Menopause: The Journal of The North American Menopause Society
Vol. 27, No. 9, pp. 000-000
DOI: 10.1097/GME.0000000000001570

REVIEW - SYSTEMATIC

Variation in outcome reporting and measurement tools in clinical trials of treatments for genitourinary symptoms in peri- and postmenopausal women: a systematic review

Monica Michelle Christmas, MD,[1] Bonnie Song, BS,[1] Robin J. Bell, MD, PhD,[2] Stamatina Iliodromiti, MD, PhD,[3] Caroline Mitchell, MD,[4] Martha Hickey, MBChB,[5] and the International COMMA (Core OutcoMes in MenopAuse) Consortium

Abstract

Importance: Genitourinary symptoms affect 40% to 60% of postmenopausal women. Evidence-based approaches to diagnosing and managing these symptoms are limited by inconsistencies in outcomes and measures used in clinical trials.

Objective: The aim of the study was to systematically review all outcomes and measurement tools reported in randomized clinical trials of interventions for genitourinary symptoms associated with menopause.

Evidence Review: We searched PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to December 2018. Randomized controlled trials with a primary or secondary outcome of genitourinary symptoms associated with menopause, English language, and sample size of 20 or more women per study arm were included. Study characteristics, outcomes, and measurement methods were collected.

Findings: The search yielded 3,478 articles of which 109 met inclusion criteria. Forty-eight different outcomes were reported with ''atrophy'' as the most common (56/109, 51%) followed by measures of sexual function (19/109, 17%). Almost all (108/109, 99%) trials included patient-reported measures, with 21 different measures and 39 symptom combinations. Clinician-reported scales of vulvovaginal appearance were used in 36 of 109 (33%) trials, with extensive variation in what was measured and reported. Cytological measures from the vaginal epithelium were the most commonly used objective tools (76/109, 70%).

Conclusions and Relevance: There is heterogeneity in reported outcomes and measures used in clinical trials of treatments for genitourinary symptoms at menopause and uncertainty as to which outcomes best reflect patient priorities and symptoms. The findings from this systematic review have informed an international survey of stakeholders to determine priorities for outcome selection and reporting. This survey will then inform the development of a Core Outcome Set for use in future clinical trials by the COMMA (**C**ore **O**utco**M**es in **M**enop**A**use) consortium.

Key Words: Atrophic vaginitis – Genitourinary atrophy – Genitourinary outcome measures – Genitourinary syndrome of menopause – Urogenital aging – Vaginal atrophy – Vulvovaginal atrophy.

Video Summary: http://links.lww.com/MENO/A599.

In 2014, ''Genitourinary Syndrome of Menopause (GSM)'' was introduced to describe menopausal symptoms associated with the vulva, vagina, and lower urinary tract, providing some consistency in terminology.[1,2] How symptoms are, however, measured and the outcomes assessed varies widely in clinical trials, limiting comparisons between treatments and directly compromising evidence-based care.[3,4] Variation in outcome measures of treatments

Received January 17, 2020; revised and accepted March 2, 2020.
From the [1]Department of Obstetrics and Gynecology, University of Chicago, Chicago, IL; [2]Women's Health Research Program, School of Public Health and Preventive Medicine, Monash University, Victoria, Australia; [3]Women's Health Division, Blizard Institute, Queen Mary University London, London, UK; [4]Vincent Obstetrics and Gynecology, Massachusetts General Hospital, Boston, MA; and [5]Department of Obstetrics and Gynaecology, University of Melbourne and The Royal Women's Hospital, Victoria, Australia.

Funding/support: Internal funds from the Department of Obstetrics and Gynecology University of Chicago and University of Melbourne.
Financial disclosure/conflicts of interest: None reported.
Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's Website (www.menopause.org).
Address correspondence to: Monica Michelle Christmas, MD, Department of Obstetrics and Gynecology, University of Chicago, 5841 S Maryland MC2050, Chicago, IL 60637. E-mail: mchristmas@bsd.uchicago.edu

for the same condition prompted the development of the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[5] COMET promotes development and implementation of Core Outcome Sets (COS), standardized, condition-specific outcomes representing the minimum dataset to be reported in clinical trials.[6] Within COMET, the Core Outcomes in Women's and Neonatal Health initiative supports COS in women's and newborn health (http://www.crown-initiative.org/core-outcome-sets/).[7,8]

The **C**ore **O**utco**M**es in **M**enop**A**use (COMMA) initiative was established to achieve consensus on a minimum set of outcome measures to be included in future clinical trials in menopause. COMMA is a global consortium of clinicians, researchers, journals, funding bodies, and consumers developing COS for vasomotor[9] and genitourinary symptoms at menopause. The steering committee comprised an international group of clinicians and researchers from a range of geographical locations with expertise working in the field of menopause. See Supplementary Digital Content 2, http://links.lww.com/MENO/A601 for steering committee. The aim of this systematic review is to describe the range of outcomes and measures reported in clinical trials for genitourinary symptoms associated with menopause, not to determine the optimal measures or treatments. This first step is essential to development of a COS.[5] These findings have informed an international Delphi survey of clinicians, researchers, and consumers to identify their priority outcome measures for the final COS as a minimum dataset for future clinical trials.

This systematic review followed the standardized process for developing a COS (http://www.comet-initiative.org/studies/details/1359).[5,6]

Key Points

Question: What outcomes and measurement tools have been reported in randomized controlled trials (RCTs) of interventions for genitourinary symptoms associated with menopause?

Findings: One hundred nine RCTs evaluating interventions for genitourinary symptoms associated with menopause were included. Most trials used both patient-reported and clinician-reported measurement tools. There was, however, substantial heterogeneity in the outcomes assessed and measurement tools used.

Meaning: Our findings demonstrate the need for greater consistency in outcomes and measurement tools in clinical trials for genitourinary symptoms associated with menopause. Outcome measures should reflect the priorities of patients, clinicians, and researchers and enable the translation of research findings into evidence-based practice.

METHODS/LITERATURE SEARCH

Eligible studies had primary or secondary outcomes of menopause-associated genitourinary symptoms, were in English, and included 20 or more women per study arm. We excluded quasirandomized, observational, diagnostic, feasibility/pilot, and pharmacokinetic studies; secondary analyses; and conference abstracts. Institutional review board approval was not required.

PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched until December 2018 using keywords: vagina/vaginal/vulva/genitourinary/vulvovaginal/menopause/menopausal/climacteric/perimenopause/peri-menopause/perimenopausal/peri-menopausal/postmenopause/post-menopause/postmenopausal/post-menopausal/dyspareunia/dryness/atrophy/itching/irritation/pain/atrophic vaginitis/sexual dysfunction. See Supplementary Digital Content 1, http://links.lww.com/MENO/A600 for the search strategies. The review was completed by two authors (M.M.C. and B.S.). Discrepancies were resolved through discussion with the coauthors.

We used the Jadad scoring system to measure the quality of randomized controlled trials (RCTs) included in this systematic review. This is a standardized approach to measuring the methodological quality of included trials.[10] The Jadad score assigns one point for each measure of trial quality: (1) whether the trial was randomized, (2) whether an appropriate randomization method was used, (3) whether researchers and participants were blinded, (4) whether an appropriate method of blinding was used, and (5) whether all participants included in the trial were accounted for. Jadad scoring for each included trial in this systematic review was independently assessed by two reviewers and given a score of 0 to 5. Discrepancies were discussed and resolved. This evaluation of trial quality is recommended as part of the process for developing a COS.[5]

A process of scoring clinical trial reporting that has been widely used in the development of COS was used for COMMA.[11] This scoring system (MOMENT) is calculated from six questions about the pre-defined trial outcomes which are assigned one point each in the calculation of the total score: (1) Is the primary outcome clearly stated?; (2) Is the primary outcome clearly defined so that another researcher could reproduce this study (eg, how the outcome was measured and time points)?; (3) Are secondary outcomes clearly stated?; (4) Are the secondary outcomes clearly defined?; (5) Do the authors explain the use of the outcomes they have selected?; and (6) Are specific methods used to enhance the quality of the outcome measurement, for example, repeated measurements, training?

RESULTS

We identified 3,478 RCTs of which 109 RCTs met inclusion criteria[12-120] (Fig. 1). Studies were from 1979 to 2018, with data from $n = 30{,}792$ women and 34 countries. Almost all (104/109), included postmenopausal women, four included both peri- and postmenopausal women,[30,35,60,118] and one only perimenopausal women.[15] Eighteen excluded surgically menopausal women[14,18,19,21,23,25,46,49,50,52,56,58,68,83,87,92,96,111] and

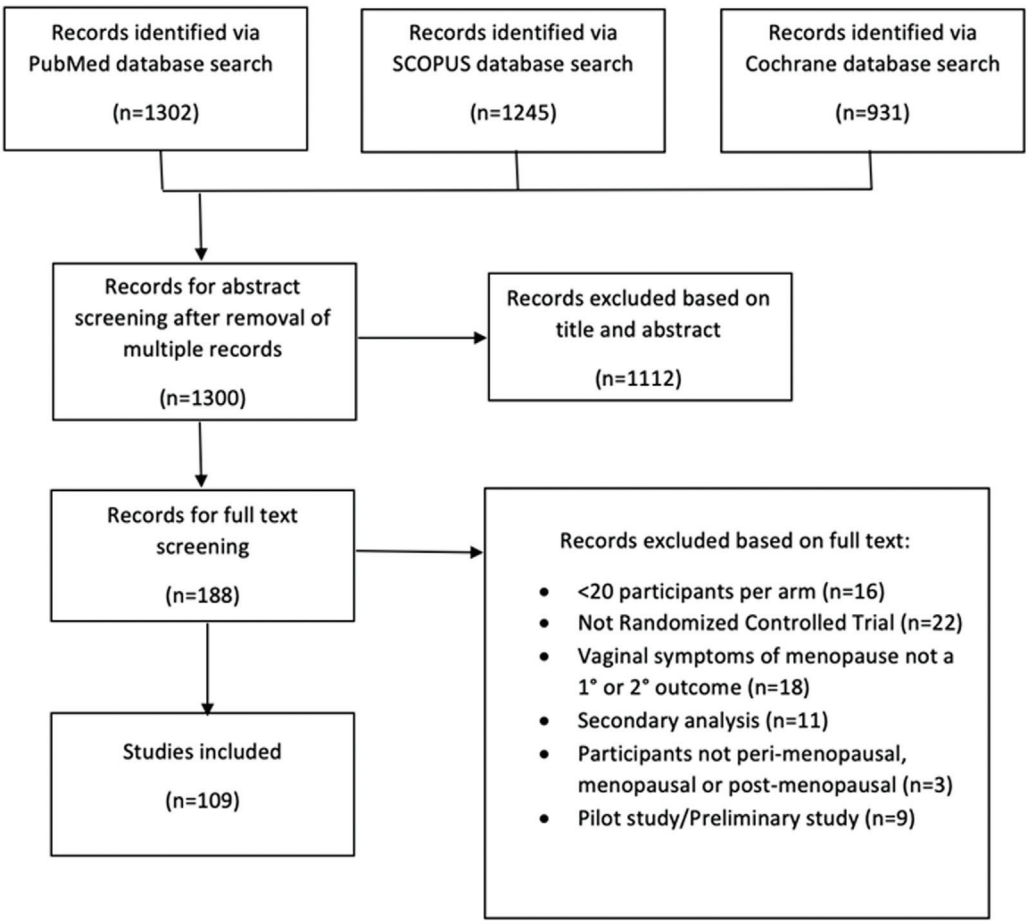

FIG. 1. Flowchart of study selection process.

two included only surgically menopausal women.[95,112] Few ($n = 4$) included women with a history of breast or gynecologic cancers.[12,26,27,33] See Supplementary Table 1, http://links.lww.com/MENO/A602 for list of all included trials.

The RCTs evaluated 153 interventions: single intervention trials ($N = 67$), 2 interventions ($N = 40$), and 3 interventions ($N = 2$). Seventy-five percent (115) of the interventions were either systemic or vaginal hormone therapies (HTs) including nine combination therapies (such as vaginal estrogen/raloxifene) (Table 1). Six (4%) were nonhormonal prescription therapies (such as antidepressants), and 32 (21%) nonhormonal, nonprescription therapies (such as herbal treatments).

Reported outcomes

Forty-eight unique outcome measures were identified from 109 trials. We categorized outcomes into three domains: (1) A single primary outcome related to a menopause-associated genitourinary symptom (71/109, 65%), (2) A secondary outcome related to a menopause-associated genitourinary symptom plus an unrelated primary outcome (13/109, 12%), and (3) Multiple primary outcomes which included menopause-associated genitourinary symptoms with other outcomes (25/109, 23%) (Table 2). Although most of the trials had a single primary outcome, this domain included 14 unique measures. In trials with more than 1 primary outcome or genitourinary symptoms as a secondary outcome, there were 21 and 13 unique outcomes, respectively.

Of all categories within these three domains, symptoms or signs associated with genital ''atrophy'' were the most commonly reported outcomes. This included ''vaginal atrophy,'', 'vulvovaginal atrophy,'' ''atrophic vaginitis,'' ''urogenital aging,'' and ''urogenital atrophy'' (56/109, 51%). The second most commonly reported outcome was sexual function (19/109, 17%). A wide range of outcomes was, however measured including dyspareunia, vaginal dryness during intercourse, and vaginal lubrication.

Because the term ''genitourinary syndrome of menopause'' was only introduced in 2014, prior publications have used a wide range of other terms.[2,121] Also, because specific diagnostic tools for GSM are still in development, even studies with GSM as an outcome measure include different definitions of symptoms.[3] For example, although the term ''atrophy'' was widely used, it was defined in 27 different ways (Table 3). In addition, some studies measured vulvovaginal or urogenital symptoms, and urogenital aging with a variety of symptom combinations.

TABLE 1. *Summary of trial interventions*

Trial interventions	Number of trials
Hormone therapies (HTs)	115
Localized to vaginal tissues	
Vaginal estrogen cream[13,36,38,45,50,51,61,68,83,90,95,99,100,102,105,110,117,120]	18
Vaginal estrogen tablet[28,31,34,50,71,82,88,99,107]	9
Vaginal estrogen ring[48,57,96,100,102,103,109,110,117]	9
Estrogen pessaries[42,48,103,109]	4
Vaginal estrogen softgel capsule[16,66]	2
Estrogen suppository[106]	1
Vaginal estrogen gel[65]	1
Estrogen vagitories[31]	1
Vaginal testosterone[27,38,105]	3
Ospemifene[20,41,78,79]	4
Dehydroepiandrosterone (DHEA)[12,29,63,74,81,85,93,94,98]	9
Systemic	
Oral estrogen[14,23,24,30,39,49,55,56,60,86,91,95,101,112,115,116,119]	17
Oral combined estrogen and progesterone[49,51,52,54,70,77,91,118]	8
Oral testosterone[17]	1
Oral combined estrogen and testosterone[112]	1
Oral estrogen and bazedoxifene[89]	1
Transdermal estrogen patch[14,25,47,62,80,84,97,108,114]	9
Intranasal estrogen[97]	1
HT combination trials	
Raloxifene + vaginal estrogen cream[72,111]	2
Vaginal estrogen ring + oral progesterone[104]	1
Vaginal estrogen cream + oral combined estrogen + progesterone[92]	1
Vaginal estrogen cream + vaginal testosterone cream[45]	1
Raloxifene and vaginal estrogen ring[96]	1
Vaginal estrogen tablet + vaginal lactobaccillus tablet[40]	1
Transdermal estrogen patch + levonorgesterol IUD[104]	1
Vaginal estrogen + pelvic floor rehabilitation[43]	1
Other	
Depot medroxyprogesterone acetate (DPMA)[39]	1
Tibolone[22,23,54,56,64,77]	6
Non-HT prescription therapies	6
Vaginal oxytocin gel[58,75]	2
Raloxifene[22,53]	2
Venlafaxine[30]	1
Pilocarpine[26]	1
Non-HT, nonprescription therapies	32
Hyaluronic acid[13,34,37,44]	4
Polyacrylic acid vaginal cream[38,105]	2
Dietary isoflavone[59,70,108]	3
Isoflavone[18,19,33,44,69]	5
Fennel[21,76,113]	3
Pueraria mirifica[73,83]	2
Black cohosh[46,60]	2
Black cohosh and St. John's wort[35]	1
Ginkgo biloba tablet[67]	1
Tribulus terrestris[15]	1
Sea buckhorn oil[32]	1
Multibotanical herbs[60]	1
Multibotanical herbs and soy diet counseling[60]	1
Vaginal moisturizer gel[28,87]	2
Oral calcium carbonate and vitamin D[53]	1
Vitamin E vaginal suppository[120]	1
Aromatherapy[67]	1

Measurement tools

Included studies used 21 patient-reported (Table 4) and 22 clinician-reported (Table 5) measurement tools for genitourinary symptoms. Clinician-reported tools included clinician observation of genital appearance and/or biological measures collected during genital examination. Most trials used a combination of patient-reported and clinician-reported tools.

Patient-reported measurement tools

The most commonly used patient-reported measure (37/109, 34%) was some version of a symptom severity/intensity scale. Included trials measured 38 different combinations of the following symptoms: vaginal dryness, itching, irritation, burning, dyspareunia, dysuria, pressure, tightness, nocturia, urinary incontinence, and urinary urgency.

Other common patient measurement tools were Most Bothersome Symptom severity scores (17/109, 15%) and symptom diaries (12/109, 11%) which included measures similar to those used in the severity scales. Again, there was wide variation in the symptoms assessed with studies evaluating a unique combination of symptoms including vaginal dryness, burning, itching, irritation, dyspareunia, bleeding after intercourse, and, urinary frequency, urgency, nocturia, and incontinence.

An additional measurement tool used by 12 trials was the Female Sexual Function Index (12/109, 11%). This validated questionnaire which measures sexual function includes patient-reported dyspareunia and vaginal lubrication. Other measurement tools included composite symptom severity scores (5/109, 4%), Visual Analogue Scales (6/109, 5%), investigator developed self-report questionnaires (5/109, 4%), and global symptom severity scores (4/109, 4%).

Although there was inconsistency in the symptoms measured and in the patient-reported measurement tools used, most tools evaluated the severity/intensity of symptoms and interference with daily living.

Clinician-reported measurement tools

There were eight different clinician-reported measurement scales. The most common was a 4-point severity scale of vulvovaginal appearance (23/109, 21%), the others were variations of 3- to 5-point scales (6/109, 5%). Of these 23 trials, 5 evaluated vaginal atrophy, dryness, pallor, integrity/friability, and petechiae; 5 evaluated vaginal color, secretions, epithelial integrity/friability, and surface thickness; and 3 evaluated vaginal dryness, integrity/friability, pallor, and petechiae. The remaining 10 trials each reported a unique combination of signs, such as vaginal elasticity, pallor, petechiae, signs of inflammation, and thickness of mucosa. Another seven trials used the Vaginal Health Index, which is a standardized tool evaluating vaginal elasticity, fluid volume, pH, epithelial integrity, and moisture on a scale of 1 to 5, from none to excellent.

Most trials assessed vaginal cytology (76/109, 70%). These findings informed a wide range of measures including the Vaginal Maturation Index (42/109, 38%); Vaginal Maturation Value (27/109, 25%); Karyopyknotic Index (8/109, 7%); the percentage of superficial, intermediate, and parabasal cells (3/109, 3%), of superficial and parabasal cells (14/109, 13%), of parabasal cells only (1/109, 1%). Vaginal pH was measured in half the studies (55/109, 50%).

Quality assessment of trials

Using the Jadad scoring system, more than half of the included RCTs were considered medium to high quality.

TABLE 2. *Outcome category distribution between the three domains of single primary outcomes, multiple primary outcomes, and secondary outcomes (with unrelated primary outcome)*

Outcome category		Number of trials
Single primary outcome genitourinary symptoms of menopause	Secondary outcome	
Vaginal atrophy[13,18,19,21,22,32,40,42,44,46,55,58,65,71,75,93,94,96,98,105,111,113]		22
Vulvovaginal atrophy[24,61,68,79,83,89]		6
Urogenital atrophy[100,102,103,110,117]		5
Urogenital atrophy[48]	Patient acceptability of treatment + physician assessment of symptoms	1
Vaginal dryness[20,26,33,37,81,87]		6
Vaginal dryness[12]	Dyspareunia + sexual function	1
Atrophic vaginitis[34,50,82,99,107]		5
Urogenital symptoms[51,70,88,104,116]		5
Dyspareunia[63,78,85]		3
Vaginal epithelium[108]		1
Vulvovaginal symptoms[28,80]		2
Vaginal symptoms[101]		1
Urogenital aging[109]		1
Sexual function[17,25,30,38,41,67,72,74,76,77,114,120]		12
Total		71
Multiple primary outcomes		
Vulvovaginal atrophy and dyspareunia[16,66,90]		3
Vulvovaginal atrophy and vaginal dryness[36]		1
Urogenital atrophy + stress urinary incontinence + recurrent urinary tract infection[43]		1
Vaginal cytology + vaginal dryness + hormone profile + menstrual cyclicity[60]		1
Urogenital atrophy, urinary incontinence, recurrent urinary tract infection[106]		1
Vaginal atrophy + vasomotor symptoms[49,52]		2
Vaginal atrophy + sexual function + health-related quality of life[22]		1
Dyspareunia + sexual function + quality of life[92]		1
Vaginal cytology + vasomotor symptoms[97]		1
Urogenital health + sexual health[45]		1
Vaginal atrophy + climacteric symptoms[35]		1
Vaginal epithelium + climacteric symptoms[53]		1
Menopausal symptoms + vaginal dryness[54]		1
Vaginal blood flow + sexual function[95]		1
Urogenital symptoms + vasomotor symptoms[57]		1
Vulvovaginal atrophy + vasomotor symptoms[84]		1
Climacteric syndrome (including vaginal dryness) + incidence of vaginal bleeding + impact on endometrium[56]		1
Menopausal symptoms (including vaginal dryness + dyspareunia)[69,118]		2
Menopausal symptoms (including vaginal dryness) + lipoprotein profile[112]		1
Menopausal symptoms (including vaginal dryness) + lipid profile + bone density[59]		1
Vaginal symptoms + vaginal health index + vaginal pH + vaginal cytology[73]		1
Total		25
Secondary outcome genitourinary symptoms of menopause	Other primary outcome	
Female Sexual Function Index + Sex hormone–binding globulin levels[14]	Sexual function	1
Dyspareunia and vaginal dryness[27]	Sexual function	1
Female Sexual Function Index[29]	Sexual function	1
Menopause Rating Scale Composite Score[15]	Total Menopausal Rating Scale	1
Vasomotor symptom + vaginal atrophy[23]	Vaginal bleeding pattern	1
Vaginal atrophy[64]	Vasomotor symptoms	1
Urogenital atrophy[86]	Vasomotor symptoms	1
Vulvovaginal atrophy + urogenital symptoms[91]	Vasomotor symptoms	1
Urogenital symptoms[119]	Vasomotor symptoms	1
Vulvovaginal atrophy[115]	Vasomotor symptoms	1
Vaginal cytology and hormone levels (FSH, estradiol, estrone)[47]	Vasomotor symptoms	1
Vaginal cytology + vasomotor symptoms (severity)[62]	Vasomotor symptoms (frequency)	1
Dyspareunia[39]	Vasomotor symptoms	1
Total		13

FSH, follicle-stimulating hormone.

Fifty-four (50%) of the included RCTs scored 5 out of 5 points, indicating the highest methodological quality. Eighteen (16%) scored 4 of 5, 23 (21%) scored 3 of 5, 11 (10%) scored 2 of 5, and 3 (2%) scored 1 of 5.

On the MOMENT scale, 32 trials (29%) scored 6 out of 6 points, 19 (17%) scored 5 of 6, 28 (26%) scored 4 of 6, 29 (27%) scored 3 of 6, and 1 (1%) scored 2 of 6.

DISCUSSION

This is the first systematic review to summarize the outcomes and measures used in RCTs of treatments for genitourinary symptoms associated with menopause. Our findings demonstrate considerable heterogeneity in both measures and outcomes and uncertainty about which outcomes best inform clinical management or matter most to patients. Our findings

TABLE 3. *Outcome definitions as specified by trial authors*

Outcome	Trial definition	Number of trials
Vaginal atrophy	Vaginal burning, dryness, itching/irritation, dyspareunia, dysuria[65]	1
	Vaginal burning, dryness, itching, dyspareunia[21]	1
	Vaginal burning, dryness, itching, secretion, dyspareunia[32]	1
	Vaginal burning, dryness, itching, soreness, dyspareunia[19]	1
	Vaginal discharge, dryness, itching, dyspareunia, pain/burning sensation[42]	1
	Vaginal discharge, dryness, irritation/itching, soreness, dyspareunia[40]	1
	Vaginal dryness and dyspareunia[18]	1
	Vaginal dryness, irritation/itching, dyspareunia[44,93,98]	3
	Vaginal dryness, itching, urinary incontinence[13]	1
	Vaginal dryness, itching, dyspareunia, dysuria, urinary urgency, vaginal mucosal bleeding [96,111]	2
	Vaginal dryness, dyspareunia, dysuria, irritation/itching, soreness, vaginal bleeding with sexual activity[71]	1
	Vaginal dryness, itching, dyspareunia, nocturia, urinary incontinence, urinary urgency[64]	1
	Vaginal dryness, itching/irritation, soreness[50,107]	2
	Dyspareunia and soreness[75]	1
Atrophic vaginitis	Vaginal discharge, dryness, irritation/itching, soreness, dyspareunia[34]	1
	Vaginal dryness, itching/irritation, dyspareunia, dysuria[99]	1
	Vaginal dryness, irritation/itching, dyspareunia, libido, dysuria[31]	1
	Vaginal burning, dryness, itching, dyspareunia, vaginal atrophy[82]	1
Vulvovaginal atrophy	Vaginal dryness[115]	1
	Vaginal dryness, dyspareunia, itching/irritation[16,66,89]	3
	Vaginal dryness, dysuria, itching[36]	1
	Difficulty passing urine, dryness, dyspareunia, dysuria, irritation/itching[24]	1
	Bleeding during intercourse, dryness, dyspareunia, irritation/itching, soreness[61]	1
	Dryness, dyspareunia[79]	1
	Vaginal dryness, soreness, irritation, dyspareunia, discharge[83]	1
	Burning, dryness, dyspareunia, itching[68]	1
	Vaginal dryness, dyspareunia, dysuria, irritation/itching, bleeding with sexual activity[84,90]	2
Urogenital atrophy	Vaginal dryness and dyspareunia[43,106]	2
	Vaginal dryness, itchiness, dyspareunia, dysuria, urinary urgency[48,100,117]	3
	Vaginal dryness, vulvar pruritus, dyspareunia, dysuria, pain at micturition, urinary urgency[103]	1
	Vaginal dryness, burning, pressure, tightness, itching, dyspareunia, urinary urgency, incontinence[102,110]	2
Vulvovaginal symptoms	Vaginal dryness, irritation/itching, dysuria, dyspareunia, and vaginal bleeding with sexual activity[80]	1
	Dryness, dyspareunia, itching[28]	1
Urogenital symptoms	Vaginal dryness, vulvar pruritus, dyspareunia, dysuria, and urinary urgency[104]	1
	Dryness, dyspareunia, urinary frequency, urgency[51]	1
	Vaginal dryness, dysuria, vaginal irritation[70]	1
	Vaginal atrophy (vaginal dryness, itching, burning, recurrent vaginitis, dyspareunia, petechiae, loss of libido) and urinary atrophy (dysuria, urinary frequency, urinary incontinence, more than two urinary tract infections in the past year)[88]	1
	Vaginal dryness, irritation, itching, difficulty passing urine, urine frequency, urine leakage, dyspareunia, pain after intercourse, bleeding after intercourse[57]	1
Urogenital aging	Vaginal dryness, vulvar pruritus, dyspareunia, dysuria, and urinary urgency[109]	1

TABLE 4. *Patient-reported measurement tools for genitourinary symptoms associated with menopause*

Patient-reported measurement tools	Number of trials
Abbreviated Sexual Function Questionnaire[74,120]	2
Brief Index of Sexual Functioning-Women[92]	1
Composite score of symptom severity[34,50,83,107,119]	5
Global score of symptom severity[40,65,96,111]	4
Female Sexual Function Index (FSFI)[12,14,17,27,28,29,30,38,41,67,76,77]	12
Investigator developed self-report questionnaire[25,26,53,88,95]	5
McCoy Female Sexuality Questionnaire[22,92,114]	3
Menopausal Rating Scale (MRS) Subscale[15,70,97]	3
Menopausal Specific Quality of Life (MENQOL)[74]	1
Most Bothersome Symptom (MBS) Score[12,24,28,42,61,63,66,68,71,78,79,80,81,84,89,93,98]	17
Three-point scale of symptom severity[43,106,117]	3
Four-point scale of symptom intensity[44,53]	2
Four-point scale of symptom severity[16,18-21,24,32,33,36,45,54,57,61,64,66,73,75,82,85,90,94,99,100,102,103,106,109,110]	28
Five-point scale of symptom severity[26,27,69]	3
0-7 Scale of symptom severity (modified from Kupperman Index)[112]	1
Sexual Activity Questionnaire[72,96]	2
Total Score Index[88]	1
Symptom Diary[31,39,51,68,84,86,87,88,92,96,111,115]	12
Visual Analogue Signals[13,31,37,42,56,118]	6
Wiklund Menopause Scale[60]	1
Yes/no presence of symptoms[48,53,59]	3

TABLE 5. *Clinician-reported measurement tools for genitourinary symptoms associated with menopause*

Clinician-reported measurement tools	Number of trials
Global score of investigator rated signs[96,111]	2
Five-point scale of sign severity[103]	1
Four-point scale of sign severity[16,21,24,31,34,36,50,57,63,65,71,81,82,85,86,88,90,93,96,100,111,109,119]	23
Four-point scale of growth of vaginal cultures (none-dominant growth)[51]	1
Three-point scale of sign severity[106,117]	2
Vaginal Health Index (VHI)[32,45,73,83,87,105,107]	7
Genital Health Clinical Evaluation Score[58,68]	2
Yes/no presence of signs[43,48,75,106]	4
Vaginal pH[13,16,18,20,21,24,27,28,34,36,37,40,42,43,48,51,55,57,61,63,65,66,68,70,71,73,78-81,84-86,89-94,96,98,100-107,109-111,113,117,119]	55
Karyopyncnotic index[22,23,43,51,59,106,108,116]	8
Vaginal Maturation Index[13,21,23,24,28,32,33,35,39,40,42,47,49-53,55,57,58,60-62,64,68,70,71,80,81,83-87,91,97,100-105]	42
Vaginal Maturation Value[18,19,22,27,31,34,44,46,48,53,58,59,62,65,70,71,73,96,103,105,107-109,111,113,116,117]	27
Percentage of superficial and parabasal cells[20,24,36,58,63,66,78-80,85,90,93,94,98]	14
Percentage of parabasal cells only[60]	1
Percentage of superficial, intermediate, and parabasal cells[40,89,92]	3
Vaginal cytology[13,18-24,27,28,31-36,39,40,42-44,46-53,55,57-66,68,70,71,73,78-81,83-87,89-94,96-98,100-109,111,113,116,117]	76
Vaginal biopsy[58,75]	2
Colposcopic examination[43,44,75]	3
Urinary pH[96,111]	2
Pulsatility Index[95]	1
Introital sonography[95]	1
Rating of vaginal cytologic maturation[95]	1

are consistent with previous systematic reviews comparing the efficacy of interventions for genitourinary symptoms in postmenopausal women, which concluded that meaningful comparisons between treatments for genitourinary symptoms were limited by inconsistency in outcome measures.[122-126] The purpose of our study was to identify and clarify the range of outcome measures used in RCTs for genitourinary symptoms associated with menopause and to assess the quality of these trials. These findings have informed an international survey of stakeholders that will determine priorities for which measures to include as a minimum dataset in future clinical trials for genitourinary symptoms associated with menopause as a COS. The intention was not to develop or evaluate a new outcome measure or to determine the optimum tool for measuring these symptoms. Nor was this systematic review designed to measure the effect sizes of treatments for genitourinary symptoms associated with menopause.

Almost all (99%, 108/109) included trials measured patient-reported symptoms, suggesting that the patient experience is considered an essential component of treatment efficacy. There was, however, considerable inconsistency in the tools selected, with 21 different patient-reported measures used and more than 39 combinations of symptoms assessed. This prevents aggregation and direct comparisons between treatments, limiting understanding about which treatments are most beneficial for patients. In addition, many different terms were used to describe similar symptoms. For example, some studies used ''vaginal atrophy,'' whereas others used ''vulvovaginal atrophy'' or ''urogenital atrophy'' or ''urogenital aging''. There was no consistency in how different studies defined these terms. Most included patient symptoms such as vaginal dryness, itching, and dyspareunia to define atrophy, whereas others included symptoms of both vaginal and vulvar itching/irritation/soreness. In addition, some studies also included urinary symptoms and pain or bleeding associated with intercourse.

Introducing the term ''genitourinary syndrome of menopause (GSM)'', by The North American Menopause Society in 2014 has improved consistency in reporting. Specific tools to measure GSM are, however, still in development. The US Food and Drug Administration (FDA) recommends three primary endpoints for clinical trials of treatment for genitourinary symptoms. These include mean change from baseline to week 12 of the Most Bothersome Symptom and the clinician obtained measures of vaginal pH and vaginal maturation index. Whether these measures, however, reflect clinical outcomes or patient priorities is uncertain (https://www.fda.gov/files/drugs/published/Estrogen-and-Estrogen-Progestin-Drug-Products-to-Treat-Vasomotor-Symptoms-and-Vulvar-and-Vaginal-Atrophy-Symptoms-—-Recommendations-for-Clinical-Evaluation.pdf).

Clinician-reported measures of genital appearance were commonly used, including visual features of the vulva and vagina and/or cellular features of the vaginal mucosa. Although these features may reflect decreased genital and vaginal estrogen exposure, their relevance to symptoms or treatment response is uncertain. Vaginal epithelial cytology was the most commonly used clinician-reported measure (76/109, 70%), and is required for FDA approval of new treatments for GSM. There was, however, considerable inconsistency in how vaginal cytology was measured. Some studies calculated the vaginal maturation index or vaginal maturation value, whereas others calculated the percentage of cells in the vaginal smear collected which were superficial, parabasal, or intermediate. Half of all studies measured vaginal pH, also an FDA requirement. This was also variably reported as a continuous variable or in some cases as a dichotomous variable (</> pH 5). Clinician estimates of genital appearance were used in approximately one third of studies with inconsistency in what was evaluated or reported. Although clinician-reported measures potentially add value to clinical

trials, only a few published studies have reported correlations between these measures and patient symptoms.[16,127] In addition, our findings from this systematic review clearly demonstrate that greater consistency is needed in collecting and interpreting clinician-reported measures.[3,122,124]

Strengths of this study include the comprehensive literature review and compilation of findings across a broad range of intervention studies using a rigorous methodological design and the inclusion of a standardized approach to measuring trial methodology for developing a COS.[5] Our measures of trial quality (using the Jadad scoring system) will inform the consensus discussion about which outcomes should be included in the COS and the most suitable and accurate tools to measure these outcomes. This systematic review was limited to studies including at least 20 participants per study arm, and excluded quasirandomized studies to enhance the quality of studies included and exclude pilot studies or those underpowered to demonstrate statistically or clinically significant differences between treatment arms. In total, 16 trials were excluded due to small sample size.[128-140] One of the excluded trials compared fractional CO_2 laser with topical estriol.[128] No new outcome measures were found in the excluded trials that were not already identified from larger studies.

Our systematic review was limited to trials published in English thereby introducing language bias, and almost half of the included trials were conducted in the United States (50/109, 46%). This is likely to have influenced the outcome measures used toward those endorsed by the FDA.[141]

Systemic and genitourinary menopausal symptoms vary by race/ethnicity and geographic location.[142,143] More information is needed about women's experiences across different racial/ethnic groups to inform the development of more clinically relevant measurement tools.[3] The next steps for developing a COS are international surveys of clinicians, researchers, and consumers to determine their priorities for which measures should be included in the final COS using the standardized Delphi approach and established methodology from the COMET process.[5,6] This Delphi process also allows respondents to identify additional outcomes that were not included in previous RCTs. The content of the final COS will be based on the findings of these Delphi surveys and through consensus at a face-to-face meeting scheduled at the World Menopause Society conference in May 2020.

CONCLUSION

This systematic review has identified a wide range of outcome measures used in RCTs of treatments for genitourinary symptoms associated with menopause with considerable heterogeneity in how these measures were applied and interpreted. The information obtained has informed an international survey of clinicians, researchers, and consumers to determine their views and priorities about outcomes to be collected in future clinical trials and identify outcomes missing from previous trials. In turn and in collaboration with researchers developing tools to measure GSM, this process will progress the development of optimal tools to reflect the patient experience.

Acknowledgments: The authors thank Gail Isenberg and Ernst Lengyel for critical review of the manuscript.

REFERENCES

1. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause* 2013; 20:888-902.
2. Portman DJ, Gass ML; Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Maturitas* 2014;79:349-354.
3. Shifren JL, Zincavage R, Cho EL, et al. Women's experience of vulvovaginal symptoms associated with menopause. *Menopause* 2019;26:341-349.
4. Lumsden MA, Davies M, Sarri G; Guideline Development Group for Menopause: Diagnosis and Management. Diagnosis and management of menopause: the National Institute of Health and Care Excellence (NICE) guideline. *JAMA Intern Med* 2016;176:1205-1206.
5. Williamson PR, Altman DG, Bagley H, et al. The COMET handbook: version 1.0. *Trials* 2017;18 (suppl 3):280.
6. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;13:132.
7. Duffy JMN, Hirsch M, Gale C, et al. A systematic review of primary outcomes and outcome measure reporting in randomized trials evaluating treatments for pre-eclampsia. *Int J Gynaecol Obstet* 2017;139:262-267.
8. Khan K; Chief Editors of Journals participating in The CROWN Initiative (Appendix 1). The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. *BJOG* 2016;123 (suppl 3):103-104.
9. Iliodromiti S, Wang W, Lumsden MA, et al. Variation in menopausal vasomotor symptoms outcomes in clinical trials: a systematic review. *BJOG* 2020;127:320-333.
10. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
11. Harman NL, Bruce IA, Callery P, et al. MOMENT—management of otitis media with effusion in cleft palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials* 2013;14:70.
12. Barton DL, Sloan JA, Shuster LT, et al. Evaluating the efficacy of vaginal dehydroepiandosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance). *Support Care Cancer* 2018;26:643-650.
13. Jokar A, Davari T, Asadi N, Ahmadi F, Foruhari S. Comparison of the hyaluronic acid vaginal cream and conjugated estrogen used in treatment of vaginal atrophy of menopause women: a randomized controlled clinical trial. *Int J Community Based Nurs Midwifery* 2016;4:69-78.
14. Taylor HS, Tal A, Pal L, et al. Effects of oral vs transdermal estrogen therapy on sexual function in early postmenopause: ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS). *JAMA Intern Med* 2017;177:1471-1479.
15. Fatima L, Sultana A. Efficacy of *Tribulus terrestris* L. (fruits) in menopausal transition symptoms: a randomized placebo controlled study. *Adv Integr Med* 2017;4:56-65.
16. Simon JA, Archer DF, Kagan R, et al. Visual improvements in vaginal mucosa correlate with symptoms of VVA: data from a double-blind, placebo-controlled trial. *Menopause* 2017;24:1003-1010.
17. Tungmunsakulchai R, Chaikittisilpa S, Snabboon T, Panyakhamlerd K, Jaisamrarn U, Taechakraichana N. Effectiveness of a low dose testosterone undecanoate to improve sexual function in postmenopausal women. *BMC Womens Health* 2015;15:113.
18. Rosa Lima SMR, Bernardo BFA, Yamada SS, Reis BF, Da Silva GMD, Longo Galvao MA. Effects of Glycine max (L.) Merr. soy isoflavone vaginal gel on epithelium morphology and estrogen receptor expression in postmenopausal women: a 12-week, randomized, double-blind, placebo-controlled trial. *Maturitas* 2014;78:205-211.
19. Lima SM, Yamada SS, Reis BF, Postigo S, Galvao da Silva MA, Aoki T. Effective treatment of vaginal atrophy with isoflavone vaginal gel. *Maturitas* 2013;74:252-258.

20. Portman D, Palacios S, Nappi RE, Mueck AO. Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: a randomised, placebo-controlled, phase III trial. *Maturitas* 2014;78:91-98.
21. Yaralizadeh M, Abedi P, Najar S, Namjoyan F, Saki A. Effect of Foeniculum vulgare (fennel) vaginal cream on vaginal atrophy in postmenopausal women: A double-blind randomized placebo-controlled trial. *Maturitas* 2016;84:75-80.
22. Nijland EA, Weijmar Schultz WC, Davis SR. Effects of tibolone and raloxifene on health-related quality of life and sexual function. *Maturitas* 2007;58:164-173.
23. Hammar ML, Van de Weijer P, Franke HR, Pornel B, Von Mauw EM, Nijland EA. Tibolone and low-dose continuous combined hormone treatment: vaginal bleeding pattern, efficacy and tolerability. *BJOG* 2007;114:1522-1529.
24. Simon JA, Reape KZ, Wininger S, Hait H. Randomized, multicenter, double-blind, placebo-controlled trial to evaluate the efficacy and safety of synthetic conjugated estrogens B for the treatment of vulvovaginal atrophy in healthy postmenopausal women. *Fertil Steril* 2008;90:1132-1138.
25. Huang A, Yaffe K, Vittinghoff E, et al. The effect of ultralow-dose transdermal estradiol on sexual function in postmenopausal women. *Am J Obstet Gynecol* 2008;198:265.e1-267.e1.
26. Loprinzi CL, Balcueva EP, Liu H, et al. A phase III randomized, double-blind, placebo-controlled study of pilocarpine for vaginal dryness: north Central Cancer Treatment group study N04CA. *J Support Oncol* 2011;9: 105-112.
27. Davis SR, Robinson PJ, Jane F, White S, White M, Bell RJ. Intravaginal testosterone improves sexual satisfaction and vaginal symptoms associated with aromatase inhibitors. *J Clin Endocrinol Metab* 2018;103:4146-4154.
28. Mitchell CM, Reed SD, Diem S, et al. Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms a randomized clinical trial. *JAMA Intern Med* 2018;178: 681-690.
29. Labrie F, Derogatis L, Archer DF, et al. Effect of intravaginal prasterone on sexual dysfunction in postmenopausal women with vulvovaginal atrophy. *J Sex Med* 2015;12:2401-2412.
30. Reed SD, Mitchell CM, Joffe H, et al. Sexual function in women on estradiol or venlafaxine for hot flushes: a randomized controlled trial. *Obstet Gynecol* 2014;124 (2 pt 1):233-241.
31. Dugal R, Hesla K, Sørdal T, Aase KH, Lilleeidet O, Wickstrøm E. Comparison of usefulness of estradiol vaginal tablets and estriol vagitories for treatment of vaginal atrophy. *Acta Obstet Gynecol Scand* 2000;79:293-297.
32. Larmo PS, Yang B, Hyssälä J, Kallio HP, Erkkola R. Effects of sea buckthorn oil intake on vaginal atrophy in postmenopausal women: a randomized, double-blind, placebo-controlled study. *Maturitas* 2014;79: 316-321.
33. Nikander E, Rutanen EM, Nieminen P, Wahlström T, Ylikorkala O, Tiitinen A. Lack of effect of isoflavonoids on the vagina and endometrium in postmenopausal women. *Fertil Steril* 2005;83:137-142.
34. Ekin M, Yaşar L, Savan K, et al. The comparison of hyaluronic acid vaginal tablets with estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. *Arch Gynecol Obstet* 2011;283: 539-543.
35. Chung DJ, Kim HY, Park KH, et al. Black cohosh and St. John's wort (GYNO-Plus) for climacteric symptoms. *Yonsei Med J* 2007;48: 289-294.
36. Archer DF, Kimble TD, Lin FDY, Battucci S, Sniukiene V, Liu JH. A randomized, multicenter, double-blind, study to evaluate the safety and efficacy of estradiol vaginal cream 0.003% in postmenopausal women with vaginal dryness as the most bothersome symptom. *J Womens Health (Larchmt)* 2018;27:231-237.
37. Chen J, Geng L, Song X, Li H, Giordan N, Liao Q. Evaluation of the efficacy and safety of hyaluronic acid vaginal gel to ease vaginal dryness: a multicenter, randomized, controlled, open-label, parallel-group, clinical trial. *J Sex Med* 2013;10:1575-1584.
38. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. *J Sex Med* 2014;11:1262-1270.
39. Lobo RA, McCormick W, Singer F, Roy S. Depo-medroxyprogesterone acetate compared with conjugated estrogens for the treatment of postmenopausal women. *Obstet Gynecol* 1984;63:1-5.
40. Jaisamrarn U, Triratanachat S, Chaikittisilpa S, Grob P, Prasauskas V, Taechakraichana N. Ultra-low-dose estriol and lactobacilli in the local treatment of postmenopausal vaginal atrophy. *Climacteric* 2013;16:347-355.
41. Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA. Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. *Climacteric* 2015;18:226-232.
42. Griesser H, Skonietzki S, Fischer T, Fielder K, Suesskind M. Low dose estriol pessaries for the treatment of vaginal atrophy: a double-blind placebo-controlled trial investigating the efficacy of pessaries containing 0.2 mg and 0.03 mg estriol. *Maturitas* 2012;71:360-368.
43. Capobianco G, Donolo E, Borghero G, Dessole F, Cherchi PL, Dessole S. Effects of intravaginal estriol and pelvic floor rehabilitation on urogenital aging in postmenopausal women. *Arch Gynecol Obstet* 2012;285:397-403.
44. Le Donne M, Caruso C, Mancuso A, et al. The effect of vaginally administered genistein in comparison with hyaluronic acid on atrophic epithelium in postmenopause. *Arch Gynecol Obstet* 2011;283:1319-1323.
45. Raghunandan C, Agrawal S, Dubey P, Choudhury M, Jain A. A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. *J Sex Med* 2010;7:1284-1290.
46. Hong SN, Kim JH, Kim HY, Kim A. Effect of black cohosh on genital atrophy and its adverse effect in postmenopausal women. *J Korean Soc Menopause* 2012;18:106-112.
47. Good WR, John VA, Ramirez M, Higgins JE. Double-masked, multicenter study of an estradiol matrix transdermal delivery system (Alora(TM)) versus placebo in postmenopausal women experiencing menopausal symptoms. *Clin Ther* 1996;18:1093-1105.
48. Casper F, Petri E. Local treatment of urogenital atrophy with an estradiol-releasing vaginal ring: a comparative and a placebo-controlled multicenter study. Vaginal Ring Study Group. *Int Urogynecol J Pelvic Floor Dysfunct* 1999;10:171-176.
49. Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril* 2001;75:1065-1079.
50. Rioux JE, Devlin C, Gelfand MM, Steinberg WM, Hepburn DS. 17Beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. *Menopause* 2000;7:156-161.
51. Chompootaweep S, Nunthapisud P, Trivijitsilp P, Sentrakul P, Dusitsin N. The use of two estrogen preparations (a combined contraceptive pill versus conjugated estrogen cream) intravaginally to treat urogenital symptoms in postmenopausal Thai women: a comparative study. *Clin Pharmacol Ther* 1998;64:204-210.
52. Tan D, Haines CJ, Limpaphayom KK, Holinka CF, Ausmanas MK. Relief of vasomotor symptoms and vaginal atrophy with three doses of conjugated estrogens and medroxyprogesterone acetate in postmenopausal Asian women from 11 countries: the Pan-Asia Menopause (PAM) study. *Maturitas* 2005;52:35-51.
53. Checa MA, Garrido A, Prat M, Conangla M, Rueda C, Carreras R. A comparison of raloxifene and calcium plus vitamin D on vaginal atrophy after discontinuation of long-standing postmenopausal hormone therapy in osteoporotic women. A randomized, masked-evaluator, one-year, prospective study. *Maturitas* 2005;52:70-77.
54. Elfituri A, Sherif F, Elmahaishi M, Chrystyn H. Two hormone replacement therapy (HRT) regimens for middle-eastern postmenopausal women. *Maturitas* 2005;52:52-59.
55. Marx P, Schade G, Wilbourn S, Blank S, Moyer DL, Nett R. Low-dose (0.3 mg) synthetic conjugated estrogens A is effective for managing atrophic vaginitis. *Maturitas* 2004;47:47-54.
56. Egarter C, Huber J, Leikermoser R, et al. Tibolone versus conjugated estrogens and sequential progestogen in the treatment of climacteric complaints. *Maturitas* 1996;23:55-62.
57. Speroff L. Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. *Obstet Gynecol* 2003;102:823-834.
58. Al-Saqi SH, Jonasson AF, Naessen T, Uvnas-Moberg K. Oxytocin improves cytological and histological profiles of vaginal atrophy in postmenopausal women. *Post Reprod Health* 2016;22:25-33.
59. Radhakrishnan G, Rashmi. Agarwal N, Vaid NB. Evaluation of isoflavone rich soy protein supplementation for postmenopausal therapy. *Pakistan J Nutr* 2009;8:1009-1017.

60. Reed SD, Newton KM, LaCroix AZ, Grothaus LC, Grieco VS, Ehrlich K. Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (HALT) Study. *Menopause* 2008;15:51-58.
61. Freedman M, Kaunitz AM, Reape KZ, Hait H, Shu H. Twice-weekly synthetic conjugated estrogens vaginal cream for the treatment of vaginal atrophy. *Menopause* 2009;16:735-741.
62. Archer DF, Pickar JH, MacAllister DC, Warren MP. Transdermal estradiol gel for the treatment of symptomatic postmenopausal women. *Menopause* 2012;19:622-629.
63. Archer DF, Labrie F, Bouchard C, et al. Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone). *Menopause* 2015;22:950-963.
64. Swanson SG, Drosman S, Helmond FA, Stathopoulos VM. Tibolone for the treatment of moderate to severe vasomotor symptoms and genital atrophy in postmenopausal women: a multicenter, randomized, double-blind, placebo-controlled study. *Menopause* 2006;13:917-925.
65. Cano A, Estevez J, Usandizaga R, et al. The therapeutic effect of a new ultra low concentration estriol gel formulation (0.005% estriol vaginal gel) on symptoms and signs of postmenopausal vaginal atrophy: results from a pivotal phase III study. *Menopause* 2012;19: 1130-1139.
66. Constantine GD, Simon JA, Pickar JH, et al. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. *Menopause* 2017;24:409-416.
67. Malakouti J, Jabbari F, Asghari-Jafarabadi M, Javadzadeh Y, Farshbaf-Khalili A. The Impact of ginkgo biloba tablet and aromatherapy inhaler combination on sexual function in females during postmenopausal period: a double-blind randomized controlled trial. *Int J Womens Health Reprod Sci* 2017;5:129-136.
68. Bachmann G, Bouchard C, Hoppe D, et al. Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. *Menopause* 2009;16:719-727.
69. Mucci M, Carraro C, Mancino P, et al. Soy isoflavones, lactobacilli, Magnolia bark extract, vitamin D3 and calcium. Controlled clinical study in menopause. *Minerva Ginecol* 2006;58:323-334.
70. Carmignani LO, Pedro AO, Montemor EB, Arias VA, Costa-Paiva LH, Pinto-Neto AM. Effects of a soy-based dietary supplement compared with low-dose hormone therapy on the urogenital system: a randomized, double-blind, controlled clinical trial. *Menopause* 2015;22:741-749.
71. Simon J, Nachtigall L, Gut R, Lang E, Archer DF, Utian W. Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. *Obstet Gynecol* 2008;112:1053-1060.
72. Kessel B, Nachtigall L, Plouffe L, Siddhanti S, Rosen A, Parsons A. Effect of raloxifene on sexual function in postmenopausal women. *Climacteric* 2003;6:248-256.
73. Manonai J, Chittacharoen A, Theppisai U, Theppisai H. Effect of Pueraria mirifica on vaginal health. *Menopause* 2007;14:919-924.
74. Labrie F, Archer D, Bouchard C, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. *Menopause* 2009;16:923-931.
75. Torky HA, Taha A, Marie H, et al. Role of topical oxytocin in improving vaginal atrophy in postmenopausal women: a randomized, controlled trial. *Climacteric* 2018;1-5.
76. Abedi P, Najafian M, Yaralizadeh M, Namjoyan F. Effect of fennel vaginal cream on sexual function in postmenopausal women: a double blind randomized controlled trial. *J Med Life* 2018;11:24-28.
77. Osmanağaoğlu MA, Atasaral T, Baltaci D, Bozkaya H. Effect of different preparations of hormone therapy on sexual dysfunction in naturally postmenopausal women. *Climacteric* 2006;9:464-472.
78. Portman DJ, Bachmann GA, Simon JA. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. *Menopause* 2013;20:623-630.
79. Bachmann GA, Komi JO; Ospemifene Study Group. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. *Menopause* 2010;17:480-486.
80. Bachmann GA, Schaefers M, Uddin A, Utian WH. Microdose transdermal estrogen therapy for relief of vulvovaginal symptoms in postmenopausal women. *Menopause* 2009;16:877-882.
81. Bouchard C, Labrie F, Archer DF, et al. Decreased efficacy of twice-weekly intravaginal dehydroepiandrosterone on vulvovaginal atrophy. *Climacteric* 2015;18:590-607.
82. Eriksen PS, Rasmussen H. Low-dose 17 beta-estradiol vaginal tablets in the treatment of atrophic vaginitis: a double-blind placebo controlled study. *Eur J Obstet Gynecol Reprod Biol* 1992;44:137-144.
83. Suwanvesh N, Manonai J, Sophonsritsuk A, Cherdshewasart W. Comparison of Pueraria mirifica gel and conjugated equine estrogen cream effects on vaginal health in postmenopausal women. *Menopause* 2017;24:210-215.
84. Simon JA, Bouchard C, Waldbaum A, Utian W, Zborowski J, Snabes MC. Low dose of transdermal estradiol gel for treatment of symptomatic postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2007;109:588-596.
85. Labrie F, Archer DF, Koltun W, et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. *Menopause* 2016;23:243-256.
86. Utian WH, Speroff L, Ellman H, Dart C. Comparative controlled trial of a novel oral estrogen therapy, estradiol acetate, for relief of menopause symptoms. *Menopause* 2005;12:708-715.
87. Nappi RE, Cagnacci A, Becorpi AM, et al. Monurelle Biogel vaginal gel in the treatment of vaginal dryness in postmenopausal women. *Climacteric* 2017;20:467-475.
88. Simunić V, Banović I, Ciglar S, Jeren L, Pavicić Baldani D, Sprem M. Local estrogen treatment in patients with urogenital symptoms. *Int J Gynaecol Obstet* 2003;82:187-197.
89. Kagan R, Williams RS, Pan K, Mirkin S, Pickar JH. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. *Menopause* 2010;17:281-289.
90. Kroll R, Archer DF, Lin Y, Sniukiene V, Liu JH. A randomized, multicenter, double-blind study to evaluate the safety and efficacy of estradiol vaginal cream 0.003% in postmenopausal women with dyspareunia as the most bothersome symptom. *Menopause* 2018;25:133-138.
91. Archer DF, Schmelter T, Schaefers M, Gerlinger C, Gude K. A randomized, double-blind, placebo-controlled study of the lowest effective dose of drospirenone with 17beta-estradiol for moderate to severe vasomotor symptoms in postmenopausal women. *Menopause* 2014;21:227-235.
92. Gast MJ, Freedman MA, Vieweg AJ, De Melo NR, Girao MJ, Zinaman MJ. A randomized study of low-dose conjugated estrogens on sexual function and quality of life in postmenopausal women. *Menopause* 2009;16:247-256.
93. Labrie F, Archer D, Bouchard C, et al. Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. *Menopause* 2009;16:907-922.
94. Labrie F, Archer DF, Bouchard C, et al. Intravaginal dehydroepiandrosterone (prasterone), a highly efficient treatment of dyspareunia. *Climacteric* 2011;14:282-288.
95. Long CY, Liu CM, Hsu SC, Wu CH, Wang CL, Tsai EM. A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women. *Menopause* 2006;13:737-743.
96. Pinkerton JV, Shifren JL, La Valleur J, Rosen A, Roesinger M, Siddhanti S. Influence of raloxifene on the efficacy of an estradiol-releasing ring for treating vaginal atrophy in postmenopausal women. *Menopause* 2003;10:45-52.
97. Odabaşi AR, Yüksel H, Demircan SS, Kaçar DF, Culhaci N, Ozkara EE. A prospective randomized comparative study of the effects of intranasal and transdermal 17 beta-estradiol on postmenopausal symptoms and vaginal cytology. *J Postgrad Med* 2007;53:221-227.
98. Labrie F, Archer D, Bouchard C, et al. High internal consistency and efficacy of intravaginal DHEA for vaginal atrophy. *Gynecol Endocrinol* 2010;26:524-532.
99. Hosseinzadeh P, Ghahiri A, Daneshmand F, Ghasemi M. A comparative study of vaginal estrogen cream and sustained-release estradiol vaginal tablet (Vagifem) in the treatment of atrophic vaginitis in Isfahan, Iran in 2010-2012. *J Res Med Sci* 2015;20:1160-1165.
100. Ayton RA, Darling GM, Murkies AL, et al. A comparative study of safety and efficacy of continuous low dose oestradiol released from a vaginal ring compared with conjugated equine oestrogen vaginal cream in the treatment of postmenopausal urogenital atrophy. *Br J Obstet Gynaecol* 1996;103:351-358.
101. Galhardo CL, Soares JM Jr, Simoes RS, Haidar MA, Rodrigues de Lima G, Baracat EC. Estrogen effects on the vaginal pH, flora and cytology in late postmenopause after a long period without hormone therapy. *Clin Exp Obstet Gynecol* 2006;33:85-89.

102. Bachmann G, Notelovitz M, Nachtigall L, Birgerson L. A comparative study of a low-dose estradiol vaginal ring and conjugated estrogen cream for postmenopausal urogenital atrophy. *Prim Care Update Ob/Gyns* 1997;4:109-115.
103. Henriksson L, Stjernquist M, Boquist L, Alander U, Selinus I. A comparative multicenter study of the effects of continuous low-dose estradiol released from a new vaginal ring versus estriol vaginal pessaries in postmenopausal women with symptoms and signs of urogenital atrophy. *Am J Obstet Gynecol* 1994;171:624-632.
104. Kalogirou D, Antoniou G, Karakitsos P, Kalogirou O, Antoniou D, Giannikos L. A comparative study of the effects of an estradiol-releasing vaginal ring combined with an oral gestagen versus transdermal estrogen combined with a levonorgestrel-releasing IUD: clinical findings and endometrial response. *Int J Fertil Menopausal Stud* 1996;41:522-527.
105. Fernandes T, Costa-Paiva LH, Pedro AO, Baccaro LF, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on vaginal atrophy: a randomized controlled trial. *Menopause* 2016;23: 792-798.
106. Dessole S, Rubattu G, Ambrosini G, et al. Efficacy of low-dose intravaginal estriol on urogenital aging in postmenopausal women. *Menopause* 2004;11:49-56.
107. Bachmann G, Lobo RA, Gut R, Nachtigall L, Notelovitz M. Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. *Obstet Gynecol* 2008;111:67-76.
108. Chiechi LM, Putignano G, Guerra V, Schiavelli MP, Cisternino AM, Carriero C. The effect of a soy rich diet on the vaginal epithelium in postmenopause: a randomized double blind trial. *Maturitas* 2003;45: 241-246.
109. Henriksson L, Stjernquist M, Boquist L, Cedergren I, Selinus I. A one-year multicenter study of efficacy and safety of a continuous, low-dose, estradiol-releasing vaginal ring (Estring) in postmenopausal women with symptoms and signs of urogenital aging. *Am J Obstet Gynecol* 1996;174 (1 pt 1):85-92.
110. Nachtigall LE. Clinical trial of the estradiol vaginal ring in the US. *Maturitas* 1995;22 (suppl):S43-S47.
111. Parsons A, Merritt D, Rosen A, Heath H 3rd, Siddhanti S, Plouffe L Jr. Effect of raloxifene on the response to conjugated estrogen vaginal cream or nonhormonal moisturizers in postmenopausal vaginal atrophy. *Obstet Gynecol* 2003;101:346-352.
112. Watts NB, Notelovitz M, Timmons MC, Addison WA, Wiita B, Downey LJ. Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause. *Obstet Gynecol* 1995;85:529-537.
113. Ghazanfarpour M, Shokrollahi P, Khadivzadeh T, et al. Effect of Foeniculum vulgare (fennel) on vaginal atrophy in postmenopausal women: A double-blind, randomized, placebo-controlled trial. *Post Reprod Health* 2017;23:171-176.
114. Nathorst-Boos J, Wiklund I, Mattsson LA, Sandin K, Von Schoultz B. Is sexual life influenced by transdermal estrogen therapy? A double blind placebo controlled study in postmenopausal women. *Acta Obstet Gynecol Scand* 1993;72:656-660.
115. Notelovitz M, Mattox JH. Suppression of vasomotor and vulvovaginal symptoms with continuous oral 17beta-estradiol. *Menopause* 2000;7: 310-317.
116. Van der Linden MC, Gerretsen G, Brandhorst MS, Ooms EC, Kremer CM, Doesburg WH. The effect of estriol on the cytology of urethra and vagina in postmenopausal women with genito-urinary symptoms. *Eur J Obstet Gynecol Reprod Biol* 1993;51:29-33.
117. Barentsen R, Van de Weijer PH, Schram JH. Continuous low dose estradiol released from a vaginal ring versus estriol vaginal cream for urogenital atrophy. *Eur J Obstet Gynecol Reprod Biol* 1997;71:73-80.
118. Vestergaard P, Hermann AP, Stilgren L, et al. Effects of 5 years of hormonal replacement therapy on menopausal symptoms and blood pressure-a randomised controlled study. *Maturitas* 2003;46:123-132.
119. Speroff L, Haney AF, Gilbert RD, Ellman H. Efficacy of a new, oral estradiol acetate formulation for relief of menopause symptoms. *Menopause* 2006;13:442-450.
120. Golmakani N, Parnan Emamverdikhan A, Zarifian A, Sajadi Tabassi SA, Hassanzadeh M. Vitamin E as alternative local treatment in genitourinary syndrome of menopause: a randomized controlled trial. *Int Urogynecol J* 2019;30:831-837.
121. Kim HK, Kang SY, Chung YJ, Kim JH, Kim MR. The recent review of the genitourinary syndrome of menopause. *J Menopausal Med* 2015;21: 65-71.
122. Biehl C, Plotsker O, Mirkin S. A systematic review of the efficacy and safety of vaginal estrogen products for the treatment of genitourinary syndrome of menopause. *Menopause* 2019;26:431-453.
123. Weber MA, Kleijn MH, Langendam M, Limpens J, Heineman MJ, Roovers JP. Local oestrogen for pelvic floor disorders: a systematic review. *PLoS One* 2015;10:e0136265.
124. Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. *Obstet Gynecol* 2014;124:1147-1156.
125. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2006;CD001500.
126. Lima SMRR, Honorato JV. Critical analysis of methods for assessing genitourinary syndrome of menopause used in clinical trials. *Menopause* 2019;26:1436-1442.
127. Tucker KM, Godha K, Mirkin S, Archer DF. Vaginal pH: a simple assessment highly correlated with vaginal morphology and symptoms in postmenopausal women. *Menopause* 2018;25:762-766.
128. Cruz VL, Steiner ML, Pompei LM, et al. Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO2 laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. *Menopause* 2018;25:21-28.
129. Mattsson LA, Cullberg G. A clinical evaluation of treatment with estriol vaginal cream versus suppository in postmenopausal women. *Acta Obstet Gynecol Scand* 1983;62:397-401.
130. Labrie F, Cusan L, Gomez JL, et al. Effect of intravaginal DHEA on serum DHEA and eleven of its metabolites in postmenopausal women. *J Steroid Biochem Mol Biol* 2008;111:178-194.
131. Palacios S, Castelo-Branco C, Cancelo MJ, Vazquez F. Low-dose, vaginally administered estrogens may enhance local benefits of systemic therapy in the treatment of urogenital atrophy in postmenopausal women on hormone therapy. *Maturitas* 2005;50:98-104.
132. Grimaldi EP, Restaino S, Inglese S, et al. Role of high molecular weight hyaluronic acid in postmenopausal vaginal discomfort. *Minerva Ginecol* 2012;64:321-329.
133. Mattsson LA, Cullberg G, Eriksson O, Knutsson F. Vaginal administration of low-dose oestradiol–effects on the endometrium and vaginal cytology. *Maturitas* 1989;11:217-222.
134. Gupta P, Ozel B, Stanczyk FZ, Felix JC, Mishell DR Jr. The effect of transdermal and vaginal estrogen therapy on markers of postmenopausal estrogen status. *Menopause* 2008;15:94-97.
135. Carranza-Lira S, MacGregor-Gooch AL. Differences in vaginal dryness according to hormone therapy schedule using pH test strip in two groups of postmenopausal women. *Int J Fertil Womens Med* 2004;49:88-90.
136. Nilsson K, Heimer G. Low-dose oestradiol in the treatment of urogenital oestrogen deficiency—a pharmacokinetic and pharmacodynamic study. *Maturitas* 1992;15:121-127.
137. Nachtigall LE. Comparative study: replens versus local estrogen in menopausal women. *Fertil Steril* 1994;61:178-180.
138. Manonai J, Songchitsomboon S, Chanda K, Hong JH, Komindr S. The effect of a soy-rich diet on urogenital atrophy: a randomized, cross-over trial. *Maturitas* 2006;54:135-140.
139. Cicinelli E, Di Naro E, De Ziegler D, et al. Placement of the vaginal 17beta-estradiol tablets in the inner or outer one third of the vagina affects the preferential delivery of 17beta-estradiol toward the uterus or periurethral areas, thereby modifying efficacy and endometrial safety. *Am J Obstet Gynecol* 2003;189:55-58.
140. Cicinelli E, Borraccino V, Petruzzi D, Mazzotta N, Cerundolo ML, Schonauer LM. Pharmacokinetics and endometrial effects of the vaginal administration of micronized progesterone in an oil-based solution to postmenopausal women. *Fertil Steril* 1996;65:860-862.
141. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) (2003). Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation. Federal Register. Draft content current as of August 24, 2018.
142. Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: results from an international survey on vaginal atrophy. *Maturitas* 2010;67:233-238.
143. Kingsberg SA, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. *J Sex Med* 2013;10:1790-1799.