



**OREGON HEALTH AND SCIENCE UNIVERSITY  
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE**

**Evidence-Based Practice Summary**

**Complementary and Alternative Medicine (CAM) Therapies for Female Cancer Patients with Low Libido**

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**BACKGROUND**

Decreased libido is one of several changes in sexual function that are often experienced by female cancer patients. (Barton 2007). Additionally, problems with sexual function frequently affect the quality of life of female cancer survivors; and sexual function ranks high on surveys of unmet needs of female patients with cancer (Schover 2014; Kornblith & Ligibel 2003; Sadovksy 2010). Contributing to low libido, cancer treatment has been shown to confer different risks of menopause depending on age at diagnosis and chemotherapy regimen and dose (Goodwin 1999). This has led to the need for treatments that have a more generalized (systemic) impact on sexual function. Symptoms can be treated medically by either hormone replacement therapy (HRT) or non-hormonal treatment modalities including clonidine, selective serotonin reuptake inhibitors (SSRI's) and gabapentin (Atema 2016). Although effective in alleviating menopausal symptoms, HRT is contra-indicated in women with a history of breast cancer (Finch 2012; Holmberg 2007). Non-hormonal treatments are moderately effective but have a range of common and bothersome side-effects (Boekout 2011; Bardia 2009; Stan 2013). The objective of this evidence brief is to examine complementary and alternative medicine (CAM) therapies available to treat low libido in female cancer patients.

**ASK THE QUESTION**

**Question 1:** In treatment of low libido in women with cancer, what are the benefits (and harms, if any) of CAM therapies such as acupuncture, chiropractic, massage, homeopathy, Ayurveda, supplements, herbs and botanicals, etc.?

**SEARCH FOR EVIDENCE**



**Databases** included Ovid MEDLINE, MEDLINEinprocess, the Cochrane Central Register of Controlled Trials (CCRCT) & Cochrane Database of Systematic Reviews (CDSR).

1. exp Libido/ (4758)
2. exp Sexual Dysfunctions, Psychological/ (24675)
3. exp Sexual Dysfunction, Physiological/ (27985)
4. 1 or 2 or 3 (34837)
5. (libido\* or ((sex\* or coit\* or intercours\* or copulat\*) adj3 (driv\* or desir\* or arous\* or want\* or need\* or function\* or dysfunction\* or initia\* or participa\*))).mp. (45106)
6. ((reduc\* or low\* or decreas\* or hypoactiv\* or rais\* or increas\* or high\* or elevat\*) adj3 (driv\* or desir\* or arous\* or function\* or dysfunction\* or want\* or need\* or function\* or initia\* or participa\*))).mp. (364319)
7. exp sexual behavior/ (98928)
8. 5 or 6 (404317)
9. 7 and 8 (15626)
10. exp Neoplasms/ (3106401)
11. exp Antineoplastic Agents/ (1001490)
12. exp Radiotherapy/ (174126)
13. exp Antineoplastic Protocols/ (132555)
14. 10 or 11 or 12 or 13 (3676993)
15. 9 and 14 (1289)
16. limit 15 to humans (1284)
17. limit 16 to female (906)
18. limit 17 to (meta analysis or systematic reviews) (37)
19. limit 17 to (controlled clinical trial or guideline or randomized controlled trial) (69)
20. limit 17 to (comparative study or evaluation studies) (91)
21. exp Epidemiologic Studies/ (2177321)
22. 17 and 21 (297)
23. 18 or 19 or 20 or 22 (416)

**Filters/limits** included articles published in English in the last 10 years.

### **CRITICALLY ANALYZE THE EVIDENCE**

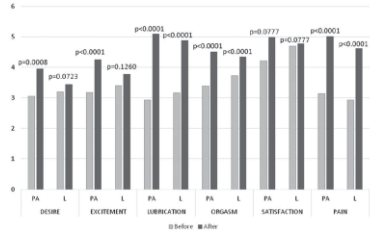


The literature search resulted in limited articles assessing the benefits and/or harms of CAM therapies for female cancer patients with low libido. Two articles were found addressing the question, an RCT testing the efficacy of non-hormonal therapies, and an observational study evaluating a combination of CAM therapies (olive oil, vaginal exercise, and moisturizer).

1. **Polyacrylic Acid:** One RCT (Juliato 2017) tested the efficacy of non-hormonal therapies (lubricant and polyacrylic acid) for vaginal dryness and assessed its effectiveness on sexual function. The polyacrylic group in the study demonstrated a sexual dysfunction from 96% to 24% ( $P < 0.0001$ ) and the lubricant group showed a decrease from 88.9% to 55.6% ( $P = 0.0027$ ).  
*Quality of Evidence: Very Low*
2. **OVERcome:** One Observational Study (Juraskova 2015) was found evaluating the acceptability, feasibility, and efficacy of a novel intervention (Olive Oil, Vaginal Exercise, and MoisturizeR [OVERcome]) to improve sexual problems following breast cancer treatment. OVERcome resulted in significant improvements in dyspareunia, sexual function, and quality of life over time (all  $P < 0.001$ ). Pelvic floor muscle (PFM) relaxation training was reported to be effective ( $P < 0.001$ ). Overall, women rated PFM relaxation exercises (92%), vaginal moisturizers (88%), and olive oil (73%) as helpful, indicating that the intervention was acceptable. Additionally, six cases (11%) of vaginal stenosis were noted during initial screening.  
*Quality of Evidence: Very Low*

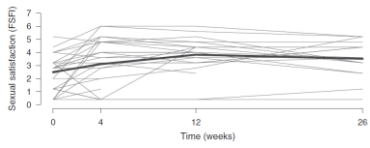
Overall, the evidence for CAM therapies for female cancer patients with low libido is very low. There were limited studies found assessing the benefits of CAM. While both of the included studies demonstrated an improvement in sexual function that was statistically significant, due to inconsistency and imprecision across studies, we cannot conclude with certainty the benefits of CAM therapies amongst female cancer patients with low libido.

PICO Question: In treatment of low libido in women with cancer, what are the benefits (and harms, if any) of CAM therapies such as acupuncture, chiropractic, massage, homeopathy, Ayurveda, supplements, herbs and botanicals, etc.						Lower Quality Rating if: <input checked="" type="checkbox"/> Studies inconsistent (wide variation of treatment effect across studies, populations, interventions, or outcomes varied)  <input type="checkbox"/> Studies are indirect (PICO question is quite different from the available evidence in regard to population,
Modality: Polyacrylic Acid						
Author/Date	Purpose of Study	Study Design & Methods	Sample	Outcomes	Design Limitations	
Total # of Studies: 1 # of RCTs: 1						
Juliato, P.T., et al., 2017, <i>Climacteric</i>	To test the efficacy of two non-hormonal therapies for vaginal dryness, lubricant and polyacrylic	RCT; Included women with breast cancer who were being treated with tamoxifen and who complained of vaginal dryness. The volunteers answered two questionnaires to evaluate sexual function (Female Sexual Function Index, FSFI) and a customized GSM questionnaire. The women were randomized	52 women with breast cancer; 25 in the polyacrylic acid group and 27 in the lubricant group	The polyacrylic acid group showed a decrease in sexual dysfunction from 96% to 24% (p<0.0001) and the lubricant group showed a decrease from 88.9% to 55.6% (p=0.0027).	Study Limitations = <input type="checkbox"/> None <b>RCTS</b> <input checked="" type="checkbox"/> Lack of blinding <input checked="" type="checkbox"/> Lack of allocation concealment <input type="checkbox"/> Stopped early for benefit <input type="checkbox"/> Incorrect analysis of ITT <input type="checkbox"/> Selective reporting of measures (e.g., no effect outcome)	

	acid	into two groups: 25 (48.1%) in the polyacrylic acid group and 27 (51.9%) in the lubricant group, using either one of the treatments for 30 days, and after they were invited to answer the questionnaires again.			<input checked="" type="checkbox"/> Large losses to F/U <input type="checkbox"/> Difference in important prognostic factors at baseline	<i>intervention, comparison, or outcome)</i>  <input checked="" type="checkbox"/> Studies are imprecise ( <i>When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain</i> )  <input type="checkbox"/> Publication Bias ( <i>e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found</i> )  <u>Increase Quality Rating if:</u> <input type="checkbox"/> Large Effect <input type="checkbox"/> Dose-response gradient <input type="checkbox"/> Plausible confounders or other biases increase certainty of effect  Quality (certainty) of evidence for studies as a whole: <input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very Low
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**PICO Question:** In treatment of low libido in women with cancer, what are the benefits (and harms, if any) of CAM therapies such as acupuncture, chiropractic, massage, homeopathy, Ayurveda, supplements, herbs and botanicals, etc.

Lower Quality Rating if:

Modality: OVERcome					
Author/Date	Purpose of Study	Study Design & Methods	Sample	Outcomes	Design Limitations
Total # of Studies: 1 # of Non-Randomized Studies: 1					
Juraskova, I., et al., 2015, <i>Journal of Sexual Medicine</i>	To prospectively evaluate the acceptability, feasibility, and efficacy of a novel intervention (Olive Oil, Vaginal Exercise, and MoisturizeR [OVERcome]) to improve sexual problems following breast cancer treatment.	Observational Study; Women with dyspareunia were instructed to perform pelvic floor muscle (PFM) relaxation exercises twice/day to prevent/manage PFM overactivity, apply a polycarbophil-based vaginal moisturizer three times/week to alleviate vaginal dryness, use olive oil as a lubricant during intercourse, and complete a weekly compliance diary. PFM relaxation training was administered by a physiotherapist at weeks 0 and 4, with follow-up at weeks 12 and 26. At each visit, women completed validated self-report questionnaires and the physiotherapist recorded objective measures of PFM functioning.	25 breast cancer survivors	<p>OVERcome resulted in significant improvements in dyspareunia, sexual function, and quality of life over time (all <math>P &lt; 0.001</math>). PFM relaxation training was reported to be effective (<math>P \leq 0.001</math>). Maximum benefits were observed at week 12. Most women rated PFM relaxation exercises (92%), vaginal moisturizer (88%), and olive oil (73%) as helpful, indicating that the intervention was acceptable. Unexpectedly, six cases (11%) of vaginal stenosis were noted during initial screening.</p> 	<p>Study Limitations =</p> <p><input type="checkbox"/> None</p> <p><b>Non-Randomized Studies</b></p> <p><input type="checkbox"/> Failure to develop and apply appropriate eligibility criteria</p> <p><input type="checkbox"/> Flawed measurement of both exposure and outcome</p> <p><input type="checkbox"/> Failure to adequately control confounding</p> <p><input checked="" type="checkbox"/> Incomplete or inadequately short follow-up</p> <p><input type="checkbox"/> Differences in important prognostic factors at baseline</p> <p><input checked="" type="checkbox"/> Studies inconsistent (wide variation of treatment effect across studies, populations, interventions, or outcomes varied)</p> <p><input type="checkbox"/> Studies are indirect (PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)</p> <p><input checked="" type="checkbox"/> Studies are imprecise (When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)</p> <p><input type="checkbox"/> Publication Bias (e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)</p> <p><u>Increase Quality Rating if:</u></p> <p><input type="checkbox"/> Large Effect</p> <p><input type="checkbox"/> Dose-response gradient</p> <p><input type="checkbox"/> Plausible confounders or other</p>



DATE: October 2017

						biases increase certainty of effect  Quality (certainty) of evidence for studies as a whole: <input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very Low
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### Guideline Recommendations:

One guideline included recommendations on CAM therapies for female cancer patients, which is outlined below.

The United Kingdom's National Institute for Health and Care Excellence (NICE)'s **National Collaborating Centre for Women's and Children's Health** in 2015 recommended the following for complementary therapies:

#### *Complementary Therapies and Unregulated Preparations*

Explain to women that the efficacy and safety of unregulated compounded bioidentical hormones are unknown.

Explain to women who wish to try complementary therapies that the quality, purity and constituents of products may be unknown.

Advise women with a history of, or at high risk of, breast cancer that, although there is some evidence that St John's wort may be of benefit in the relief of vasomotor symptoms, there is uncertainty about:

- Appropriate doses
- Persistence of effect
- Variation in the nature and potency of preparations
- Potential serious interactions with other drugs (including tamoxifen, anticoagulants and anticonvulsants)



DATE: October 2017

### Guideline Ratings

Guideline Issuer and Date	NICE 2015
1. Transparency	A
2. Conflict of interest	A
3. Development group	A
4. Systematic Review	A
5. Supporting evidence	A
6. Recommendations	B
7. External Review	NR
8. Currency and updates	B

See appendix B for full description of the Trustworthy Guideline grading system.

## **REFERENCES:**

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3. Barton, D. L., et al. (2007). "Randomized controlled trial to evaluate transdermal testosterone in female cancer survivors with decreased libido; North Central Cancer Treatment Group protocol N02C3." *Journal of the National Cancer Institute* 99(9): 672-679.
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9. Juliato, P. T., et al. (2017). "Can polyacrylic acid treat sexual dysfunction in women with breast cancer receiving tamoxifen?" *Climacteric* 20(1): 62-66.
10. Juraskova, I., et al. (2013). "The acceptability, feasibility, and efficacy (phase I/II study) of the OVERcome (Olive Oil, Vaginal Exercise, and MoisturizeR) intervention to improve dyspareunia and alleviate sexual problems in women with breast cancer." *Journal of Sexual Medicine* 10(10): 2549-2558.
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13. Sadovsky, R., et al. (2010). "Cancer and Sexual Problems." *The Journal of Sexual Medicine* 7(1, Part 2): 349-373.
14. Schover, L. R., et al. (2014). "Sexual dysfunction and infertility as late effects of cancer treatment." *European Journal of Cancer Supplements* 12(1): 41-53.
15. Stan, D., et al. "Breast Cancer Survivorship Issues." *Hematology/Oncology Clinics* 27(4): 805-827.





## Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

### ***Grades and interpretations:***

High: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low: Any estimate of effect is very uncertain.

### ***Type of evidence and starting level***

Randomized trial—high

Observational study—low

Any other evidence—very low

### ***Criteria for increasing or decreasing level***

#### **Reductions**

Study quality has serious (–1) or very serious (–2) problems

Important inconsistency in evidence (–1)

Directness is somewhat (–1) or seriously (–2) uncertain

Sparse or imprecise data (–1)

Reporting bias highly probable (–1)

#### **Increases**

Evidence of association† strong (+1) or very strong (+2)

†Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.



## Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

### 1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:  
Who wrote the initial draft  
How the committee voted on or otherwise approved recommendations  
Evidence review, external review and methods used for updating are not addressed in this standard.

### 2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything,



this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

### 3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

### 4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:

Describe itself as systematic or report search strategies using multiple databases

Define the scope of the review (including key questions and the applicable population)

Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

### 5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.



To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

## 6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

## 7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

## 8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers’ stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst’s discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.