National Institute for Health and Care Excellence

Draft for consultation

Pelvic floor dysfunction: prevention and non-surgical management

[Q] Pharmacological management

NICE guideline number tbc

Evidence review underpinning recommendations 1.6.33, 1.6.34 and a research recommendation in the NICE guideline

Evidence reviews

June 2021

Draft for consultation

These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

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Pharmacological management

Review question

What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

Introduction

Pharmacological management options are available to reduce the individual symptoms of pelvic floor dysfunction especially those of overactive bladder. Since other guidelines have already covered the effectiveness of pharmacological management of the symptoms of pelvic floor dysfunction for example: urinary incontinence (NG123), faecal incontinence (CG49) and pelvic organ prolapse (NG123), this review question only covers pharmacological management for pelvic floor dysfunction as a whole and not for each individual symptom.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women and young women (aged 12 years and older) with symptoms associated with pelvic floor dysfunction
Intervention	Pharmacological intervention used to target symptoms associated with pelvic floor dysfunction will include: • Intravaginal oestrogen • Anticholinergic medication • Mirabegron • Antidiarrhoeal drugs (for example: Loperamide hydrochloride) • Duloxetine • Desmopressin (low dose only, 25ug) • Muscle relaxants (for example: benzodiazepine) • Laxatives (for example: movicol / lactulose / macrogol / glycerol suppository) • Botulinum toxin A • Hylaurodinase • Amitriptyline • Gabapentin • Pregabalin • Capsaicin cream • Local anaesthetic gel • Opiates • Any combination of the listed interventions
Comparison	• Any of the above • No treatment/usual care • Pelvic floor muscle training (PFMT) (for example Kegel exercises, pelvic floor relaxation exercise, biofeedback training, weighted cones) • Behavioural training (for example bladder training, bladder diaries, seating training, urge suppression techniques)
Outcome	**Critical**

	• Subjective measure of change in the following symptoms: ○ urinary incontinence, ○ emptying disorders of the bladder, ○ faecal incontinence, ○ emptying disorders of the bowel, ○ pelvic organ prolapse, ○ sexual dysfunction ○ chronic pelvic pain syndromes • Health related QOL **Important** • Adherence to intervention • Anxiety and depression (only validated scales will be included) • Adverse events ○ leading to withdrawal/discontinuation ○ total reported events

PFMT: pelvic floor muscle training; QOL: quality of life

For further details, see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

Two randomised controlled trial (RCT) studies were included in this review (Crisp 2013, Holland 2019).

The included studies are summarised in Table 2.

Both studies compared vaginal diazepam to vaginal placebo, were set in the USA and had a 4 week follow- up (Crisp 2013, Holland 2019). Crisp 2013 treated women with high-tone pelvic floor dysfunction and Holland 2019 treated women with pelvic floor hypertonic disorder.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Crisp 2013 RCT USA	N=21 Women with high-tone pelvic floor dysfunction (n=10 diazepam n=11 placebo) Age, mean (SD): Diazepam 35.9 (12.0); Placebo 26.3 (16.6)	Diazepam 2g suppository containing 10mg of diazepam	Placebo 2g suppository	• Short-form health survey (physical and mental) • Patient global impression scale • Female sexual function index (FSFI)
Holland 2019 RCT USA	N=49 Women with pelvic floor hypertonic disorder (n=25 diazepam n=24 placebo) Age, median (95% CI): Diazepam 36 (27-52); Placebo 42 (31-52)	Diazepam Suppository containing 10mg of diazepam	Placebo Matching suppository	• POPDI-6 • CRADI-8 • UDI-6 • PFDI-20 • Dyspareunia score

CRADI: colorectal distress inventory; FSFI: female sexual function index; PFDI-20: Pelvic Floor Distress Inventory-20; POPDI: pelvic organ prolapse distress inventory; RCT: randomised controlled trial; SD: standard deviation; UDI-6: Urinary Distress Inventory

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of studies included in the evidence review

See the evidence profiles in appendix F.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Brief summary of the evidence

Diazepam vs Placebo

- Moderate to low quality evidence showed that diazepam had no effect on the physical or mental component of the short-form health survey or on the patient global impression of improvement or severity compared to placebo after both 2 and 4 weeks for women with high-tone pelvic floor dysfunction.
- Moderate quality evidence showed no reduction in distress (as measured by to the pelvic organ prolapse distress inventory) due to symptoms of pelvic floor dysfunction in women with pelvic floor hypertonic disorder.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that improvement in symptoms of pelvic floor dysfunction and health related quality of life were the most critical outcomes for this review question. These outcomes are likely to have the most impact on the woman's life, and the interventions included specifically target the management of these symptoms. Anxiety and depression were considered important outcomes as many women report the psychological impact that pelvic floor dysfunction has on their lives. Other important outcomes were adherence to the intervention and adverse events as these outcomes were considered the most relevant to determining if, and potentially why the intervention was or was not successful.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE and ranged from low to moderate. The evidence was downgraded due to the precision of the data, with either one or both of the confidence intervals crossing both the line of no effect and minimal important differences (MIDs).

No evidence was available for intravaginal oestrogen, anticholinergic medication, mirabegron, antidiarrhoeal drugs, duloxetine, desmopressin, laxatives, botulinum toxin A, hylaurodinase, amitriptyline, gabapentin, pregabalin, capsaicin cream, local anaesthetic gel or opiates.

Benefits and harms

The recommendation was made on the basis of two randomised trials (Crisp 2013, Holland 2019) which varied in quality and were based on a small sample of women. These studies showed that intravaginal diazepam had no effect on psychological or physical symptoms of pelvic floor dysfunction, including sexual dysfunction, urinary incontinence, pelvic organ prolapse and anal incontinence. In addition, and in view of the risks of dependency from diazepam usage, the committee decided that a recommendation not to use diazepam was indicated.

The evidence came from women with high muscle tone which is the group where potentially a benefit of diazepam could be expected (because of its muscle relaxing properties). However, the evidence did not show this to be the case. The committee therefore agreed that it is important to explicitly highlight that even in women with high muscle tone vaginal diazepam should not be given.

The committee made a research recommendation about topical intravaginal oestrogen, given that it is often offered to women with pelvic floor dysfunction but there is a lack of evidence about its effectiveness in this group.

Cost effectiveness and resource use

The committee recommended that vaginal diazepam should not be used due to a lack of evidence for its effectiveness and therefore cost-effectiveness.

No other recommendations were made but for cost-effective pharmacological management the committee made cross reference to the NICE guidelines on Urinary incontinence and pelvic organ prolapse in women (NG123), and for faecal incontinence referred to the NICE guideline on Faecal incontinence in adults: management (CG49).

Other considerations

The committee were aware that restricting search terms to pelvic floor dysfunction for this review would have missed out evidence relevant to urinary incontinence and potentially other symptoms where pelvic floor dysfunction was not mentioned in the title or abstract. That made it difficult to generalise from the very limited evidence that was identified. The committee therefore decided to cross refer to the NICE guidelines on Urinary incontinence and pelvic organ prolapse in women (NG123), and for faecal incontinence referred to the NICE guideline on Faecal incontinence in adults: management (CG49).

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.33, 1.6.34 and a research recommendation on vaginal oestrogen in the NICE guideline.

References

Crisp 2013

Crisp, C. C., Vaccaro, C. M., Estanol, M. V., Oakley, S. H., Kleeman, S. D., Fellner, A. N., & Pauls, R. N. Intra-vaginal diazepam for high-tone pelvic floor dysfunction: a randomized placebo-controlled trial. International urogynecology journal, 24(11), 1915-1923, 2013

Holland 2019

Holland, M. A., Joyce, J. S., Brennaman, L. M., Drobnis, E. Z., Starr, J. A., Foster Sr, R. T. Intravaginal diazepam for the treatment of pelvic floor hypertonic disorder: A double-blind, randomized, placebo-controlled trial. Female Pelvic Medicine & Reconstructive Surgery, 25(1), 76-81, 2019

Appendices

Appendix A – Review protocol

Review protocol for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42020176357
1.	Review title	Pharmacological management
2.	Review question	What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?
3.	Objective	The objective of this review is to determine whether pharmacological interventions can effectively improve symptoms (including urinary incontinence, pelvic organ prolapse, emptying disorders of the bladder, faecal incontinence, emptying disorders of the bowel, sexual dysfunction and chronic pelvic pain syndromes) associated with pelvic floor dysfunction.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE & Medline in Process • CINAHL or Emcare • PsycINFO Searches will be restricted by: • Date limit: 1980 onwards (see section 10 for justification) • English language • Human studies Other searches: • Inclusion lists of potentially relevant systematic reviews The full search strategies for MEDLINE database will be published in the final review.

ID	Field	Content
		For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
5.	Condition or domain being studied	The following symptoms will be addressed only if they are associated with pelvic floor dysfunction: urinary incontinence, emptying disorders of the bladder, faecal incontinence, emptying disorders of the bowel, pelvic organ prolapse, sexual dysfunction and chronic pelvic pain syndromes.
6.	Population	Inclusion: • Women and young women (aged 12 years and older) with symptoms associated with pelvic floor dysfunction Exclusion: • Studies which include women with urinary incontinence, emptying disorders of the bladder, faecal incontinence, emptying disorders of the bowel, pelvic organ prolapse, sexual dysfunction and chronic pelvic pain syndromes which are not due to pelvic floor dysfunction will be excluded. For example women who have urinary incontinence due to a neurological condition or pelvic cancer will be excluded. During the screening stage, the reported inclusion/exclusion criteria of studies will be examined carefully. We will only include studies which explicitly state "associated with pelvic floor dysfunction" therefore this will be a pragmatic decision based on the description of the condition provided by the study authors. If any ambiguity exists, at least two reviewers will make the final decision if to include or exclude the study. • Men • Babies and children
7.	Intervention/Exposure/Test	Pharmacological intervention used to target symptoms associated with pelvic floor dysfunction will include: • Intravaginal oestrogen • Anticholinergic medication • Mirabegron • Antidiarrhoeal drugs (for example: Loperamide hydrochloride) • Duloxetine • Desmopressin (low dose only, 25ug) • Muscle relaxants (for example: benzodiazepine) • Laxatives (for example: movicol / lactulose / macrogol / glycerol suppository) • Botulinum toxin A • Hylaurodinase • Amitriptyline • Gabapentin

ID	Field	Content
		• Pregabalin • Capsaicin cream • Local anaesthetic gel • Opiates • Any combination of the listed interventions
8.	Comparator/Reference standard/Confounding factors	• Any of the above • No treatment/usual care • Pelvic floor muscle training (PFMT) (for example Kegel exercises, pelvic floor relaxation exercise, biofeedback training, weighted cones) • Behavioural training (for example bladder training, bladder diaries, seating training, urge suppression techniques)
9.	Types of study to be included	• Systematic reviews of RCTs • RCTs Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
10.	Other exclusion criteria	• Pharmaceutical weight loss drugs (for example orlistat) • We will not include flavoxate, propantheline, imipramine, or systemic hormone replacement therapy interventions (in accordance with NG 123) • We will not include cannabi sativa, capsaicin patch, lacosamide, lamptigine, levetiacetam, morphine, oxcarbazepine, topiramate, tramadol, venlafaxine, sodium valporate (in accordance with CG173) • Studies with a mixed population (that is women with symptoms such as urinary incontinence which are associated with pelvic floor dysfunction and women with symptoms that are not associated with pelvic floor dysfunction) will be excluded, unless subgroup analysis for those women with symptoms associated with pelvic floor dysfunction has been reported • Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias • Percutaneous sacral nerve stimulation (also known as sacral neruomodulatoin) will be excluded as this is an invasive technique which involves an incision to the skin (in comparison to a puncture to the skin, for example in transcutaneous posterior tibial nerve stimulation which is included) • Only articles published after 1980 will be included. This was agreed by the committee as this is the date that the condition “pelvic floor dysfunction” was recognised to include agreed terminology on symptoms. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2815805/

ID	Field	Content
11.	Context	Studies which explicitly demonstrate a change in outcomes for symptoms associated with pelvic floor dysfunction will be prioritised for decision making in regards to recommendations, and these recommendations will apply to those receiving care in any healthcare settings (for example community, primary, secondary care). Specific recommendations for groups listed in the Equality Considerations section of the scope may be also be made as appropriate.

12.	Primary outcomes (critical outcomes)	• Subjective measure of change in the following symptoms:
		  ○ urinary incontinence,
		  ○ emptying disorders of the bladder,
		  ○ faecal incontinence,
		  ○ emptying disorders of the bowel,
		  ○ pelvic organ prolapse,
		  ○ sexual dysfunction
		  ○ chronic pelvic pain syndromes
		• Health related QOL
		
		For primary outcomes listed, only validated tools will be included (for example: ICIQ-UI, ICIQ-VS, BFLUTS, KHQ, UDI, ISI, ePAQ, POP-SS, PISQ, POPQ, FSFI, FIQL, GIQLI, PAC-QM, PAC –SYM, PDI, BPI)

13.	Secondary outcomes (important outcomes)	• Adherence to intervention
		• Anxiety and depression (only validated scales will be included)
		• Adverse events
		  ○ leading to withdrawal/discontinuation
		  ○ total reported events
		Outcomes are in line with those described in the core outcome set …..

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will not be performed for this review question.

ID	Field	Content
		Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. The full list of included and excluded studies will be sent to the committee for review and comment. A standardised form will be used to extract data from studies. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer. Information to be extracted from studies includes: study type, study dates, location of study, funding, inclusion and exclusion criteria, participant characteristics, and details of the intervention and comparator.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Quality assessment of individual studies will be performed using the following checklists • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. <u>Data Synthesis</u> Where possible, pair wise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events Mean differences or standardised mean differences will be calculated for continuous outcomes. <u>Heterogeneity</u> Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity sub-group analysis will be conducted 1) According to risk of bias of individual studies 2) According to socioeconomic status of population included

ID	Field	Content
		3) By ethnicity of included populations Exact subgroup analysis may vary depending on differences identified within included studies. . If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis. If heterogeneity remains above 80% reviewers will consider if meta-analysis is appropriate given the characteristics of included <u>Minimal important differences (MIDs)</u> For outcomes where validated tools are included (for example ICIQ), then the published MIDs will be used. Where no published MID is available, default MIDs will be used: • For risk ratios: 0.8 and 1.25. • For continuous outcomes: ○ For one study: the MID is calculated as +/-0.5 times the baseline SD of the control arm. ○ For two studies: the MID is calculated as +/-0.5 times the mean of the SDs of the control arms at baseline. If baseline SD is not available, then SD at follow up will be used. ○ For three or more studies (meta-analysed): the MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. ○ For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries. <u>Validity</u> The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	<u>Stratification</u> All data will initially be pooled for overall analysis; however, if data is available, separate analysis will also be conducted on: • Women who are pregnant or after pregnancy • Women before and after gynaecological surgery

ID	Field	Content			
		• Women aged 65 or older • Young women (aged 12 to 18) • Women with physical disabilities • Women with cognitive impairment • Women who are in perimenopause (pre- and post-) • According to those who do not identify themselves as women, but who have female pelvic organs *Recommendations will apply to all those with pelvic floor dysfunction unless there is evidence of a difference in these stratified groups*			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	July 2020			
22.	Anticipated completion date	August 2021			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☐
		Piloting of the study selection process		☐	☐
		Formal screening of search results against eligibility criteria		☐	☐
		Data extraction		☐	☐

ID	Field	Content
		Risk of bias (quality) assessment ☐ ☐
		Data analysis ☐ ☐
24.	Named contact	**5a. Named contact** National Guideline Alliance **5b Named contact e-mail** PreventionofPOP@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Alliance
25.	Review team members	• NGA technical team
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10123/
29.	Other registration details	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=176357
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

ID	Field	Content	
		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Pelvic floor dysfunction	
33.	Details of existing review of same topic by same authors	No applicable	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

BFLUTS: Bristol Female Lower Urinary Tract Symptoms Questionnaire; BPI: Brief pain inventory; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; ePAQ: Electronic personal health questionnaire; FIQL: Faecal incontinence quality of life scale; FISI: Faecal incontinence severity index; GIQLI: Gastrointestinal quality of life index; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ICIQ-UI: International Consultation on Incontinence Questionnaire- Urinary incontinence; ICIQ-VS: International Consultation on Incontinence questionnaire – vaginal symptoms; ISI: Incontinence symptom index; KHQ: Kings health questionnaire; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PAC-QL: patient assessment of constipation - quality of life; PAC-SYM: Patient assessment of constipation symptoms; PDI: Pain disability index; PFMT: pelvic floor muscle training; PISQ: Pelvic organ prolapse/urinary incontinence sexual questionnaire; POPQ: Pelvic organ prolapse quantification system; POP-SS: Pelvic organ prolapse symptom score; QoL: Quality of Life; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation: UDI: Urinary distress index

Appendix B – Literature search strategies

Literature search strategies for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

Clinical Search

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2020 May 26; **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to May 26, 2020
Date of last search: 27 May 2020

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Pelvic Floor/ or Pelvic Floor Disorders/
2	1 use ppez
3	pelvis floor/ or pelvic floor disorder/
4	3 use emczd
5	(pelvi$ adj (floor$ or diaphragm$) adj3 (dysfunction$ or disorder$ or fail$ or impair$ or incompeten$ or insufficien$ or dyssynerg$ or symptom$ or laxity or change$ or care$ or health$ or wellbeing$ or well-being$ or prevent$ or rehabilitat$ or weak$ or hypertonic$ or overactiv$ or over-activ$)).tw.
6	(pelvi$ adj (dysfunction$ or disorder$ or fail$ or impair$ or incompeten$ or insufficien$ or dyssynerg$ or symptom$ or laxity or care$ or health$ or wellbeing$ or well-being$ or prevent$ or rehabilitat$ or weak$ or hypertonic$ or overactiv$ or over-activ$)).tw.
7	or/2,4-6
8	Estrogens/ use ppez
9	"Estrogens, Conjugated (USP)"/ use ppez
10	Estradiol/ use ppez
11	Estriol/ use ppez
12	estrogen/ use emczd
13	conjugated estrogen/ use emczd
14	estrogen derivative/ use emczd
15	estradiol/ use emczd
16	estriol/ use emczd
17	((oestrogen$ or estrogen$ or oestradiol$ or estradiol$ or oestriol$ or estriol$ or oestron$ or estron$) adj2 (local or vagina$ or intra-vagina$ or intravaginal$ or topical)).tw.
18	or/8-17
19	Adrenergic beta-3 Receptor Agonists/ use ppez
20	beta 3 adrenergic receptor stimulating agent/ use emczd
21	beta 3 adrenergic receptor/ use emczd
22	mirabegron/ use emczd
23	vibegron/ use emczd
24	solabegron/ use emczd
25	(mirabegron$ or myrbetriq$ or betmiga$ or YM-178$ or vibegron$ or MK-4618$ or solabegron$ or GW427353$).tw.
26	or/19-25
27	Antidiarrheals/ use ppez
28	Loperamide/ use ppez
29	Diphenoxylate/ use ppez
30	antidiarrheal agent/ use emczd
31	loperamide/ use emczd
32	diphenoxylate/ use emczd
33	(anti-diarrh?eal$ or antidiarrh?eal$ or loperamide$ or Imodium$ or Imotil$ or diphenoxylate$ or Lomotil$).tw.
34	or/27-33
35	Duloxetine Hydrochloride/ use ppez
36	duloxetine/ use emczd
37	(duloxetin$ or Cymbalta$ or Depalta$ or Duciltia$).tw.
38	or/35-37
39	Deamino Arginine Vasopressin/ use ppez
40	desmopressin/ use emczd
41	(desmopressin$ or DDAVP$).tw.
42	or/39-41
43	Muscle Relaxants, Central/ use ppez
44	Benzodiazepines/ use ppez

#	Searches
45	Lorazepam/ use ppez
46	Temazepam/ use ppez
47	Diazepam/ use ppez
48	central muscle relaxant/ use emczd
49	muscle relaxant agent/ use emczd
50	benzodiazepine derivative/ use emczd
51	lorazepam/ use emczd
52	temazepam/ use emczd
53	diazepam/ use emczd
54	(muscle$ adj relax?nt$).tw.
55	(benzodiazepine$ or lorazepam$ or Ativan$ or temazepam$ or Restoril$ or diazepam$ or Valium$).tw.
56	or/43-55
57	Laxatives/ use ppez
58	Polyethylene Glycols/ use ppez
59	Lactulose/ use ppez
60	Glycerol/ use ppez
61	laxative/ use emczd
62	macrogol/ use emczd
63	macrogol derivative/ use emczd
64	lactulose/ use emczd
65	glycerol/ use emczd
66	(macrogol$ or movicol$ or lactulose$ or glycerol$).tw.
67	or/57-66
68	exp Botulinum Toxins/ use ppez
69	exp botulinum toxin/ use emczd
70	botulinum toxin A/ use emczd
71	botulinum$.tw.
72	(botul$ adj2 tox$).tw.
73	(BTA or BTX or CNBTX or BoNT$ or BoTx).tw.
74	(botox or dysport or azzalure or oculinum or prosigne or purtox or vistabel or xeomin or bocouture or myobloc or rimabotulinum$ or abobotuli$ or onabotulinum$ or Neuronox or Meditoxin).tw.
75	or/68-74
76	Hyaluronoglucosaminidase/ use ppez
77	hyaluronidase/ use emczd
78	(hyaluronidas$ or hyaluronoglucosaminidas$).tw.
79	or/76-78
80	Amitriptyline/ use ppez
81	amitriptyline/ use emczd
82	(amitriptylin$ or Amitid$ or Amitril$ or Elavil$ or Endep).tw.
83	or/80-82
84	Gabapentin/ use ppez
85	gabapentin/ use emczd
86	(gabapentin$ or Horizant$ or Neurontin$).tw.
87	or/84-86
88	Pregabalin/ use ppez
89	pregabalin/ use emczd
90	(Pregabalin$ or Lyrica$).tw.
91	or/88-90
92	Capsaicin/ use ppez
93	capsaicin/ use emczd
94	((local or topical) adj3 capsaicin$).tw.
95	(capsaicin$ adj (cream$ or ointment$)).tw.
96	or/92-95
97	Anesthetics, Local/ use ppez
98	local anesthetic agent/ use emczd
99	*Lidocaine/ use ppez
100	*lidocaine/ use emczd
101	((local or topical) adj (an?esthetic$ or lidocaine$)).tw.
102	(lidocaine$ adj (cream$ or ointment$)).tw.
103	or/97-102
104	exp Opiate Alkaloids/ use ppez
105	exp Analgesics, Opioid/ use ppez
106	opiate/ use emczd
107	opiate derivative/ use emczd
108	(opiate$ or opioid$).tw.
109	or/104-108
110	cholinergic receptor blocking agent/ use emczd
111	(anticholinergic$ or anti-cholinergic$).mp.
112	*Muscarinic Antagonists/ use ppez
113	*Mandelic Acids/ use ppez

#	Searches
114	*muscarinic receptor blocking agent/ use emczd
115	*mandelic acid derivative/ use emczd
116	*Tolterodine Tartrate/ use ppez
117	*Solifenacin Succinate/ use ppez
118	*tolterodine/ use emczd
119	*solifenacin/ use emczd
120	*oxybutynin/ use emczd
121	(tolterodine$ or Detrol$ or oxybutynin$ or Ditropan$ or solifenacin$ or VESIcare$).tw.
122	or/110-121
123	Injections/mt use ppez
124	*injections/ use emczd
125	Pessaries/ use ppez
126	*vagina pessary/ use emczd
127	pessar$.tw.
128	(prosecretory$ or lubiprostone$ or linaclotide$ or plecanatide$ or prucalopride$ or phytoestrogen$).mp.
129	((acetylcholinesterase$ or acetyl-cholinesterase$ or cholinesterase$) adj inhibitor$).tw.
130	pharmaceutical care/ use emczd
131	((pharmacolog$ or drug$) adj (therap$ or treatment$)).ti.
132	or/123-131
133	18 or 26 or 34 or 38 or 42 or 56 or 67 or 75 or 79 or 83 or 87 or 91 or 96 or 103 or 109 or 122 or 132
134	7 and 133
135	Pelvic Floor Disorders/dt use ppez
136	pelvic floor disorder/dt use emczd
137	or/134-136
138	limit 137 to english language
139	limit 138 to yr="1980 -Current" [General Exclusions filter applied]

Database(s): Cochrane Library – Wiley interface
Cochrane Database of Systematic Reviews, Issue 5 of 12, May 2020; **Cochrane Central Register of Controlled Trials**, Issue 5 of 12, May 2020
Date of last search: 27 May 2020

#	Searches
#1	MeSH descriptor: [Pelvic Floor] this term only
#2	MeSH descriptor: [Pelvic Floor Disorders] this term only
#3	(((pelvi* NEXT (floor* or diaphragm*) NEAR/3 (dysfunction* or disorder* or fail* or impair* or incompeten* or insufficien* or dyssynerg* or symptom* or laxity or change* or care* or health* or wellbeing* or well-being* or prevent* or rehabilitat* or weak* or hypertonic* or overactiv* or over-activ* or "over activ*")))):ti,ab,kw
#4	(((pelvi* NEXT (dysfunction* or disorder* or fail* or impair* or incompeten* or insufficien* or dyssynerg* or symptom* or laxity or care* or health* or wellbeing* or well-being* or prevent* or rehabilitat* or weak* or hypertonic* or overactiv* or over-activ* or "over activ*")))):ti,ab,kw
#5	#1 OR #2 OR #3 OR #4
#6	MeSH descriptor: [Estrogens] this term only
#7	MeSH descriptor: [Estrogens, Conjugated (USP)] this term only
#8	MeSH descriptor: [Estradiol] this term only
#9	MeSH descriptor: [Estriol] this term only
#10	(((oestrogen* or estrogen* or oestradiol* or estradiol* or oestriol* or estriol* or oestron* or estron*) NEAR/2 (local or vagina* or intra-vagina* or intravaginal* or topical))):ti,ab,kw
#11	MeSH descriptor: [Adrenergic beta-3 Receptor Agonists] this term only
#12	((mirabegron* or myrbetriq* or betmiga* or YM-178* or vibegron* or MK-4618* or solabegron* or GW427353*)):ti,ab,kw
#13	MeSH descriptor: [Antidiarrheals] this term only
#14	MeSH descriptor: [Loperamide] this term only
#15	MeSH descriptor: [Diphenoxylate] this term only
#16	((anti-diarrh?eal* or antidiarrh?eal* or loperamide* or Imodium* or Imotil* or diphenoxylate* or Lomotil*)):ti,ab,kw
#17	MeSH descriptor: [Duloxetine Hydrochloride] this term only
#18	((duloxetin* or Cymbalta* or Depalta* or Duciltia*)):ti,ab,kw
#19	MeSH descriptor: [Deamino Arginine Vasopressin] this term only
#20	((desmopressin* or DDAVP*)):ti,ab,kw
#21	MeSH descriptor: [Muscle Relaxants, Central] this term only
#22	MeSH descriptor: [Benzodiazepines] this term only
#23	MeSH descriptor: [Lorazepam] this term only
#24	MeSH descriptor: [Temazepam] this term only
#25	MeSH descriptor: [Diazepam] this term only
#26	((muscle* NEXT relax?nt*)):ti,ab,kw
#27	((benzodiazepine* or lorazepam* or Ativan* or temazepam* or Restoril* or diazepam* or Valium*)):ti,ab,kw
#28	MeSH descriptor: [Laxatives] this term only
#29	MeSH descriptor: [Polyethylene Glycols] this term only
#30	MeSH descriptor: [Lactulose] this term only
#31	MeSH descriptor: [Glycerol] this term only
#32	((macrogol* or movicol* or lactulose* or glycerol*)):ti,ab,kw

#	Searches
#33	MeSH descriptor: [Botulinum Toxins] explode all trees
#34	(botulinum*):ti,ab,kw
#35	((botul* NEAR/2 tox*)):ti,ab,kw
#36	((BTA or BTX or CNBTX or BoNT* or BoTx)):ti,ab,kw
#37	((botox or dysport or azzalure or oculinum or prosigne or purtox or vistabel or xeomin or bocouture or myobloc or rimabotulinum* or abobotuli* or onabotulinum* or Neuronox or Meditoxin)):ti,ab,kw
#38	MeSH descriptor: [Hyaluronoglucosaminidase] this term only
#39	((hyaluronidas* or hyaluronoglucosaminidas*)):ti,ab,kw
#40	MeSH descriptor: [Amitriptyline] this term only
#41	((amitriptylin* or Amitid* or Amitril* or Elavil* or Endep)):ti,ab,kw
#42	MeSH descriptor: [Gabapentin] this term only
#43	((gabapentin* or Horizant* or Neurontin*)):ti,ab,kw
#44	MeSH descriptor: [Pregabalin] this term only
#45	((Pregabalin* or Lyrica*)):ti,ab,kw
#46	MeSH descriptor: [Capsaicin] this term only
#47	(((local or topical) NEAR/3 capsaicin*)):ti,ab,kw
#48	((capsaicin* NEXT (cream* or ointment*))):ti,ab,kw
#49	MeSH descriptor: [Anesthetics, Local] this term only
#50	MeSH descriptor: [Lidocaine] this term only
#51	(((local or topical) NEXT (anesthetic* or anaesthetic* or lidocaine*))):ti,ab,kw
#52	((lidocaine* NEXT (cream* or ointment*))):ti,ab,kw
#53	MeSH descriptor: [Opiate Alkaloids] explode all trees
#54	MeSH descriptor: [Analgesics, Opioid] explode all trees
#55	((opiate* or opioid*)):ti,ab,kw
#56	((anticholinergic* or anti-cholinergic*)):ti,ab,kw
#57	MeSH descriptor: [Muscarinic Antagonists] this term only
#58	MeSH descriptor: [Mandelic Acids] this term only
#59	MeSH descriptor: [Tolterodine Tartrate] this term only
#60	MeSH descriptor: [Solifenacin Succinate] this term only
#61	((tolterodine* or Detrol* or oxybutynin* or Ditropan* or solifenacin* or VESIcare*)):ti,ab,kw
#62	MeSH descriptor: [Injections] explode all trees and with qualifier(s): [methods - MT]
#63	MeSH descriptor: [Pessaries] this term only
#64	(pessar*):ti,ab,kw
#65	((prosecretory* or lubiprostone* or linaclotide* or plecanatide* or prucalopride* or phytoestrogen*)):ti,ab,kw
#66	(((acetylcholinesterase* or acetyl-cholinesterase* or cholinesterase*) NEXT inhibitor*)):ti,ab,kw
#67	(((pharmacolog* or drug*) NEXT (therap* or treatment*))):ti
#68	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 or #22 or #23 or #24 or #25 or #26 or #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67
#69	#5 AND #68
#70	MeSH descriptor: [Pelvic Floor Disorders] this term only and with qualifier(s): [drug therapy - DT]
#71	#69 OR #70

Database(s): Database of Abstracts of Reviews of Effects (DARE); HTA Database – CRD interface

Date of last search: 27 May 2020

#	Searches
1	MeSH DESCRIPTOR Pelvic Floor IN DARE,HTA
2	MeSH DESCRIPTOR Pelvic Floor Disorders IN DARE,HTA
3	(((((pelvi* NEXT (floor* or diaphragm*) NEAR3 (dysfunction* or disorder* or fail* or impair* or incompeten* or insufficien* or dyssynerg* or symptom* or laxity or change* or care* or health* or wellbeing* or well-being* or prevent* or rehabilitat* or weak* or hypertonic* or overactiv* or over-activ*))))) IN DARE, HTA
4	(((((pelvi* NEXT (dysfunction* or disorder* or fail* or impair* or incompeten* or insufficien* or dyssynerg* or symptom* or laxity or care* or health* or wellbeing* or well-being* or prevent* or rehabilitat* or weak* or hypertonic* or overactiv* or over-activ*))))) IN DARE, HTA
5	#1 OR #2 OR #3 OR #4
6	((((oestrogen* or estrogen* or oestradiol* or estradiol* or oestriol* or estriol* or oestron* or estron*) NEAR2 (local or vagina* or intra-vagina* or intravaginal* or topical)))) IN DARE, HTA
7	(((mirabegron* or myrbetriq* or betmiga* or YM-178* or vibegron* or MK-4618* or solabegron* or GW427353* or anti-diarrh?eal* or antidiarrh?eal* or loperamide* or Imodium* or Imotil* or diphenoxylate* or Lomotil* or duloxetin* or Cymbalta* or Depalta* or Duciltia* or desmopressin* or DDAVP* or benzodiazepine* or lorazepam* or Ativan* or temazepam* or Restoril* or diazepam* or Valium* or macrogol* or movicol* or lactulose* or glycerol*))) IN DARE, HTA
8	(((muscle* NEXT relax?nt*))) IN DARE, HTA
9	(((botul* NEAR2 tox*))) IN DARE, HTA
10	((botulinum* or BTA or BTX or CNBTX or BoNT* or BoTx or botox or dysport or azzalure or oculinum or prosigne or purtox or vistabel or xeomin or bocouture or myobloc or rimabotulinum* or abobotuli* or onabotulinum* or

#	Searches
	Neuronox or Meditoxin or hyaluronidas* or hyaluronoglucosaminidas* or amitriptylin* or Amitid* or Amitril* or Elavil* or Endep or gabapentin* or Horizant* or Neurontin* or Pregabalin* or Lyrica*)) IN DARE, HTA
11	((((local or topical) NEAR3 capsaicin*))) IN DARE, HTA
12	(((capsaicin* NEXT (cream* or ointment*)))) IN DARE, HTA
13	((((local or topical) NEXT (anesthetic* or anaesthetic* or lidocaine*)))) IN DARE, HTA
14	(((lidocaine* NEXT (cream* or ointment*)))) IN DARE, HTA
15	(((opiate* or opioid* or anticholinergic* or anti-cholinergic* or tolterodine* or Detrol* or oxybutynin* or Ditropan* or solifenacin* or VESIcare* or pessar* or prosecretory* or lubiprostone* or linaclotide* or plecanatide* or prucalopride* or phytoestrogen*))) IN DARE, HTA
16	((((acetylcholinesterase* or acetyl-cholinesterase* or cholinesterase*) NEXT inhibitor*))) IN DARE, HTA
17	(((pharmacolog* or drug*) NEXT (therap* or treatment*))):TI IN DARE, HTA
18	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19	#5 AND #18
20	MeSH DESCRIPTOR Pelvic Floor Disorders WITH QUALIFIER DT IN DARE,HTA
21	#19 OR #20

Database(s): EMCare & PsycINFO (Multifile) – OVID interface
EMCare 1995 to present; **APA PsycINFO** 1806 to May Week 3 2020
Date of last search: 27 May 2020

Multifile database codes: emcr = Emcare; psyh = APA PsycINFO

#	Searches
1	pelvis floor/ use emcr
2	pelvic floor disorder/ use emcr
3	(pelvi$ adj (floor$ or diaphragm$) adj3 (dysfunction$ or disorder$ or fail$ or impair$ or incompeten$ or insufficien$ or dyssynerg$ or symptom$ or laxity or change$ or care$ or health$ or wellbeing$ or well-being$ or prevent$ or rehabilitat$ or weak$ or hypertonic$ or overactiv$ or over-activ$)).tw.
4	(pelvi$ adj (dysfunction$ or disorder$ or fail$ or impair$ or incompeten$ or insufficien$ or dyssynerg$ or symptom$ or laxity or care$ or health$ or wellbeing$ or well-being$ or prevent$ or rehabilitat$ or weak$ or hypertonic$ or overactiv$ or over-activ$)).tw.
5	or/1-4
6	Estrogens/ use emcr,psyh
7	conjugated estrogen/ use emcr
8	estrogen derivative/ use emcr
9	Estradiol/ use emcr,psyh
10	estriol/ use emcr
11	((oestrogen$ or estrogen$ or oestradiol$ or estradiol$ or oestriol$ or estriol$ or oestron$ or estron$) adj2 (local or vagina$ or intra-vagina$ or intravaginal$ or topical)).tw.
12	or/6-11
13	beta 3 adrenergic receptor stimulating agent/ use emcr
14	beta 3 adrenergic receptor/ use emcr
15	mirabegron/ use emcr
16	vibegron/ use emcr
17	solabegron/ use emcr
18	(mirabegron$ or myrbetriq$ or betmiga$ or YM-178$ or vibegron$ or MK-4618$ or solabegron$ or GW427353$).tw.
19	or/13-18
20	antidiarrheal agent/ use emcr
21	loperamide/ use emcr
22	diphenoxylate/ use emcr
23	(anti-diarrh?eal$ or antidiarrh?eal$ or loperamide$ or Imodium$ or Imotil$ or diphenoxylate$ or Lomotil$).tw.
24	or/20-23
25	duloxetine/ use emcr
26	(duloxetin$ or Cymbalta$ or Depalta$ or Duciltia$).tw.
27	25 or 26
28	desmopressin/ use emcr
29	(desmopressin$ or DDAVP$).tw.
30	28 or 29
31	Muscle Relaxing Drugs/ use psyh
32	Benzodiazepines/ use emcr,psyh
33	central muscle relaxant/ use emcr
34	muscle relaxant agent/ use emcr
35	Lorazepam/ use emcr,psyh
36	temazepam/ use emcr
37	Diazepam/ use emcr,psyh
38	(muscle$ adj relax?nt$).tw.
39	(benzodiazepine$ or lorazepam$ or Ativan$ or temazepam$ or Restoril$ or diazepam$ or Valium$).tw.
40	or/31-39
41	laxative/ use emcr
42	macrogol/ use emcr

#	Searches
43	macrogol derivative/ use emcr
44	lactulose/ use emcr
45	glycerol/ use emcr
46	(macrogol$ or movicol$ or lactulose$ or glycerol$).tw.
47	or/41-46
48	exp Botulinum Toxin/ use emcr,psyh
49	botulinum toxin A/ use emcr
50	botulinum$.tw.
51	(botul$ adj2 tox$).tw.
52	(BTA or BTX or CNBTX or BoNT$ or BoTx).tw.
53	(botox or dysport or azzalure or oculinum or prosigne or purtox or vistabel or xeomin or bocouture or myobloc or rimabotulinum$ or abobotuli$ or onabotulinum$ or Neuronox or Meditoxin).tw.
54	or/48-53
55	hyaluronidase/ use emcr
56	(hyaluronidas$ or hyaluronoglucosaminidas$).tw.
57	55 or 56
58	Amitriptyline/ use emcr,psyh
59	(amitriptylin$ or Amitid$ or Amitril$ or Elavil$ or Endep).tw.
60	58 or 59
61	Gabapentin/ use emcr,psyh
62	(gabapentin$ or Horizant$ or Neurontin$).tw.
63	61 or 62
64	Pregabalin/ use emcr,psyh
65	(Pregabalin$ or Lyrica$).tw.
66	64 or 65
67	Capsaicin/ use emcr,psyh
68	((local or topical) adj3 capsaicin$).tw.
69	(capsaicin$ adj (cream$ or ointment$)).tw.
70	or/67-69
71	exp Local Anesthetics/ use psyh
72	local anesthetic agent/ use emcr
73	Lidocaine/ use emcr,psyh
74	((local or topical) adj (an?esthetic$ or lidocaine$)).tw.
75	(lidocaine$ adj (cream$ or ointment$)).tw.
76	or/71-75
77	opiate/ use emcr
78	opiate derivative/ use emcr
79	(opiate$ or opioid$).tw.
80	or/77-79
81	exp Cholinergic Blocking Drugs/ use psyh
82	cholinergic receptor blocking agent/ use emcr
83	(anticholinergic$ or anti-cholinergic$).tw.
84	muscarinic receptor blocking agent/ use emcr
85	mandelic acid derivative/ use emcr
86	tolterodine/ use emcr
87	solifenacin/ use emcr
88	oxybutynin/ use emcr
89	(tolterodine$ or Detrol$ or oxybutynin$ or Ditropan$ or solifenacin$ or VESIcare$).tw.
90	or/81-89
91	*Injections/ use emcr,psyh
92	exp Medical Therapeutic Devices/ use psyh
93	*vagina pessary/ use emcr
94	pessar$.tw.
95	(prosecretory$ or lubiprostone$ or linaclotide$ or plecanatide$ or prucalopride$ or phytoestrogen$).mp.
96	((acetylcholinesterase$ or acetyl-cholinesterase$ or cholinesterase$) adj inhibitor$).tw.
97	Drug Therapy/ use emcr,psyh
98	pharmaceutical care/ use emcr
99	((pharmacolog$ or drug$) adj (therap$ or treatment$)).ti.
100	or/91-99
101	12 or 19 or 24 or 27 or 30 or 40 or 47 or 54 or 57 or 60 or 63 or 66 or 70 or 76 or 80 or 90 or 100
102	5 and 101
103	limit 102 to english language
104	limit 103 to yr="1980 -Current") [General Exclusions filter applied]

1
2

Economic Search

One global search was conducted for economic evidence across the guideline.

Database(s): NHS Economic Evaluation Database (NHS EED); HTA Database – CRD interface

Date of last search: 3 February 2021

#	Searches
1	MeSH DESCRIPTOR Pelvic Floor IN NHSEED,HTA
2	MeSH DESCRIPTOR Pelvic Floor Disorders IN NHSEED,HTA
3	MeSH DESCRIPTOR Urinary Bladder, Overactive IN NHSEED,HTA
4	(((pelvi* NEXT (floor* or diaphragm*) NEAR3 (dysfunction* or disorder* or fail* or impair* or incompeten* or insufficien* or dyssynerg* or symptom* or laxity or change* or care* or health* or wellbeing* or well-being* or prevent* or rehabilitat* or weak* or hypertonic* or overactiv* or over activ* or over-activ*)))) IN NHSEED, HTA
5	MeSH DESCRIPTOR Urinary Incontinence EXPLODE ALL TREES IN NHSEED,HTA
6	MeSH DESCRIPTOR Urinary Bladder, Overactive IN NHSEED,HTA
7	((((stress* or mix* or urg* or urin*) NEAR5 incontinen*))) IN NHSEED, HTA
8	(((bladder* NEAR5 (overactiv* or over activ* or over-activ* or instabilit* or hyper-reflex* or hyperreflex* or hyper reflex* or incontinen*)))) IN NHSEED, HTA
9	(((detrusor* NEAR5 (overactiv* or over activ* or over-activ* or instabilit* or hyper-reflex* or hyperreflex* or hyper reflex*)))) IN NHSEED, HTA
10	((((urgency NEAR2 frequency) or (frequency NEAR2 urgency)))) IN NHSEED, HTA
11	((((urin* or bladder*) NEAR2 (urg* or frequen*)))) IN NHSEED, HTA
12	(((SUI or OAB))) IN NHSEED, HTA
13	MeSH DESCRIPTOR Pelvic Organ Prolapse EXPLODE ALL TREES IN NHSEED,HTA
14	MeSH DESCRIPTOR Rectocele IN NHSEED,HTA
15	(((pelvic* NEAR3 organ* NEAR3 prolaps*))) IN NHSEED, HTA
16	(((urinary NEAR3 bladder NEAR3 prolaps*))) IN NHSEED, HTA
17	((((vagin* or urogenital* or genit* or uter* or viscer* or anterior* or posterior* or apical or pelvi* or vault* or urethr* or bladder* or cervi* or rectal or rectum) NEAR3 prolaps*))) IN NHSEED, HTA
18	(((splanchnoptos* or visceroptos*))) IN NHSEED, HTA
19	(((hernia* NEAR3 (pelvi* or vagin* or urogenital* or uter* or bladder* or urethr* or viscer*)))) IN NHSEED, HTA
20	(((urethroc?ele* or enteroc?ele* or sigmoidoc?ele* or proctoc?ele* or rectoc?ele* or cystoc?ele* or rectoenteroc?ele* or cystourethroc?ele*))) IN NHSEED, HTA
21	MeSH DESCRIPTOR Fecal Incontinence IN NHSEED,HTA
22	((((faecal or fecal or faeces or feces or fecally or faecally or anal or anally or stool or stools or bowel or double or defecat* or defaecat*) NEAR5 (incontinence or incontinent or urge* or leak or leaking or leakage or soiling or seeping or seepage or impacted or impaction)))) IN NHSEED, HTA
23	MeSH DESCRIPTOR Urinary Retention IN NHSEED,HTA
24	(((urin* NEAR3 (retention* or retain*)))) IN NHSEED, HTA
25	(((voiding NEXT (disorder* or dysfunction* or problem*)))) IN NHSEED, HTA
26	(((empty* NEXT disorder* NEAR3 (bowel* or bladder* or vesical* or stool*)))) IN NHSEED, HTA
27	((((urogeni* or anorec* or ano-rec* or ano rec*) NEAR3 dysfunction*))) IN NHSEED, HTA
28	MeSH DESCRIPTOR Fecal Impaction IN NHSEED,HTA
29	((((difficult* or delay* or irregular* or infrequen* or pain*) NEAR3 (defecat* or defaecat* or stool* or faecal or fecal or faeces or feces or fecally or faecally or bowel movement*)))) IN NHSEED, HTA
30	(((obstruct* NEAR3 (defecat* or defaecat*)))) IN NHSEED, HTA
31	((((defecat* or defaecat* or evacuat*) NEAR3 (disorder* or dysfunction*)))) IN NHSEED, HTA
32	((((outlet* NEXT dysfunction* NEXT constipa*)))) IN NHSEED, HTA
33	(((dys?ynerg* NEXT (defecat* or defaecat*)))) IN NHSEED, HTA
34	(((pelvi* NEAR3 dyskines*))) IN NHSEED, HTA
35	(((pelvi* NEXT outlet* NEXT obstruct*))) IN NHSEED, HTA
36	(((anismus*))) IN NHSEED, HTA
37	(((puborectal* NEXT contract*))) IN NHSEED, HTA
38	((((rectal or rectum) NEAR3 urge*))) IN NHSEED, HTA
39	(((female NEXT sex* NEXT (dysfunct* or satisf* or problem* or symptom* or arous* or activit* or disorder*)))) IN NHSEED, HTA
40	(((obstruct* NEAR3 intercourse))) IN NHSEED, HTA
41	(((vagin* NEAR3 laxity*))) IN NHSEED, HTA
42	(((vagin* NEXT wind))) IN NHSEED, HTA
43	MeSH DESCRIPTOR Vaginismus IN NHSEED,HTA
44	(((vaginismus*))) IN NHSEED, HTA
45	(((vagin* NEXT penetrat* NEXT disorder*))) IN NHSEED, HTA
46	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45) IN NHSEED, HTA

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2021 February 01; **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to February 01, 2021
Date of last search: 3 February 2021

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Pelvic Floor/ use ppez
2	Pelvic Floor Disorders/ use ppez
3	pelvis floor/ use emczd
4	pelvic floor disorder/ use emczd
5	(pelvi$ adj (floor$ or diaphragm$) adj3 (dysfunction$ or disorder$ or fail$ or impair$ or incompeten$ or insufficien$ or dyssynerg$ or symptom$ or laxity or change$ or care$ or health$ or wellbeing$ or well-being$ or prevent$ or rehabilitat$ or weak$ or hypertonic$ or overactiv$ or over activ$ or over-activ$)).tw.
6	(pelvi$ adj (dysfunction$ or disorder$ or fail$ or impair$ or incompeten$ or insufficien$ or dyssynerg$ or symptom$ or laxity or care$ or health$ or wellbeing$ or well-being$ or prevent$ or rehabilitat$ or weak$ or hypertonic$ or overactiv$ or over activ$ or over-activ$)).tw.
7	or/1-6
8	exp *Urinary Incontinence/ use ppez
9	*Urinary Bladder, Overactive/ use ppez
10	exp *urine incontinence/ use emczd
11	*overactive bladder/ use emczd
12	*bladder instability/ use emczd
13	((stress$ or mix$ or urg$ or urin$) adj5 incontinen$).ti.
14	(bladder$ adj5 (overactiv$ or over activ$ or over-activ$ or instabilit$ or hyper-reflex$ or hyperreflex$ or hyper reflex$ or incontinen$)).ti.
15	(detrusor$ adj5 (overactiv$ or over activ$ or over-activ$ or instabilit$ or hyper-reflex$ or hyperreflex$ or hyper reflex$)).ti.
16	((urgency adj2 frequency) or (frequency adj2 urgency)).ti.
17	((urin$ or bladder$) adj2 (urg$ or frequen$)).ti.
18	(SUI or OAB).ti.
19	or/8-18
20	exp *Pelvic Organ Prolapse/ use ppez
21	exp *pelvic organ prolapse/ use emczd
22	*Rectocele/ use ppez
23	*rectocele/ use emczd
24	(pelvic$ adj3 organ$ adj3 prolaps$).ti.
25	(urinary adj3 bladder adj3 prolaps$).ti.
26	((vagin$ or urogenital$ or genit$ or uter$ or viscer$ or anterior$ or posterior$ or apical or pelvi$ or vault$ or urethr$ or bladder$ or cervi$ or rectal or rectum) adj3 prolaps$).ti.
27	(splanchnoptos$ or visceroptos$).ti.
28	(hernia$ adj3 (pelvi$ or vagin$ or urogenital$ or uter$ or bladder$ or urethr$ or viscer$)).ti.
29	(urethroc?ele$ or enteroc?ele$ or sigmoidoc?ele$ or proctoc?ele$ or rectoc?ele$ or cystoc?ele$ or rectoenteroc?ele$ or cystourethroc?ele$).ti.
30	or/20-29
31	*Fecal Incontinence/ use ppez
32	*feces incontinence/ use emczd
33	((faecal or fecal or faeces or feces or fecally or faecally or anal or anally or stool or stools or bowel or double or defecat$ or defaecat$) adj5 (incontinence or incontinent or urge$ or leak or leaking or leakage or soiling or seeping or seepage or impacted or impaction)).ti.
34	or/31-33
35	Urinary Retention/ use ppez
36	urine retention/ use emczd
37	(urin$ adj3 (retention$ or retain$)).tw.
38	(voiding adj (disorder$ or dysfunction$ or problem$)).tw.
39	(empty$ adj disorder$ adj3 (bowel$ or bladder$ or vesical$ or stool$)).tw.
40	((urogeni$ or anorec$ or ano-rec$ or ano rec$) adj3 dysfunction$).tw.
41	defecation disorder/ use emczd
42	Fecal Impaction/ use ppez
43	Feces Impaction/ use emczd
44	((difficult$ or delay$ or irregular$ or infrequen$ or pain$) adj3 (defecat$ or defaecat$ or stool$ or faeces or feces or bowel movement$)).tw.
45	(obstruct$ adj3 (defecat$ or defaecat$)).tw.
46	((defecat$ or defaecat$ or evacuat$) adj3 (disorder$ or dysfunction$)).tw.
47	outlet$ dysfunction$ constipa$.tw.
48	(dys?ynerg$ adj (defecat$ or defaecat$)).tw.
49	(pelvi$ adj3 dyskines$).tw.
50	pelvi$ outlet$ obstruct$.tw.
51	anismus$.tw.

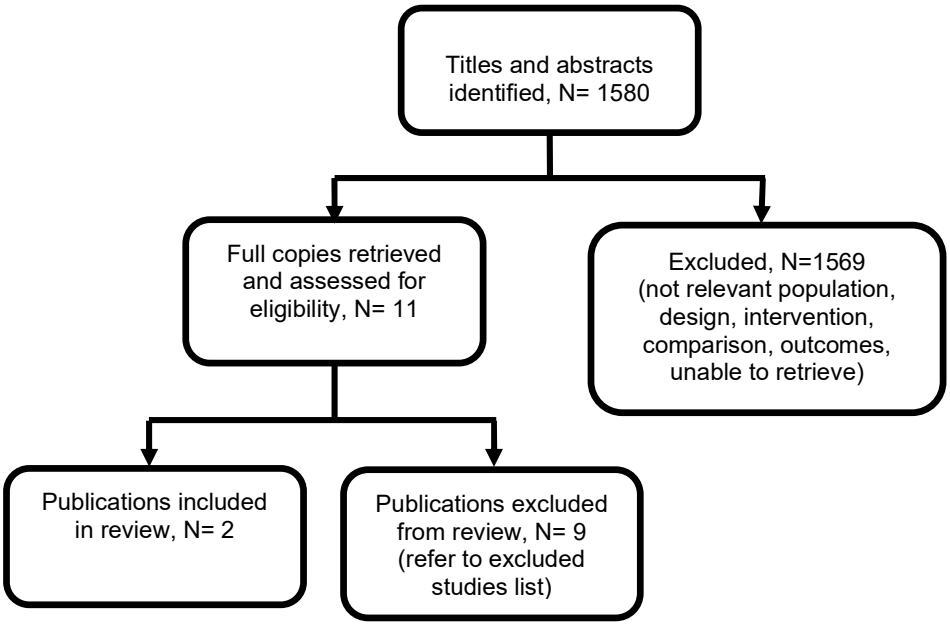
#	Searches
52	puborectal$ contract$.tw.
53	((rectal or rectum) adj3 urge$).tw.
54	or/35-53
55	female sexual dysfunction/ use emczd
56	(female adj sex$ adj (dysfunct$ or satisf$ or problem$ or symptom$ or arous$ or activit$ or disorder$)).tw.
57	(obstruct$ adj3 intercourse).tw.
58	(vagin$ adj3 laxity$).tw.
59	(vagin$ adj wind).tw.
60	Vaginismus/ use ppez
61	vaginism/ use emczd
62	vaginismus$.tw.
63	(vagin$ adj penetrat$ adj disorder$).tw.
64	or/55-63
65	7 or 19 or 30 or 34 or 54 or 64
66	Economics/ use ppez
67	Value of life/ use ppez
68	exp "Costs and Cost Analysis"/ use ppez
69	exp Economics, Hospital/ use ppez
70	exp Economics, Medical/ use ppez
71	Economics, Nursing/ use ppez
72	Economics, Pharmaceutical/ use ppez
73	exp "Fees and Charges"/ use ppez
74	exp Budgets/ use ppez
75	health economics/ use emczd
76	exp economic evaluation/ use emczd
77	exp health care cost/ use emczd
78	exp fee/ use emczd
79	budget/ use emczd
80	funding/ use emczd
81	budget*.ti,ab.
82	cost*.ti.
83	(economic* or pharmaco?economic*).ti.
84	(price* or pricing*).ti,ab.
85	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
86	(financ* or fee or fees).ti,ab.
87	(value adj2 (money or monetary)).ti,ab.
88	or/66-87
89	65 and 88
90	limit 89 to english language

1

Appendix C – Clinical evidence study selection

Study selection for: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

Figure 1: Study selection flow chart



Appendix D – Evidence tables

Evidence tables for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

Table 4: Evidence tables

Study details	Participants	Interventions	Methods	Outcomes	Comments
Full citation Crisp, C. C., Vaccaro, C. M., Estanol, M. V., Oakley, S. H., Kleeman, S. D., Fellner, A. N., Pauls, R. N., Intra-vaginal diazepam for high-tone pelvic floor dysfunction: a randomized placebo-controlled trial, International Urogynecology JournalInt Urogynecol J Pelvic Floor Dysfunct, 24, 1915-23, 2013 **Ref Id** 1200041 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study**	**Sample size** Randomised: N=21; n=11 to placebo and n=10 to diazepam Analysed n=14; n=7 to placebo and n=7 to diazepam **Characteristics** Age, mean (SD): Diazepam 35.9 (12.0); Placebo 26.3 (16.6) Race, Caucasian, n (%): Diazepam 6 (85.7); Placebo 6 (85.7) Race, African-American, n (%): Diazepam 1 (14.3); Placebo 1 (14.3) BMI, mean (SD): Diazepam 26.7 (9.2); Placebo 30.4 (10.0) Gravida, median (IQR): Diazepam 2 (0, 6); Placebo 2 (0, 3) **Inclusion criteria** • English-speaking • At least 18 years of age	**Interventions** Both written and verbal instructions for appropriate use and application of the vaginal suppository were provided. Subjects were asked to place the suppository as high in the vagina as possible. Subjects were given the option to place the suppository digitally or with an applicator. Instructions were given to use one suppository every night for 28 consecutive nights before going to sleep. The suppositories were white in colour, weighed about 2 g each, and contained 10 mg of diazepam.	**Details** A modified Oxford scale was obtained at baseline and repeated at 4 weeks. The functional status of the pelvic floor muscles was also categorized as: normal muscles that can voluntarily and involuntarily contract and relax, overactive muscles that do not relax, or may even contract when relaxation is functionally needed, underactive muscles, which cannot voluntarily contract when appropriate, and non-functioning muscles, where there is no palpable muscle action. Validated questionnaires were completed at baseline. 2 and 4 weeks: the Female Sexual Function Index (FSFI), a quadruple Visual Analog Scale (VAS), the Short Form Health Survey 12 (SF-12), the Patient Global Impression of Severity (PGI-S) and the	**Results** **Short-form health survey** Physical Component Score, mean (SD): Baseline: Diazepam 45.13 (17.26); Placebo 38.66 (14.29) 2 weeks: Diazepam 46.31 (8.84); Placebo 38.66 (14.29) 4 weeks: Diazepam 47.63 (15.20); Placebo 41.30 (14.82) Mental Component Score, mean (SD): Baseline: Diazepam 36.88 (13.92); Placebo 40.94 (12.20) 2 weeks: Diazepam 38.89 (15.56); Placebo 42.02 (13.90) 4 weeks: Diazepam 39.35 (18.49); Placebo 47.70 (13.19) **Patient Global Impression Scales** PGI-I, mean (SD) Baseline: Diazepam n/a; Placebo n/a	**Limitations** Cochrane risk of bias (Version 2.0) Domain 1: Randomisation: Low risk 1.1: Yes, patients were randomly allocated to treatments 1.2: Yes, randomisation used opaque, sequentially numbered, sealed envelopes 1.3: No, no significant differences between groups at baseline Domain 2: Deviations from intended interventions: Low risk 2.1: No, participants were blinded 2.2: No, carers and people delivering the interventions blinded 2.3: No information whether there were any deviations from the intended intervention Domain 3: Missing outcome data: Low risk

Study details	Participants	Interventions	Methods	Outcomes	Comments
To evaluate the use of intra-vaginal diazepam suppositories compared with placebo for the treatment for high-tone pelvic floor dysfunction **Study dates** September 2010 to December 2011 **Source of funding** TriHealth Medical Education Research Fund.	• Diagnosed with high-tone pelvic floor dysfunction by the treating urogynecologist • Concurrent diagnosis of comorbid conditions, such as endometriosis or painful bladder syndrome, were included. **Exclusion criteria** • An allergy to diazepam or any benzodiazepine • Currently receiving pelvic floor physical therapy (therapy received over 6 months previous was allowed) • Had undergone pelvic surgery within the 3 months prior to enrolment • Currently pregnant • Contraindication to diazepam • Use of any benzodiazepines, narcotics, or alcohol on a regular basis (defined as daily use)		Patient Global Impression of improvement (PGI-I).	2 weeks: Diazepam 3.50 (0.84); Placebo 2.86 (0.90) 4 weeks: Diazepam 3.67 (1.03); Placebo 2.71 (1.11) PGI-S, mean (SD) Baseline: Diazepam 2.67 (0.52); Placebo 3.00 (0.82) 2 weeks: Diazepam 2.33 (0.52); Placebo 2.00 (0.82) 4 weeks: Diazepam 2.08 (0.80); Placebo 2.14 (0.69) **Female Sexual Function Index** Total, median (IQR): Baseline: Diazepam 13.5 (11.9, 16.8); Placebo 13.4 (5.6, 20.5) 2 weeks: Diazepam 7.0 (2.4, 17.3); Placebo 17.2 (4.6, 18.9) 4 weeks: Diazepam 9.5 (3.2, 15.2); Placebo 13.9 (4.8, 23.6)	3.1: Probably no, 70% of the intervention group and 63% in the control group completed all measures 3.2: Probably no, no evidence that the results were not biased by missing outcome data 3.3: Probably no, missingness of the outcome was not dependent on its true value Domain 4: Measurement of the outcome: Low risk 4.1: No, outcomes clearly defined and information on how they were assessed and by whom 4.2: Probably no, outcomes unlikely to differ between treatment arms 4.3: No, outcome assessors were blinded Domain 5: Selection of the reported result: Low risk 5.1: Yes, pre-panned analysis and protocol available through trial registry 5.2: No, descriptive data presented 5.3: No, data presented as expected Domain 6: Overall judgment of bias: Low risk

Study details	Participants	Interventions	Methods	Outcomes	Comments

Full citation
 	
Holland, Michael A., Joyce, John S., Brennaman, Lisa M., Drobnis, Erma Z., Starr, Julie A., Foster, Raymond T., Intravaginal Diazepam for the Treatment of Pelvic Floor Hypertonic Disorder: A Double-blind, Randomized, Placebo-Controlled Trial, Obstetrical & gynecological survey, 74, 273-274, 2019
 	
Ref Id
 	
1257074
 	
Country/ies where the study was carried out
 	
USA
 	
Study type
RCT
 	
Aim of the study
To determine the efficacy of intravaginal diazepam for the treatment of pelvic pain secondary to levator ani muscle spasm in comparison to placebo.
 	
Study dates
September 2013 and August 2016
	Sample size
	Randomised: N=49; n=25 to Diazepam and n=24 to placebo
	
	Characteristics
	Age, median (95% CI): Diazepam 36 (27-52); Placebo 42 (31-52)
	BMI, median (95% CI): Diazepam 27 (25-30); Placebo 27 (25-35)
	Gravida, median (95% CI): Diazepam 2 (0-4); Placebo 2 (1-4)
	
	Inclusion criteria
	• Women 18 years or older
	• presented with the primary complaint of acute or chronic pelvic pain
	  ○ with or without dyspareunia,
	  ○ with pelvic examination findings consistent with levator muscle spasm, including hypertonicity of the levator muscles and/or reproduction of the subjects' pain with palpation of the levator muscles.
	
	Exclusion criteria
		Interventions
		The diazepam tablets contained 10 mg of active drug. Identical-appearing capsules containing only cellulose were used as the placebo.
		Each research subject was instructed to self-administer 1 capsule vaginally, 1 to 2 times daily as needed for pelvic pain. Subjects were dispensed 60 capsules with no refills. Subjects also received instructions for conservative therapy consisting of a psyllium-based bowel regimen, heat therapy, pelvic stretching exercises, and Kegel exercises.
			Details
			Subjects also completed a 100-mm visual analogue pain scale (VAS), Pelvic Floor Distress Inventory-20 (PFDI-20), McGill Pain Questionnaire, and Global Response Assessment on the day of enrolment. Patients with dyspareunia were asked to rate their pain on a scale of 1 to 10. These surveys were completed again by each participant 4 weeks after initiation of treatment.
				Results
				<u>POPDI-6, median (95% CI):</u>
				Baseline: Diazepam 46 (21-50); Placebo 29 (18-54)
				4 weeks: Diazepam 33 (17-46); Placebo 40 (17-58)
				
				<u>CRADI-8, median (95% CI):</u>
				Baseline: Diazepam 22 (13-41); Placebo 36 (6-44)
				4 weeks: Diazepam 28 (6-41); Placebo 27 (13-38)
				
				<u>UDI-6, median (95% CI):</u>
				Baseline: Diazepam 54 (33-75); Placebo 42 (17-71)
				4 weeks: Diazepam 33 (25-46); Placebo 50 (8-54)
				
				<u>PFDI-20, median (95% CI):</u>
				Baseline: Diazepam 116 (94-158); Placebo 92 (63-163)
				4 weeks: Diazepam 96 (56-116); Placebo 107 (45-164)
				
				<u>Dyspareunia score, median (95%CI)</u>
				Baseline: Diazepam 6.7 (3.5-8); Placebo 7.5 (2-8)
				4 weeks: Diazepam 6 (1-8); Placebo 7 (0-10)
					Limitations
					Cochrane risk of bias (Version 2.0)
					Domain 1: Randomisation: Low risk
					1.1: Yes, patients were randomly allocated to treatments using a computer-derived random number sequence
					1.2: Yes, only dispensing pharmacy knew allocation
					1.3: No, no significant differences between groups at baseline
					
					Domain 2: Deviations from intended interventions: Low risk
					2.1: No, participants were blinded
					2.2: No, health care providers were blinded
					2.3: No information whether there were any deviations from the intended intervention
					
					Domain 3: Missing outcome data: Low risk
					3.1: Probably no, 76% of the intervention group and 67% in the control group completed all measures
					3.2: Probably no, no evidence that the results were not biased by missing outcome data
					3.3: Probably no, missingness of the outcome was not

Study details	Participants	Interventions	Methods	Outcomes	Comments
Source of funding Department of Obstetrics, Gynecology, and Women's Health, University of Missouri Health Care, Columbia, MO departmental research funds.	• pregnant or breastfeeding • currently or previously treated with pelvic floor therapy or intravaginal Valium • had a contraindication to benzodiazepines • were incarcerated • were non–English-speaking • had stage III or greater pelvic organ prolapse				dependent on its true value Domain 4: Measurement of the outcome: Low risk 4.1: No, outcomes clearly defined and information on how they were assessed and by whom 4.2: Probably no, outcomes unlikely to differ between treatment arms 4.3: No, outcome assessors were blinded Domain 5: Selection of the reported result: Low risk 5.1: Yes, pre-panned analysis and protocol available through trial registry 5.2: No, descriptive data presented 5.3: No, data presented as expected Domain 6: Overall judgment of bias: Low risk

BMI: body mass index; CI: confidence interval; CRADI: colorectal distress inventory; FSFI: female sexual function index; IQR: inter quartile range; PGI-I: Patient Global Impression of Improvement; PGI-S: Patient Global Impression of Severity; PFDI-20: Pelvic Floor Distress Inventory-20; POPDI: pelvic organ prolapse distress inventory; RCT: randomised controlled trial; SD: standard deviation; SF-12: Short Form Health Survey 12; UDI-6: Urinary Distress Inventory; VAS: visual analogue pain scale

Appendix E – Forest plots

Forest plots for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F – GRADE tables

GRADE tables for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

Table 5: Clinical evidence profile for comparison Diazepam to Placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam	Placebo	Relative (95% CI)	Absolute		
Short-form Physical component - 2 weeks (Scores of 50 or higher are considered average or better health)												
Crisp 2013	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	5	7	-	MD 7.65 higher (5.47 lower to 20.77 higher)	MODERATE	CRITICAL
Short-form Physical component - 4 weeks (Scores of 50 or higher are considered average or better health)												
Crisp 2013	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5	7	-	MD 6.33 higher (10.93 lower to 23.59 higher)	LOW	CRITICAL
Short-form Mental component - 2 weeks (Scores of 50 or higher are considered average or better health)												
Crisp 2013	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	5	7	-	MD 3.13 lower (20.22 lower to 13.96 higher)	LOW	CRITICAL
Short-form Mental component - 4 weeks (Scores of 50 or higher are considered average or better health)												
Crisp 2013	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	5	7	-	MD 8.35 lower (27.27 lower to 10.57 higher)	LOW	CRITICAL
Patient Global Impression of Improvement - 2 weeks (Likert scale with range of 1 to 7, better indicated by lower values)												
Crisp 2013	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	7	7	-	MD 0.64 higher (0.27 lower to 1.55 higher)	MODERATE	CRITICAL
Patient Global Impression of Improvement - 4 weeks (Likert scale with range of 1 to 7, better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam	Placebo	Relative (95% CI)	Absolute		
Crisp 2013	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	7	7	-	MD 0.96 higher (0.16 lower to 2.08 higher)	MODERATE	CRITICAL
Patient Global Impression of Severity - 2 weeks (Likert scale with range of 1 to 4, better indicated by lower values)												
Crisp 2013	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	7	7	-	MD 0.33 higher (0.39 lower to 1.05 higher)	MODERATE	CRITICAL
Patient Global Impression of Severity - 4 weeks (Likert scale with range of 1 to 4, better indicated by lower values)												
Crisp 2013	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	7	7	-	MD 0.06 lower (0.84 lower to 0.72 higher)	LOW	CRITICAL
Female Sexual Function Index - 2 weeks (Range 0 to 36, better indicated by lower values)												
Crisp 2013	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	7	7	-	Median 10.2 lower Median (IQR): Diazepam 7.0 (2.4, 17.3); Placebo 17.2 (4.6, 18.9)	MODERATE	CRITICAL
Female Sexual Function Index - 4 weeks (Range 0 to 36, better indicated by lower values)												
Crisp 2013	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	7	7	-	Median 5.7 lower Median (IQR): Diazepam 9.5 (3.2, 15.2); Placebo 13.9 (4.8, 23.6)	MODERATE	CRITICAL
POPDI-6 - 4 weeks (Range 0 to 100, better indicated by lower values)												
Holland 2019	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	25	24	-	Median 7 lower Diazepam median 33 (95% CI: 17-46); Placebo median 40 (95% CI: 17-58)	MODERATE	CRITICAL
CRADI-8 - 4 weeks (Range 0 to 100, better indicated by lower values)												
Holland 2019	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	25	24	-	Median 1 lower Diazepam median 28 (95% CI 6-41); Placebo median 27 (95% CI 13-38)	MODERATE	CRITICAL
UDI-6 - 4 weeks (Range 0 to 100, better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam	Placebo	Relative (95% CI)	Absolute		
Holland 2019	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	25	24	-	Median 7 lower Diazepam median 33 (95% CI 25-46); Placebo median 50 (95% CI 8-54)	MODERATE	CRITICAL
PFDI-20 - 4 weeks (Range 0 to 300, better indicated by lower values)												
Holland 2019	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	25	24	-	Median 11 lower Diazepam median 96 (95% CI 56-116); Placebo median 107 (95% CI 45-164)	MODERATE	CRITICAL
Dyspareunia score - 4 weeks (range 0 to 10, better indicated by lower values)												
Holland 2019	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	25	24	-	Median 1 lower Diazepam median 6 (95% CI 1-8); Placebo median 7 (95% CI 0-10)	MODERATE	CRITICAL

CI: confidence interval; CRADI: colorectal distress inventory; FSFI: female sexual function index; MD: mean difference; PFDI-20: Pelvic Floor Distress Inventory-20; POPDI: pelvic organ prolapse distress inventory; RCT: randomised controlled trial; SD: standard deviation; UDI-6: Urinary Distress Inventory

1 95% CI crosses 1 MID (0.5 x SD at baseline of placebo arm = 7.15)

2 95% CI crosses 2 MIDs (0.5 x SD at baseline of placebo arm = 7.15)

3 95% CI crosses 2 MIDs (0.5 x SD at baseline of placebo arm = 6.1)

4 95% CI crosses 1 MID (0.5 x SD at 2 weeks (baseline data NR) of placebo arm = 0.45)

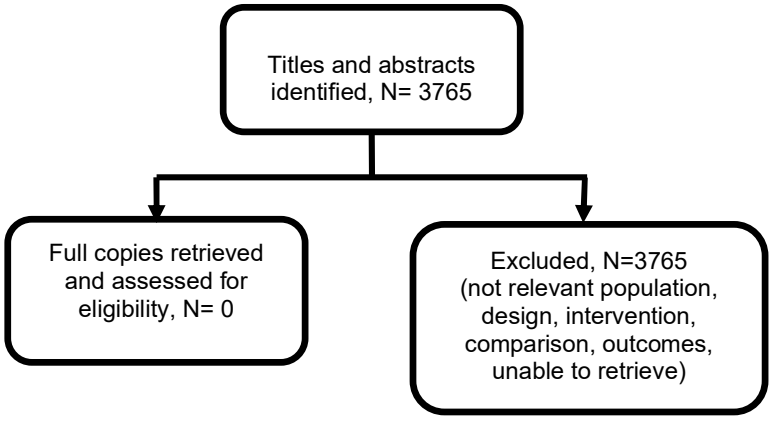
5 95% CI crosses 1 MID (0.5 x SD at baseline of placebo arm = 0.41)

6 95% CI crosses 2 MIDs (0.5 x SD at baseline of placebo arm = 0.41)

7 Subjective assessment

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?



Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

No evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

Clinical studies

Table 34: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Chiarioni, G., Whitehead, W. E., Pezza, V., Morelli, A., Bassotti, G., Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia, Gastroenterology, 130, 657-64, 2006	Population contained males with no subgroup analysis for sex
Euctr, G. B., A double blinded randomised controlled trial of injection of botulinum toxin versus normal saline into the puborectalis muscle in patients with pelvic floor dyssynergia, http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2005-001378-29-GB, 2005	Trial registry - no published paper reported
Goldstein, A. T., Burrows, L. J., Kellogg-Spadt, S., Intralevator injection of botulinum toxin for the treatment of hypertonic pelvic floor muscle dysfunction and vestibulodynia, Journal of sexual medicine, 8, 1287-90, 2011	Techniques paper
Heymen, S., Scarlett, Y., Jones, K., Ringel, Y., Drossman, D., Whitehead, W. E., Randomized, controlled trial shows biofeedback to be superior to alternative treatments for patients with pelvic floor dyssynergia-type constipation, Diseases of the Colon & RectumDis Colon Rectum, 50, 428-41, 2007	Population contained males with no subgroup analysis for sex
Isrctn,, BOD Trial: a double blinded randomised controlled trial of injection of botulinum toxin versus normal saline into the puborectalis muscle in patients with pelvic floor dyssynergia, http://www.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN34573685, 2006	Trial registry - no published papers reported
Nct,, Intravaginal Diazepam for the Treatment of Pelvic Pain Among Women With Pelvic Floor Hypertonic Disorder: a Double Blind, Randomized, Placebo Controlled Trial, Http://clinicaltrials.gov/show/nct01938092, 2013	Trial registry - published paper identified in main search
Rahn, D. D., Ward, R. M., Sanses, T. V., Carberry, C., Mamik, M. M., Meriwether, K. V., Olivera, C. K., Abed, H., Balk, E. M., Murphy, M., Society of Gynecologic Surgeons Systematic Review, Group, Vaginal estrogen use in postmenopausal women with pelvic floor disorders: systematic review and practice guidelines, International Urogynecology Journal, 26, 3-13, 2015	Systematic review - included studies checked for relevance
Weber, M. A., Kleijn, M. H., Langendam, M., Limpens, J., Heineman, M. J., Roovers, J. P., Local Oestrogen for Pelvic Floor Disorders: A Systematic Review, PLoS ONE [Electronic Resource], 10, e0136265, 2015	Systematic review - included studies checked for relevance
Yan, B., Ma, J., Jiang, G., Wang, Y., Ma, Q. L., Effects of pueraria root (pueraria radix) on the content of collagen and elastin in pelvic floor dysfunction patients, International journal of clinical and experimental medicine, 9, 21988-21995, 2016	Outcomes not relevant

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: What is the effectiveness of pharmacological management for improving symptoms associated with pelvic floor dysfunction?

Research question

Is topical vaginal oestrogen effective for treatment of the symptoms of pelvic floor dysfunction?

Why this is important

Topical intravaginal oestrogen is often offered to postmenopausal women who have urogenital symptoms linked to vaginal atrophy but it is also commonly offered to women with pelvic floor dysfunction who have pelvic organ prolapse, urinary symptoms or sexual dysfunction. However, there is very limited evidence to guide whether topical oestrogen is associated with symptomatic improvement or whether this treatment would benefit particular groups of individuals.

Table 6: Research recommendation rationale

Research question	
Why is this needed	
Importance to 'patients' or the population	There is very limited evidence to guide whether oestrogen is associated with improvement of symptoms in women with pelvic floor dysfunction who have prolapse, urinary symptoms or sexual dysfunction symptoms or whether this treatment would benefit particular groups of individuals.
Relevance to NICE guidance	The relative absence of evidence regarding this topic restricts NICE guidance from making recommendations regarding oestrogen in pelvic floor dysfunction. This was also identified as an issue in NG123, in relation to prolapse. The outcome of this research would allow such recommendations to be developed and become part of NICE guidance
Relevance to the NHS	Topical oestrogen is a low cost intervention and its use may reduce the need for interventions with higher cost impacts on the NHS. It may be that the recommendations could be combined with existing advice, such as ring pessaries or devices.
National priorities	N/A
Current evidence base	There is little evidence on the use of oestrogen for the treatment of PFD. The majority of evidence for oestrogen relates to urogenital atrophy
Equality	None identified
Feasibility	RCTs of topical intravaginal oestrogen versus placebo have been carried out in women with OAB and vaginal atrophy, so the research is feasible.

OAB: overactive bladder; PFD: pelvic floor dysfunction; RCT: randomised controlled trial

Table 7: Research recommendation modified PICO table

Criterion	Explanation
Population	Post-menopausal women with symptoms of PFD
Intervention	Topical oestrogen

Criterion	Explanation
Comparator	placebo
Outcomes	• POP symptoms (change in POP-Q) • change in other symptoms of pelvic floor dysfunction • measures of urogenital atrophy
Study design	RCT
Timeframe	6-12 months
Additional information	Include measures of urogenital atrophy

POP: pelvic organ prolapse; POP-Q: Pelvic Organ Prolapse Quantification System; RCT: randomised controlled trial