-up are included.
Rabley A, O'Shea T, Terry R et al. (2018) Laser therapy for genitourinary syndrome of menopause. <i>Current Urology Reports</i> 19: 83	Review	Although laser therapy for the treatment of the symptoms of GSM appears promising, there is currently a lack of high-level and long-term evidence regarding its safety and efficacy.	A systematic review with a meta-analysis is included.
Robinson D, Flint R, Veit-Rubin N et al. (2020) Is there enough evidence to justify the use of laser and other thermal therapies in female lower urinary tract dysfunction? Report from the ICI-RS 2019. <i>Neurourology and Urodynamics</i>	Review	While the evidence base supporting the use of laser therapy in GSM is relatively comprehensive, there remains a need for well-designed long-term studies to assess the efficacy and safety of these emerging technologies.	A systematic review with a meta-analysis is included.
Romero-Otero J, Lauterbach R, Aversa A et al. (2020) Laser-based devices for	Review	It is too early in the evolution and research of laser-based devices to make decisive recommendations regarding	A systematic review with a meta-analysis is included.

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female genitourinary indications: position statements from the European Society for Sexual Medicine (ESSM). Journal of Sexual Medicine 17: 841–8		vaginal treatments. There is need for randomised controlled trials with proper design for safety reasons, possible harm, and short- and long-term benefits for the different indications studied.	
Salvatore S, Nappi RE, Parma M et al. (2015) Sexual function after fractional microablative CO <sub>2</sub> laser in women with vulvovaginal atrophy. Climacteric: the journal of the International Menopause Society 18: 219–25	Case series n=77 FU=12 weeks	Fractional microablative CO <sub>2</sub> laser treatment is associated with a statistically significant improvement of sexual function and satisfaction with sexual life in postmenopausal women with vulvovaginal atrophy symptoms.	Case series with more patients or longer follow-up are included. Study is included in Pitsouni et al. (2017).
Salvatore S, Athanasiou S, Candiani M (2015) The use of pulsed CO <sub>2</sub> lasers for the treatment of vulvovaginal atrophy. Current Opinion in Obstetrics & Gynecology 27: 504–8	Review	Increasing evidence with histological and clinical data supports the use of pulsed CO <sub>2</sub> lasers in the treatment of vulvovaginal atrophy; however, no randomised control trial (sham compared with treatment) has yet been produced and no data on the duration of therapy are currently available.	A more recent systematic review with a meta-analysis is included.
Salvatore S, Pitsouni E, Del Deo F et al. (2017) Sexual function in women suffering from genitourinary syndrome of menopause treated with fractionated CO <sub>2</sub> laser. Sexual Medicine Reviews 5: 486–94	Review n=273 (6 studies)	Fractional CO <sub>2</sub> laser can improve sexual function in postmenopausal women affected by GSM by restoring a better trophism in the lower genitourinary tract.	Another systematic review, which includes more outcomes, is included.
Salvatore S, Nappi RE, Zerbinati N et al. (2014) A 12-week	Case series n=50	Fractional CO <sub>2</sub> laser treatment was effective to improve vulvovaginal	Case series with more patients or

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treatment with fractional CO <sub>2</sub> laser for vulvovaginal atrophy: a pilot study. Climacteric 17: 363–9	FU=12 weeks	atrophy symptoms (vaginal dryness, vaginal burning, vaginal itching, dyspareunia, dysuria; p<0.001) as well as the VHIS (13.1 ± 2.5 at baseline compared with 23.1 ± 1.9; p<0.001). Both physical and mental scores of quality of life were significantly improved in comparison with baseline (p<0.001). Satisfaction with the laser procedure was reported by 42 women (84%).	longer follow-up are included. Study is included in Pitsouni et al. (2017).
Samuels JB, Garcia MA (2019) Treatment to external labia and vaginal canal with CO <sub>2</sub> laser for symptoms of vulvovaginal atrophy in postmenopausal women. Aesthetic Surgery Journal 39: 83–93	Case series n=40 FU=12 months	Fractional CO <sub>2</sub> laser treatments were well tolerated and were associated with improvement in vaginal health and amelioration of symptoms of vulvovaginal atrophy. Histological changes in the epithelium and lamina propria after treatment correlated with clinical restoration of vaginal hydration and pH to premenopausal levels.	Case series with more patients or longer follow-up are included.
Siliquini GP, Tuninetti V, Bounous VE et al. (2017) Fractional CO <sub>2</sub> laser therapy: a new challenge for vulvovaginal atrophy in postmenopausal women. Climacteric: the journal of the International Menopause Society 20: 379–84	Case series n=87 FU=15 months	This study shows that CO <sub>2</sub> laser treatment induces a significant and long-lasting improvement of symptoms.	Case series with more patients or longer follow-up are included.
Singh P, Chong CYL, Han HC (2019) Effects of vulvovaginal laser therapy on postmenopausal	Case series n=45 FU=6 months	Vulvovaginal laser therapy appears to be a promising option for managing genitourinary symptoms of menopause. Further randomised controlled trials	Case series with more patients or longer follow-up are included.

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vaginal atrophy: A prospective study. Journal of Gynecologic Surgery 35: 99–104		with long-term follow-up data are needed before routine use of the therapy for this indication.	
Sipos AG, Kozma B, Poka R et al. (2019) The effect of fractional CO <sub>2</sub> laser treatment on the symptoms of pelvic floor dysfunctions: Pelvic Floor Distress Inventory-20 questionnaire. Lasers in Surgery and Medicine: 51: 882–6	Case series n=40 FU=4 weeks	Three sessions of microablative fractional CO <sub>2</sub> vaginal laser treatment significantly improves patient reported urinary and pelvic organ prolapse symptoms.	Case series with more patients or longer follow-up are included.
Sokol ER, Karram MM (2017) Use of a novel fractional CO <sub>2</sub> laser for the treatment of genitourinary syndrome of menopause: 1-year outcomes. Menopause 24: 810–4	Case series n=30 FU=1 year	Based on study data up to 1 year, the fractional CO <sub>2</sub> laser may be an effective and safe treatment for women suffering from symptoms of GSM, although additional studies with larger populations and placebo control is needed to confirm these results.	Case series with more patients or longer follow-up are included.
Sokol ER, Karram MM (2016) An assessment of the safety and efficacy of a fractional CO <sub>2</sub> laser system for the treatment of vulvovaginal atrophy. Menopause 23: 1102–7	Case series n=30 FU=3 months	In this sample, the data suggest that the fractional CO <sub>2</sub> laser is effective and safe for treatment of the symptoms associated with GSM.	Case series with more patients or longer follow-up are included. Study is included in Pitsouni et al. (2017).
Song S, Budden A, Short A et al. (2018) The evidence for laser treatments to the vulvo-vagina: Making sure we do not repeat past mistakes. The Australian & New Zealand Journal of	Systematic review n=761 (vulvovaginal symptoms) FU=none to 2 years	Current scientific evidence in support of laser therapy is limited to observational data and is not enough to demonstrate robust clinical safety and efficacy. While this treatment may well be safe and efficacious, these claims must be validated through large-scale	A systematic review with a meta-analysis is included.

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Obstetrics & Gynaecology 58: 148–62		randomised controlled trials, which can provide stronger evidence, to ensure responsible representation of this new treatment to the public.	
Tovar-Huamani J, Mercado-Olivares F, Grandez-Urbina JA et al. (2019) Efficacy of fractional CO <sub>2</sub> laser in the treatment of genitourinary syndrome of menopause in Latin-American Population: First Peruvian experience. Lasers in Surgery and Medicine 51: 509–15	Case series n=60 FU=4 months	In this sample, the data suggests that fractionated CO <sub>2</sub> laser is an effective alternative for GSM treatment with positive outcomes that persists over time.	Case series with more patients or longer follow-up are included.
Tranoulis A, Georgiou D, Michala L (2019) Laser treatment for the management of genitourinary syndrome of menopause after breast cancer. Hope or hype? International Urogynecology Journal 30: 1879–86	Systematic review n=192 (6 studies)	The findings suggest that lasers appear to be effective and practical treatment options in breast cancer survivors with GSM. Evidence on long-term effects is lacking. The rationale for repeated treatment remains uncertain. Randomised controlled trials that collate different frequencies, intensities and durations are warranted to ascertain a dose-response relationship and adherence.	A systematic review with a meta-analysis is included.
Vizintin Z, Lukac M, Kazic M et al. (2015) Erbium laser in gynecology. Climacteric: the journal of the International Menopause Society 18: 4-8	Review	The results show that SMOOTH-mode erbium laser seems to be an effective and safe method for treating vaginal laxity, stress urinary incontinence, pelvic organ prolapses and vaginal atrophy.	A more recent systematic review with a meta-analysis is included.

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