



OncANP

Oncology Association of Naturopathic Physicians

FONO: Endocrine Therapy in Breast Cancer
& Naturopathic Co-management

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www.knowoncology.org





Disclosures

- This presentation is based on current best evidence as of August 2023. The research will definitely change with time...
- Dedicated to all of the people living with cancer who participated in the trials included in this talk. We all benefit so much from their participation
- I have no commercial affiliations





Webinar Two: MANAGING SIDE EFFECTS

- Drug Interactions with ET
- Tamoxifen support
- Hot flashes
- AIMSS (AI Induced Musculoskeletal Syndrome)
- Genitourinary syndrome of Menopause
- Sexual dysfunction
- Cardiac late effects
- Cognitive Changes
- Bonus: Fatigue, Mood Support

(Note: Bone density support is included in webinar 3)





Some Practice Principles

- Stay curious/letting go of preconceived notions
- Deep listening/empty vessel
- Reinforce peoples' strengths
- Meet people where they are at
- Say "I can get back to you with that information" when we are unsure or don't know
- Love



("patients who are hardest to love are usually the people who need love the most" –
Dr Sat Dharam Kaur ND)

Drug Interactions with Tam

- ▶ Tam metabolized mainly by CYP2D6 & UDP-glucuronyltransferase-2B7. Minor metabolism by p-glycoprotein, CYP3A4.
- ▶ Endoxifen most clinically relevant metabolite (14,15) but threshold level questionable bec 1mg Tam and 5 mg Tam caused similar effect on KI67 as 20mg, blood parameters did slightly differ (eg. IGF-1)(29)
- ▶ Don't combo with Paroxetine/Paxil (1), Fluoxetine/Prozac (2), diphenhydramine/Benadryl, cimetidine/tagamet (3)
- ▶ Safe to use citalopram/Celexa & venlafaxine/Effexor (4)

1. <https://pubmed.ncbi.nlm.nih.gov/20141708/>,
<https://pubmed.ncbi.nlm.nih.gov/20142325/>
2. <https://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet#r17>
3. https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf
4. Adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer. UpToDate.March 2020.
5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5571834/>
6. <https://www.mdpi.com/2072-6694/11/3/403/htm>
7. <https://pubmed.ncbi.nlm.nih.gov/24312387>
8. [Red clover and lifestyle changes to contrast menopausal symptoms in premenopausal patients with hormone-sensitive breast cancer receiving tamoxifen - PubMed \(nih.gov\)](#)
9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5950942/>
10. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3625417/>
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13. <https://pubmed.ncbi.nlm.nih.gov/23881421/>
14. <https://www.pharmgkb.org/pathway/PA145011119>

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16. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562884/>
17. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1865122/>
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19. <https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0032-1315117#RW0183-59>
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21. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562884/>
22. <http://onlinelibrary.wiley.com/doi/10.1067/mcp.2002.126913/abstract>
23. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1858666/>
24. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1894911/>
25. <https://www.ncbi.nlm.nih.gov/pubmed/15328251>
26. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1865122/>

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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1858666>

/

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Drug Interactions with Tam

- ▶ Tam contraindicated with DIM 300mg (caused endoxifen levels to drop below proposed therapeutic threshold) (5)
- ▶ 3.6 g curcumin with bioperine lowered endoxifen levels (7.7% for curcumin alone, 12.4% for curcumin + piperine (6) (can evaluate risk/benefit of lower doses of curcumin)
- ▶ Panax Ginseng 1500mg standardized to 5% ginsenosides caused ~7% change in CYP2D6 metabolism which was deemed not clinically relevant (23)
- ▶ Based on human studies, safe to combine Tam with; Soy (7), Red Clover (8) Fucoidan 1000mg (9), Ginkgo 240mg (10) Flaxseeds (11) Green tea (12) Grape seed extract 300mg (13) Black Cohosh 80mg (16,17, 27, 28), Garlic (18,19), Milk Thistle 900mg (20,21) Valerian 1000mg (24,25)

1. <https://pubmed.ncbi.nlm.nih.gov/20141708/>,
<https://pubmed.ncbi.nlm.nih.gov/20142325/>
2. <https://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet#r17>
3. https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf
4. Adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer. UpToDate. March 2020.
5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5571834/>
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9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5950942/>
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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562884>

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28.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1858666>

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Drug Interactions with AI's & SERD's

- Anastrozole & letrozole metabolized primarily by p-glycoprotein, no drug-drug interactions so no expected herb-drug interactions other than avoid anything raising serum estrogen (1,6)
- Exemestane/Aromasin extensively metabolized by CYP3A4 so caution with CYP3A4 inducers or inhibitors
- Fulvestrant/Faslodex/SERD is IM so limited concerns
- Elacestrant/Orserdu metabolized by CYP3A4 so avoid with CYP3A4 inducers or inhibitors. To a lesser extent, metabolized by CYP2A6 & CYP2C9. It is a strong P-gp and BCRP inhibitor. Taking it with a high fat meal greatly increases AUC and C_{max} (14)

CYP3A4 in webinar 3

1. <https://pubmed.ncbi.nlm.nih.gov/24312387>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4077601/>
3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5950942/>
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Tamoxifen Support

- Mediterranean diet (1)
- High vegetable intake associated with reduced breast cancer recurrence in Tam users (2)
- Organic soy to be included regularly (eg. organic soymilk, tofu, tempeh and miso). High soy consumption was associated with reduced risk of death from all causes, often with Tam users benefitting most (3-5)
- Exercise (6)
- **CoQ10** 100-200mg daily to rebalance lipids, lower inflammation, improve cognitive function and improve quality of life (7-14)
- Vit D3 2000-10,000IU daily, individualized to the patient (15,16)
- Melatonin 6-20mg nightly to work synergistically with tamoxifen (17,18). Improves sleep (19)

1. [Red clover and lifestyle changes to contrast menopausal symptoms in premenopausal patients with hormone-sensitive breast cancer receiving tamoxifen - PubMed \(nih.gov\)](#)
2. <https://www.ncbi.nlm.nih.gov/pubmed/20607600>
3. Kaczor, Tina. The Effects of Soy Consumption on Breast Cancer Prognosis, NMJ. Nov 7, 20120.
http://www.naturalmedicinejournal.com/article_content.asp?article=377
4. <https://www.ncbi.nlm.nih.gov/pubmed/21357380>
5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3470874/#!po=7.14286>
6. <https://pubmed.ncbi.nlm.nih.gov/34480935/>
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25. <https://www.pubmed.com/pubmed/25471334>
26. <https://www.ncbi.nlm.nih.gov/pubmed/16047556>
27. <https://www.ncbi.nlm.nih.gov/pubmed/25809414>

Tamoxifen Support

Other therapeutic considerations;

- Multivitamin with B Complex and vitamin C to correct lipids and antioxidant status issues with Tamoxifen (20,21)
- Omega 3 fatty acids to support joints and decrease inflammation (27)
- Green tea extract for recurrence prevention (23) [safety of green tea with Tamoxifen (24)]
- Coriolus/Turkeytail hot water extract for immune support (26)



1. [Red clover and lifestyle changes to contrast menopausal symptoms in premenopausal patients with hormone-sensitive breast cancer receiving tamoxifen - PubMed \(nih.gov\)](#)
2. <https://www.ncbi.nlm.nih.gov/pubmed/20607600>
3. Kaczor, Tina. The Effects of Soy Consumption on Breast Cancer Prognosis, NMJ. Nov 7, 20120.
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26. <https://www.ncbi.nlm.nih.gov/pubmed/16047556>
27. <https://www.ncbi.nlm.nih.gov/pubmed/25809414>

Tamoxifen Adjuncts:

<https://oncanp.org/wp-content/uploads/2019/12/tamoxifen-hyperlinks.pdf>

TAMOXIFEN AND INTEGRATIVE CARE

Tamoxifen is an important medication for preventing breast cancer recurrence, however it sometimes causes side effects such as hot flashes, weight gain, mood changes, and increased inflammation and lipid levels. Complementary approaches may be helpful in managing some side effects from tamoxifen. Adding herbs or supplements to your cancer care plan is not always safe. It is important to consider interactions, dosing, and quality of products. Please consult with a naturopathic doctor (https://oncanp.org) or integrative oncology professional (https://oncanp.org) for specific guidance.

NUTRITION AND TAMOXIFEN

High vegetable intake is associated with reduced breast cancer recurrence in tamoxifen users.^{1,2}



Soy foods are safe for breast cancer survivors taking tamoxifen.^{3,4} Some studies have found that soy intake improves survival or recurrence⁵ in people with a history of breast cancer, while other studies found no evidence of improved survival with no risk of harm.⁶ Soy may be beneficial for cardiovascular disease prevention and risk of stroke.⁷ Aim for organic whole soy foods such as soy milk, tofu, edamame, tempeh, and miso.

Drinking green tea may help prevent recurrence and is safe to combine with tamoxifen.⁸



NATURAL THERAPIES

Some natural therapies can work well with tamoxifen to improve overall health and quality of life.

- Melatonin may reduce depression in breast cancer survivors.⁹ In people with advanced breast cancer, melatonin seemed to help tamoxifen work better¹⁰ and it may improve quality of life.¹¹
- CyG10 can normalize blood lipid levels, lower inflammation and lower tumor markers in tamoxifen users.¹²
- Vitamin C can help lower inflammation and markers of oxidative stress in tamoxifen users.¹³
- Cerular vesicitor (burley root mushroom) may support immune function¹⁴ and Cordyceps lucidus (cord) mushroom may boost energy levels in breast cancer survivors.¹⁵
- Vitamin D3 supports mood, bone integrity, energy levels and immunity.¹⁶
- Black cohosh may be associated with a lower risk of breast cancer and lower recurrence in some studies, and has had no association with breast cancer risk in other studies.¹⁷
- In breast cancer survivors, adding vitamin E to tamoxifen for 5 years did not improve survival.¹⁸

To individualize your care plan, consult with a naturopathic doctor (https://oncanp.org) or integrative oncology professional (https://oncanp.org). For more information on quality and sources for supplements, see loc4.org.



NATURAL APPROACHES FOR HOT FLASHES

- Acupuncture¹⁹ and Traditional Chinese Medicine²⁰ may reduce hot flashes in patients with breast cancer. Consult a trained practitioner including a Licensed Naturopathic Doctor or acupuncturist for treatment.
- Taking magnesium alongside tamoxifen may reduce hot flashes.²¹
- Black cohosh has been studied for hot flashes, but studies have mixed results.²²
- Two randomized controlled trials in breast cancer survivors with hot flashes showed that homogeneity did not help hot flashes, but did help quality of life more than placebo.²³



PRECAUTIONS

- Disodiumbutane (DBM) may reduce the effectiveness of tamoxifen.²⁴
- High-dose curcumin, either with or without piperine, may decrease the effectiveness of tamoxifen by changing how it is processed.²⁵

<https://oncanp.org/wp-content/uploads/2019/12/tamoxifen-hyperlinks.pdf>

Hot Flashes from ET

- Note: Severe hot flashes may be problematic for heart disease risk (23)
- Ddx hyperthyroid, niacin flushes, hypoglycemia
- Sleep is sacred
- **Lifestyle**; Stress reduction (1) Group Cognitive Behavioral Therapy (2) Relaxation therapies (3) Yoga and relaxation training (4) Cool pad pillow topper (5) or cooling blanket, watch for dietary triggers like spicy food, sugar and alcohol
- **Black Cohosh** 40-80mg
 - In an RCT of women taking Tam, black cohosh improved hot flashes (6) and sexual function (7) [caution if history of bipolar (8)]
 - In an RCT, Remifemin combined with Goserelin or Leuprorelin improved Kupperman menopause index scores (18)
 - Black cohosh is not estrogenic. 2 studies reported significant reductions in risk of primary BC and risk of BC recurrence (19)

Tam hot flashes are generally worse than AI,
most research conducted on the aged extract Remifemin

1. [A randomized controlled trial of relaxation training to reduce hot flashes in women with primary breast cancer - PubMed \(nih.gov\)](#)
2. [Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment](#)

- (MENOS 1): a randomised controlled trial - PMC (nih.gov)
3. A randomized controlled trial of cognitive-behavioral stress management in breast cancer: survival and recurrence at 11-year follow-up - PMC (nih.gov)
 4. Yoga of Awareness program for menopausal symptoms in breast cancer survivors: results from a randomized trial - PubMed (nih.gov)
 5. A randomised trial of the cool pad pillow topper versus standard care for sleep disturbance and hot flushes in women on endocrine therapy for breast cancer - PubMed (nih.gov)
 6. Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer - PubMed (nih.gov)
 7. Effects of Cimicifuga racemosa (L.) Nutt on sexual function in women receiving tamoxifen for breast cancer: Journal of Obstetrics and Gynaecology: Vol 42, No 7 (tandfonline.com)
 8. <https://pubmed.ncbi.nlm.nih.gov/32955954/>
 9. The comparison of the effect of soybean and fish oil on supplementation on menopausal symptoms in postmenopausal women: A randomized, double-blind, placebo-controlled trial - ScienceDirect
 10. Omega-3 versus isoflavones in the control of vasomotor symptoms in postmenopausal women - PubMed (nih.gov)
 11. <https://pubmed.ncbi.nlm.nih.gov/24518152>
 12. <https://pubmed.ncbi.nlm.nih.gov/23881421/>

13. [Evaluation of the effect of Silybum marianum extract on menopausal symptoms: A randomized, double-blind placebo-controlled trial - PubMed \(nih.gov\)](#)
14. [Relevance of in vitro and clinical data for predicting CYP3A4-mediated herb-drug interactions in cancer patients.](#)
<https://www.ncbi.nlm.nih.gov/pubmed/23394826>
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19. [Black cohosh and breast cancer: a systematic review - PubMed \(nih.gov\)](#)
20. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4442087/>
21. www.ncbi.nlm.nih.gov/pubmed/25423327
22. [Hypomagnesemia and Its Relationship with Oxidative Stress Markers in Women with Breast Cancer - PubMed \(nih.gov\)](#)
23. [Vasomotor menopausal symptoms and risk of cardiovascular disease: a pooled analysis of six prospective studies - PubMed \(nih.gov\)](#)

Hot Flashes in Breast Cancer

Acupuncture mixed research for hot flashes in people living with cancer (5-8)

- Combined data from six studies indicates at least 3 months of positive effects after the end of acupuncture treatment for flashes in women with breast cancer (9)
- According to meta-analysis, acupuncture improves quality of life in breast cancer survivors taking hormone blockers (10) and especially useful for joint pain from AI's (11)
- In an RCT, women undergoing ET received 12 weeks of acupuncture vs venlafaxine, both groups had similarly decreased hot flashes, depressive symptoms, and QOL at 1 yr. Venlafaxine had 18 adverse effects (eg, nausea, dry mouth, dizziness, anxiety) vs none in acupuncture. Acupuncture had added benefit of increased sex drive in some women (14)
- HT 8, KI 10, LV 2, GV 20, M-HN-3/Yintang between eyebrows for anxiety (12)
- DU/GV 20, PC 6, HT 7, LV 3, LI 4, LI 11, KI 3, SP 6, ST 36, REN/CV 17, REN/CV 6 and then DU/GV 14, BL 15, BL 18, BL 20, BL 23, GB 34 and KI 3 (13)

1. <https://pubmed.ncbi.nlm.nih.gov/12884894/>
2. <https://pubmed.ncbi.nlm.nih.gov/15750359/>
3. <https://www.ncbi.nlm.nih.gov/pubmed/26051564>
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5. [Systematic review of acupuncture to control hot flashes in cancer patients - PubMed \(nih.gov\)](#)
6. [Acupuncture for hot flashes in patients with prostate cancer - PubMed \(nih.gov\)](#)
7. [Acupuncture for treating hot flushes in men with prostate cancer: a systematic review - PubMed \(nih.gov\)](#)
8. [Effect of acupuncture on hot flush and menopause symptoms in breast cancer- A systematic review and meta-analysis - PubMed \(nih.gov\)](#)
9. [How long do the effects of acupuncture on hot flashes persist in cancer patients? - PubMed \(nih.gov\)](#)
10. [Systematic Review with Meta-Analysis: Effectiveness and Safety of Acupuncture as Adjuvant Therapy for Side Effects Management in Drug Therapy-Receiving Breast Cancer Patients - PubMed \(nih.gov\)](#)
11. [Acupuncture for Arthralgia Induced by Aromatase Inhibitors in Patients with Breast Cancer: A Systematic Review and Meta-analysis - PubMed \(nih.gov\)](#)
12. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3731680/>

13. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3246091/>
14. <https://pubmed.ncbi.nlm.nih.gov/20038728/>

Hot Flashes in Breast Cancer

Homeopathy mixed research with one study showing benefit (1) and one without benefit (2)

- In cancer patients, improved global health status and subjective wellbeing (3)
- Improved Insomnia Severity Index Score (4)

Magnesium mixed research because placebo had such good efficacy (20,21)

- Women with breast cancer more likely to have low magnesium (22)
- Consider if signs of mag def (leg cramps, heart palpitations, tight muscles, headache, constipation, difficulty sleeping)

Chicory and Fumitory syrup (traditional Iranian medicine): In an RCT of 96 breast cancer survivors taking endocrine therapy, those who took Chicory and Fumitory syrup 5mL 3x daily for 4 weeks had reduced frequency & severity of hot flashes (14)

Caution or avoid: Maca, Vit E

Homeopathic constitutional remedy helps;
Sep, Lach, Carc, Sulph, Puls most common

1. <https://pubmed.ncbi.nlm.nih.gov/12884894/>
2. <https://pubmed.ncbi.nlm.nih.gov/15750359/>
3. <https://www.ncbi.nlm.nih.gov/pubmed/26051564>
4. <https://www.ncbi.nlm.nih.gov/pubmed/30935555>
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12. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3731680/>

13. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3246091/>
14. <https://www.liebertpub.com/doi/full/10.1089/jicm.2022.0624>

Hot Flashes in Menopause (not cancer population studies)

- **Ground flax seeds** (27)
- **Omega 3 Fatty Acids/Fish oil** (10,11)
- **Grape seed extract** 200mg (18) [safety of 300mg with Tamoxifen (19)]. Also for depression, anxiety, sleep, blood pressure (23) metabolic syndrome (24)
- **Pine bark extract/pycnogenol**. Improved hot flashes + blood pressure (26)
- **Milk Thistle** (12) [safety studies showing no CYP interactions (13-17)]
- **Saffron** – Improved hot flashes + depression (8)
- **Rheum raphonticum/ ERr731** (20,21) [Safety: No change in estradiol levels or endometrial thickness (22)]. Also decreases anxiety (25)
- **Bioflavonoids/hesperidin** (9)
- **St John's Wort** (28). Contraindicated with CDK4/6 Inhibitors. Caution Tam

1. [Systematic review of acupuncture to control hot flashes in cancer patients - PubMed \(nih.gov\)](#)
2. [Acupuncture for hot flashes in patients with prostate cancer - PubMed \(nih.gov\)](#)
3. [Acupuncture for treating hot flushes in men with prostate cancer: a systematic review - PubMed \(nih.gov\)](#)
4. [Effect of acupuncture on hot flush and menopause symptoms in breast cancer- A systematic review and meta-analysis - PubMed \(nih.gov\)](#)
5. [How long do the effects of acupuncture on hot flashes persist in cancer patients? - PubMed \(nih.gov\)](#)
6. [Systematic Review with Meta-Analysis: Effectiveness and Safety of Acupuncture as Adjuvant Therapy for Side Effects Management in Drug Therapy-Receiving Breast Cancer Patients - PubMed \(nih.gov\)](#)
7. [Acupuncture for Arthralgia Induced by Aromatase Inhibitors in Patients with Breast Cancer: A Systematic Review and Meta-analysis - PubMed \(nih.gov\)](#)
8. [Efficacy of Crocus sativus \(saffron\) in treatment of major depressive disorder associated with post-menopausal hot flashes: a double-blind, randomized, placebo-controlled trial - PubMed \(nih.gov\)](#)
9. Philp HA. Hot flashes - a review of the literature on

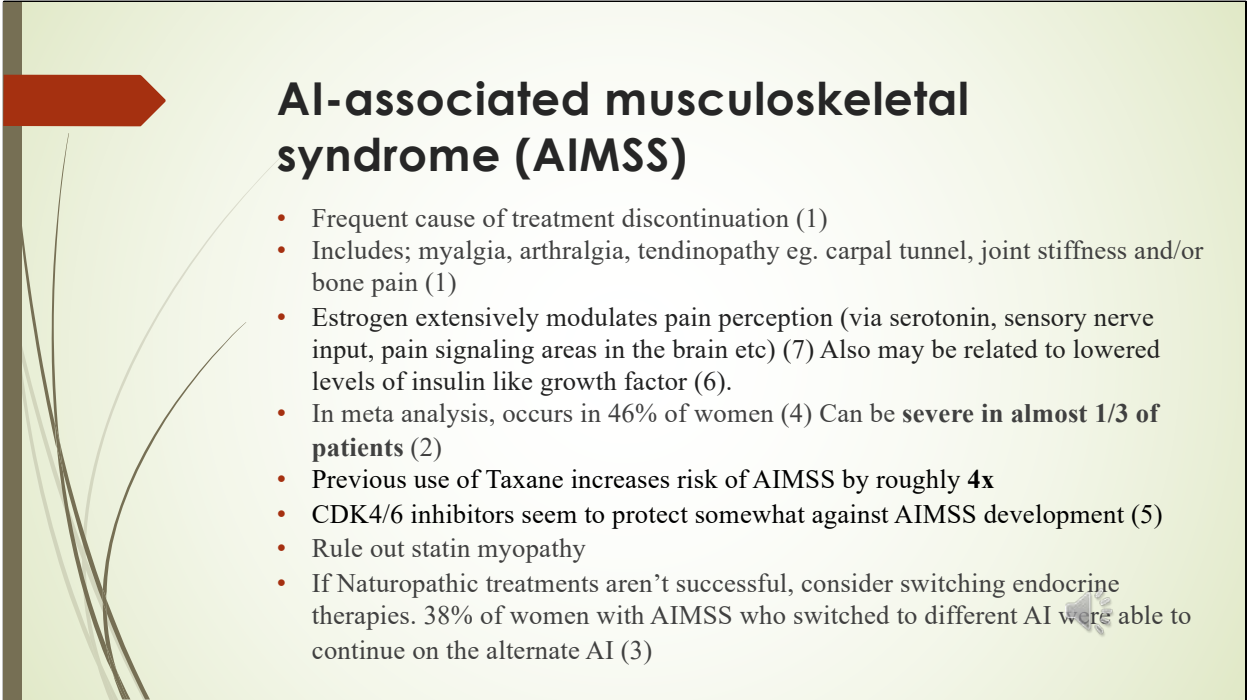
- alternative and complementary treatment approaches. *Altern Med Rev.* 2003;8(3):284-302.
10. [The comparison of the effect of soybean and fish oil on supplementation on menopausal symptoms in postmenopausal women: A randomized, double-blind, placebo-controlled trial – ScienceDirect](#)
 11. [Omega-3 versus isoflavones in the control of vasomotor symptoms in postmenopausal women - PubMed \(nih.gov\)](#)
 12. [Evaluation of the effect of Silybum marianum extract on menopausal symptoms: A randomized, double-blind placebo-controlled trial - PubMed \(nih.gov\)](#)
 13. [Relevance of in vitro and clinical data for predicting CYP3A4-mediated herb-drug interactions in cancer patients.](#)
 14. <https://www.ncbi.nlm.nih.gov/pubmed/23394826>
 15. [See comment in PubMed Commons below](#)
[Clinical assessment of CYP2D6-mediated herb-drug interactions in humans: Effects of milk thistle, black cohosh, goldenseal, kava kava, St. John's wort, and Echinacea - PMC \(nih.gov\)](#)
 16. <https://www.ncbi.nlm.nih.gov/pubmed/15536458>
 17. [The effect of silymarin on oral nifedipine pharmacokinetics - PubMed \(nih.gov\)](#)
 18. <https://pubmed.ncbi.nlm.nih.gov/24518152>
 19. <https://pubmed.ncbi.nlm.nih.gov/23881421/>
 20. <https://pubmed.ncbi.nlm.nih.gov/18978638/>
 21. <https://pubmed.ncbi.nlm.nih.gov/16894335/>
 22. <https://pubmed.ncbi.nlm.nih.gov/18978638/>
 23. <https://pubmed.ncbi.nlm.nih.gov/24518152>
 24. <https://www.ncbi.nlm.nih.gov/pubmed/24518152>
 25. [The special extract ERr 731 of the roots of Rheum rhaponticum decreases anxiety and improves health](#)

[state and general well-being in perimenopausal women - PubMed \(nih.gov\)](#)

26. <https://obgyn.onlinelibrary.wiley.com/doi/full/10.1080/00016340701446108>

27. <https://pubmed.ncbi.nlm.nih.gov/25882265>

28. <https://pubmed.ncbi.nlm.nih.gov/19194342/>



AI-associated musculoskeletal syndrome (AIMSS)

- Frequent cause of treatment discontinuation (1)
- Includes; myalgia, arthralgia, tendinopathy eg. carpal tunnel, joint stiffness and/or bone pain (1)
- Estrogen extensively modulates pain perception (via serotonin, sensory nerve input, pain signaling areas in the brain etc) (7) Also may be related to lowered levels of insulin like growth factor (6).
- In meta analysis, occurs in 46% of women (4) Can be **severe in almost 1/3 of patients** (2)
- Previous use of Taxane increases risk of AIMSS by roughly **4x**
- CDK4/6 inhibitors seem to protect somewhat against AIMSS development (5)
- Rule out statin myopathy
- If Naturopathic treatments aren't successful, consider switching endocrine therapies. 38% of women with AIMSS who switched to different AI were able to continue on the alternate AI (3)

1. **Adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer. UpToDate. March 2020**
2. <https://pubmed.ncbi.nlm.nih.gov/18021478/>
3. <https://pubmed.ncbi.nlm.nih.gov/22331951/>
4. <https://pubmed.ncbi.nlm.nih.gov/28204994/>
5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8353230/>
6. <https://pubmed.ncbi.nlm.nih.gov/21273342/>
7. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6656561/>

AIMSS: Vitamin D3

- Vit D3 deficiency **extremely common** in women taking AI's: One study 86% of women <30ng/mL (9), another study 63% women < 30ng/mL (10)
- Supplementing vitamin D3 improves joint and muscle pain (11,12)
- For breast cancer recurrence prevention, aim for Vitamin D in the middle to upper quarter of reference range (**40-80 ng/ml in US or in Canada 100-200 nmol/L**) (13,14)
- In a cohort study, **40 ng/mL = 100nmol/L found** to be threshold needed to reduce AI arthralgia in (6)
- In a double-blind RCT, women receiving adjuvant Anastrozole who took 50,000IU Vitamin D weekly for 8-16 weeks had improved musculoskeletal symptoms and less bone loss (5)



1. <https://pubmed.ncbi.nlm.nih.gov/27914569/>
2. <https://pubmed.ncbi.nlm.nih.gov/25439039/>
3. <https://pubmed.ncbi.nlm.nih.gov/12963976/>
4. <https://pubmed.ncbi.nlm.nih.gov/21868542>
5. <https://pubmed.ncbi.nlm.nih.gov/21691817/>
6. <https://pubmed.ncbi.nlm.nih.gov/20665105/>
7. <https://pubmed.ncbi.nlm.nih.gov/19125120>
8. <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199265>
9. <https://pubmed.ncbi.nlm.nih.gov/19125120>
10. <https://pubmed.ncbi.nlm.nih.gov/19655244/>
11. <https://pubmed.ncbi.nlm.nih.gov/21691817/>
12. <https://pubmed.ncbi.nlm.nih.gov/28770449/>
13. <https://pubmed.ncbi.nlm.nih.gov/20665105/>
14. <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199265>

AIMSS Treatment Options



- **Acupuncture:** Multiple systematic reviews show acupuncture to be effective for AI arthralgia (3-5) Acupuncture is recommended in the UpToDate endocrine therapy section (6) In a systematic review comparing clinical effectiveness, acu was the highest ranked intervention to improve pain (15)
- **Exercise:** In a systematic review, aerobic exercise was effective at decreasing pain scores in women with AI-associated arthralgia (1)
- **Yoga:** In an RCT, yoga reduced AI-associated knee joint pain while reducing inflammation/serum cytokines (2)
- **Tart Cherry juice concentrate** 1 oz (2 TBSP): In a double blind RCT, women taking AI's who took tart cherry juice 1 oz in 8 oz water daily for 6 weeks had reduced joint pain (7) (note: tart cherry juice also improves cognition in older adults 8)
- **Yi Shen Jian Gu Granules** : In a double blind RCT, women experiencing AIMSS who took Yi Shen Jian Gu Granules twice daily in hot water for 12 weeks had improved pain (1) Two other uncontrolled trials on YiShen Jian Gu Granules also showed benefit (2,3)

Tart cherry: <https://www.gardenia.net/plant/prunus-cerasus-montmorency><https://www.gardenia.net/plant/prunus-cerasus-montmorency>

1. <https://pubmed.ncbi.nlm.nih.gov/30415752/>
2. <https://pubmed.ncbi.nlm.nih.gov/34290337/>
3. <https://pubmed.ncbi.nlm.nih.gov/30415752/>
4. [Acupuncture for Arthralgia Induced by Aromatase Inhibitors in Patients with Breast Cancer: A Systematic Review and Meta-analysis - PubMed \(nih.gov\)](#)
5. <https://pubmed.ncbi.nlm.nih.gov/30415752/>
6. Adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer. UpToDate. March 2020
7. <https://pubmed.ncbi.nlm.nih.gov/34275765/>
8. <https://pubmed.ncbi.nlm.nih.gov/31287117/>
9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6681817/>
10. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6681817/>
11. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5809189/>
12. https://aacrjournals.org/cancerres/article/75/9_Supplement/P1-09-03/606734/Abstract-P1-09-03-Prevention-of-aromatase
13. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4451174/>
14. <https://pubmed.ncbi.nlm.nih.gov/29890985/>

15. <https://pubmed.ncbi.nlm.nih.gov/36535489/>

Kinesio Taping

In an RCT, women taking AI's or Tamoxifen who received 3 neuromuscular taping sessions over 5 weeks had significantly reduced pain (VAS) and improved QOL(1)



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5996544/figure/Fig1/>

1 carpal tunnel, 2 cervical 3 lumbar 4,5 and 6 all sham
No changes in CRP

1. <https://pubmed.ncbi.nlm.nih.gov/29890985/>

AIMSS Treatment Options



- **Omega 3 fatty acids:** for women with BMI > 30 (9) Omega 3 fatty acids may or may not be more effective than placebo for non-obese women (11-13)
- **Homeopathic Ruta 5C and Rhus Tox 9C:** In a controlled trial, women with breast cancer who were planning to start treatment with an aromatase inhibitor who took homeopathic Ruta graveolens 5CH and Rhus tox 9CH twice daily for 3 months experienced less joint pain (4) Clinical Tip: Combo homeopathics exist
- **Moringa Oleifera 600mg/d.** In a controlled trial, women who took Moringa 600mg daily for 1 month had improve AI joint pain, lower inflammation (ESR) and improved quality of life (5)
- **Glucosamine 1500mg + chondroitin sulfate 1200mg:** In an uncontrolled trial, women with AI induced joint pain who took glucosamine-sulfate and chondroitin-sulfate for 3 months experienced moderate symptom relief (6)
- **Clinical tips:** Hydration v important for pain perception and joint lubrication, anti-inflammatory diet, Bioflavonoid powder with type II collagen (collagen controversial but does help) Epsom salt baths, curcumin (also bone density support) (7,8), Boswellia (7)

1. <https://pubmed.ncbi.nlm.nih.gov/24885324>
2. <https://pubmed.ncbi.nlm.nih.gov/30062634>
3. <https://pubmed.ncbi.nlm.nih.gov/29059538/>
4. <https://pubmed.ncbi.nlm.nih.gov/27914569/>
5. [Effect of Moringa Oleifera Extract on Erythrocyte Sedimentation Rate And SF-36 Scores In Aromatase Inhibitor-Associated Musculoskeletal Syndrome Breast Cancer Patients \(neuroquantology.com\)](https://neuroquantology.com/Effect-of-Moringa-Oleifera-Extract-on-Erythrocyte-Sedimentation-Rate-And-SF-36-Scores-In-Aromatase-Inhibitor-Associated-Musculoskeletal-Syndrome-Breast-Cancer-Patients)
6. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3810608/>
7. <https://pubmed.ncbi.nlm.nih.gov/29622343/>
8. <https://pubmed.ncbi.nlm.nih.gov/34537344/>

AIMSS Treatment Options

- Hydroxytyrosol, omega-3 fatty acids and curcumin (Oliventure): In an uncontrolled trial, women with AI arthralgia who took hydroxytyrosol, omega-3 fatty acids, and curcumin for a month had lowered inflammation (CRP) and less pain (1)
- Vitamin B12 : In an uncontrolled trial, women with AI induced joint pain who took daily sublingual vitamin B12 2.5mg/d for 3 months significantly reduced their pain scores (2)
- Alpha lipoic acid 240 mg, Boswellia serrata 40 mg, Bromelain 20 mg, MSM 200 mg (OPERA): In an uncontrolled study, women with AI arthralgia who took OPERA for 6 months had reduced pain (3)
- Sodium selenite 300 µg/d, Bromelain 400 mg/d, papain 400 mg/d, Lentil lectin 20 mg/d: In an uncontrolled trial, breast cancer patients treated with sodium selenite, proteolytic enzymes and L. culinaris lectin for 1 month had improved arthralgia and mucosal dryness improved compared to baseline (4)
- Testosterone is controversial in breast cancer survivors. In a double blind RCT, oral Testosterone 80 mg/d improved AI induced joint pain (5). In a double blind RCT, testosterone gel vaginally 10.4 mg daily for six months in women on AI's improved fatigue, mood, hot flashes and urinary incontinence but not AIMSS (6)

1. [A combination of hydroxytyrosol, omega-3 fatty acids and curcumin improves pain and inflammation among early stage breast cancer patients receiving adjuvant hormonal therapy: results of a pilot study - PubMed \(nih.gov\)](#)
2. <https://onlinelibrary.wiley.com/doi/abs/10.1111/tbj.12951>
3. <https://pubmed.ncbi.nlm.nih.gov/35666314/>
4. <https://pubmed.ncbi.nlm.nih.gov/26709132/>
5. https://aacrjournals.org/cancerres/article/69/24_Supplement/804/551428
6. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7644633/>

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Search: All Years All Cancer Types 1 Conventional Treatment Types 1 Side Effects All Natural Therapy Agents

Search Clear All Conventional Treatment Agents

Pediatric Results Only

Results (20) Systematic Reviews: 4 Clinical Trials: 10 Observational Studies: 2 Case Reports: 2 Support Literature: 1

▶ Systematic Reviews and/or Meta-Analyses

▼ Clinical Trials

- Effect of Moringa Oleifera Extract on Erythrocyte Sedimentation Rate And SF-36 Scores In Aromatase Inhibitor-Associated Musculoskeletal Syndrome Breast Cancer Patients (2022)
- Omega-3 fatty acid use for obese breast cancer patients with aromatase inhibitor-related arthralgia (SWOG S0927) (2018)[Summary]
- Effects of the Chinese medicine Yi Shen Jian Gu granules on aromatase inhibitor-associated musculoskeletal symptoms: A randomized, controlled clinical trial (2018)[Summary]
- Single arm phase II study of oral vitamin B12 for the treatment of musculoskeletal symptoms associated with aromatase inhibitors in women with early stage breast cancer (2018)[Summary]
- Treatment with Ruta graveolens 5CH and Rhus toxicodendron 9CH may reduce joint pain and stiffness linked to aromatase inhibitors in women with early breast cancer: results of a pilot observational study (2016)[Summary]
- Large-scale Survey of the Impact of Complementary Medicine on Side-effects of Adjuvant Hormone Therapy in Patients with Breast Cancer (2016)[Summary]
- Phase II study of glucosamine with chondroitin on aromatase inhibitor-associated joint symptoms in women with breast cancer (2013)[Summary]
- Vitamin D and aromatase inhibitor-induced musculoskeletal symptoms (AIMSS): A phase II, double-blind, placebo-controlled, randomized trial (2011)[Summary]
- Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer (2010)[Summary]
- Reduced side-effects of adjuvant hormone therapy in breast cancer patients by complementary medicine (2010)[Summary]

▶ Observational Studies

▶ Case Reports/Series



Questions Break...



Genitourinary syndrome of menopause/GSM

- GSM includes vaginal dryness, itching, burning, dyspareunia, dysuria, incontinence, pain, discomfort, and impairment of sexual function. Vulvovaginal atrophy is an important component of GSM (1)
- Related to low estrogen causing decreased blood flow, thinner vaginal lining, less fluid, decreased elasticity, and also dysbiosis (low lactobacillus species, low lactic acid, elevated pH, increased risk BV and candidiasis)
- Current guidelines recommend first line use of non-hormonal therapies such as moisturizing and lubricating vaginal creams (especially those with hyaluronic acid)
- More frequent dosing (three to five versus one to two times per week) may be required compared with postmenopausal patients without cancer (1)
- Second line options including hormonal vaginal creams (2,3)
- Systemic HRT is not recommended for estrogen positive breast cancer survivors because of two trials demonstrating increased recurrence rates (4)

1. <https://pubmed.ncbi.nlm.nih.gov/32358778/>
2. <https://pubmed.ncbi.nlm.nih.gov/30358733/>
3. <https://pubmed.ncbi.nlm.nih.gov/31291560/>
4. <https://pubmed.ncbi.nlm.nih.gov/15812079/>
5. <https://pubmed.ncbi.nlm.nih.gov/25739642/>
6. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5977164/>

Lubricants & Dilators

- **Regular orgasm** maintains blood flow and boosts endorphins (empirical)
- Lubricants considerations: avoid hyperosmolar lubricants bec may harm epithelial barrier (eg. high concentrations of glycerol, propylene glycol, polyquaternary compounds) (6)
- Plain coconut oil or paraben-free lubricants with hyaluronic acid or CBD
- Discover local pelvic floor PT's to refer to!
- Dilators if needed



Good Clean Love 'Bionourish' (has hyaluronic acid, can have samples in office),
Flower Child CBD 'Yoni Delight CBD sensual Lube',
<https://www.intimaterose.com/collections/vaginal-dilators>

<https://pubmed.ncbi.nlm.nih.gov/30358733/>

1. <https://pubmed.ncbi.nlm.nih.gov/31291560/>
2. <https://pubmed.ncbi.nlm.nih.gov/15812079/>
3. <https://pubmed.ncbi.nlm.nih.gov/25739642/>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5977164/>

First Line Treatment for GSM

- **Yoga and meditation:** In an RCT, breast cancer survivors who received 12 weeks of yoga & meditation had improved urogenital menopausal symptoms, less fatigue and improved quality of life (1)
- **Hyaluronic acid vaginal moisturizer:** In an RCT, women taking AI who received hyaluronic acid vaginal moisturizer for six months + sexual counseling had less painful intercourse and sexual distress than women who received prebiotic vaginal moisturizer + sexual counseling (2)
- **Vitamin E vaginally:**
 - In a triple blind RCT, women taking Tamoxifen who used vaginal vitamin E and D suppositories had reduced vaginal atrophy after 8 weeks (3)
 - In an uncontrolled trial in post menopausal women, Vit E 100IU suppositories for was compared to .5mg estrogen cream for 12 weeks. Estrogen 100% effective vs 76.9% vitamin E suppositories (4)

Key E suppositories cheap, not messy...vs compounded creams better for labia involvement

1. <https://pubmed.ncbi.nlm.nih.gov/25739642/>
2. <https://pubmed.ncbi.nlm.nih.gov/28229275/>
3. <https://pubmed.ncbi.nlm.nih.gov/30729333/>
4. <https://pubmed.ncbi.nlm.nih.gov/27904630/>
5. <https://pubmed.ncbi.nlm.nih.gov/23635341/>

Probiotics for GSM

- Postmenopausal women with high *Gardnerella vaginalis* and low *Lactobacillus* develop vaginal atrophy much more easily than postmenopausal women with a microbiota high in *Lactobacillus* (1)
- Vaginal probiotic suppositories or boric acid suppositories if candida/BV. If tissue damaged, avoid boric acid suppositories bec burn (empirical)
- In a meta-analysis of probiotics in breast cancer, eight trials were included (N=571)
 - Use of *Lactobacillus/Bifidobacterium/Streptococcus/FOS* and *Lactobacillus/Bifidobacterium/Enterococcus* in breast cancer survivors showed potential benefits in countering obesity and dyslipidemia
 - *Lactobacillus/Bifidobacterium/Streptococcus/FOS* decreases pro-inflammatory TNF- α in breast cancer survivors and improved quality of life in those with breast-cancer-associated lymphedema.
 - Supplementing probiotics capsules (109 CFU) with a prebiotic and using an intake duration of 10 weeks could provide a better approach than probiotics alone (2)

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8361365/>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10004677/>
3. <https://pubmed.ncbi.nlm.nih.gov/31227415/>
4. <https://pubmed.ncbi.nlm.nih.gov/31522958/>
5. <https://pubmed.ncbi.nlm.nih.gov/12725664/> ,
<https://pubmed.ncbi.nlm.nih.gov/22903687/>
6. <https://pubmed.ncbi.nlm.nih.gov/29533365/>
7. <https://pubmed.ncbi.nlm.nih.gov/27832260/>
8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3396801/>
9. <https://pubmed.ncbi.nlm.nih.gov/26223323/>
10. <https://pubmed.ncbi.nlm.nih.gov/19117185/>
11. <https://pubmed.ncbi.nlm.nih.gov/28921241/Intrarosa>

Structural approaches to GSM

- ▶ **Pelvic rehab:** Twenty-five breast cancer survivors with dyspareunia were given 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, and used olive oil as a lubricant during intercourse. After 12 weeks there were significant improvements in dyspareunia, sexual function, and quality of life (5)
- ▶ **Vaginal CO(2) Laser:** In a meta analysis of 10 observational studies on breast cancer survivors, vaginal laser therapy was effective in treating GSM. There were improvements in the Vaginal Health Index, Visual Analogue Scale score for dyspareunia and vaginal dryness, sexual function, and overall satisfaction in the short term with minimal adverse events (no randomized trials) (3)



1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8361365/>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10004677/>
3. <https://pubmed.ncbi.nlm.nih.gov/31227415/>
4. <https://pubmed.ncbi.nlm.nih.gov/31522958/>
5. <https://pubmed.ncbi.nlm.nih.gov/12725664/> ,
<https://pubmed.ncbi.nlm.nih.gov/22903687/>
6. <https://pubmed.ncbi.nlm.nih.gov/29533365/>
7. <https://pubmed.ncbi.nlm.nih.gov/27832260/>
8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3396801/>
9. <https://pubmed.ncbi.nlm.nih.gov/26223323/>
10. <https://pubmed.ncbi.nlm.nih.gov/19117185/>
11. <https://pubmed.ncbi.nlm.nih.gov/28921241/Intrarosa>



Slide Courtesy of Edra Spevack ND, FABNO


Isoflavone Vaginal Gel

- Maturitis. 2013, Mar;74(3):252-8.
- **Objective:** To assess efficacy and tolerability of a isoflavone (Glycine max L. Merr.) vaginal gel to the treatment of vaginal atrophy in postmenopausal women.
- **Methods:** The **double-blind, randomized, placebo-controlled, clinical trial**. Ninety women were treated for 12 weeks with isoflavone vaginal gel 4% (1g/day) and a placebo gel and conjugated equine estrogen cream (0.3mg/day). After 4 and 12 weeks, the vaginal atrophy symptoms were classified at none, mild, moderate and severe and the vaginal cytology were taken to determine the maturation value. The endometrial safety (by transvaginal ultrasonography) was evaluated through at screening and the end of the trial.
- **Results:** Isoflavone vaginal gel appears to be effective for relief of vaginal dryness and dyspareunia symptoms and an increase in the intermediate and superficial cells was noted. These results were similar to the effects with use of conjugated equine estrogens and superior to placebo gel. No changes in endometrial thickness, sera FSH and estradiol levels were observed at study endpoint.
- **Conclusion:** Glycine max (L.) Merr. at 4% vaginal gel on a daily basis in postmenopausal women led to improvements in vaginal atrophy symptoms and a significant increase in cell maturation values. Isoflavones proved good treatment options for relief of vulvovaginal symptoms especially in women who do not wish to use hormonal therapy or have contra-indications for this treatment.

GSM: The Hormone Controversy

If non hormonal therapies fail, vaginal estrogen, DHEA or testosterone options

Vaginal estrogens;

- In a meta analysis of 11 studies, post menopausal breast cancer survivors taking an aromatase inhibitor who took vaginal estrogen for 2 months did not have increased serum estradiol (4). In 2 retrospective studies, vaginal estrogen was not associated with increased risk of breast cancer recurrence (5) or increased breast density (6)
- Contraindication with estradiol ring (7.5 µg/d) because it raised estradiol serum levels (7,8).
- Ultra low dose (.03mg) Estriol + lactobacillus/Gynoflor (9) proposed as safer because it is metabolized faster (10) 

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8361365/>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10004677/>
3. <https://pubmed.ncbi.nlm.nih.gov/31227415/>
4. <https://pubmed.ncbi.nlm.nih.gov/31522958/>
5. <https://pubmed.ncbi.nlm.nih.gov/12725664/> ,
<https://pubmed.ncbi.nlm.nih.gov/22903687/>
6. <https://pubmed.ncbi.nlm.nih.gov/29533365/>
7. <https://pubmed.ncbi.nlm.nih.gov/27832260/>
8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3396801/>
9. <https://pubmed.ncbi.nlm.nih.gov/26223323/>
10. <https://pubmed.ncbi.nlm.nih.gov/19117185/>
11. <https://pubmed.ncbi.nlm.nih.gov/28921241/>Intrarosa
12. <https://pubmed.ncbi.nlm.nih.gov/32721007/>

GSM: The Hormone Controversy

- Vaginal Estrogen Clinical tips: Estriol suppositories less messy than creams but creams best if vulvar area needs rehab, wish I had adapted to estriol suppositories for BC survivors sooner!
- WHI Long term RCT follow up: Estrogen only HRT lowers breast cancer incidence/breast cancer mortality vs placebo while Estrogen + Prog HRT raises breast cancer incidence but with no difference in breast cancer mortality vs placebo (12)
- DHEA 6.5 mg/Intrarosa: In a large RCT, breast and gynecological cancer survivors who received either plain moisturizer or DHEA had improved vaginal symptoms at 12 weeks. However, vaginal DHEA, 6.5 mg, significantly improved sexual health (11)



1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8361365/>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10004677/>
3. <https://pubmed.ncbi.nlm.nih.gov/31227415/>
4. <https://pubmed.ncbi.nlm.nih.gov/31522958/>
5. <https://pubmed.ncbi.nlm.nih.gov/12725664/> ,
<https://pubmed.ncbi.nlm.nih.gov/22903687/>
6. <https://pubmed.ncbi.nlm.nih.gov/29533365/>
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8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3396801/>
9. <https://pubmed.ncbi.nlm.nih.gov/26223323/>
10. <https://pubmed.ncbi.nlm.nih.gov/19117185/>
11. <https://pubmed.ncbi.nlm.nih.gov/28921241/Intrarosa>

Sexual Dysfunction

- **Screen for zinc deficiency:** In a controlled trial, post menopausal women with serum zinc below 62 who used zinc supplementation had significantly improved sexual desire, arousal, orgasm, satisfaction, vaginal moisture, and pain during intercourse (3)
- **Referral to sex therapist**
- **Aromatherapy:** In a meta analysis of 3 RCT's, the use of aromatherapy improved sexual problems in menopausal women. Aromatherapy interventions included inhaled neroli oil (which did not alter serum estrogen levels), inhaled lavender, and 2-3 drops of an oral combination lavender, fennel, geranium, and rose with ginkgo 40mg⁽⁴⁾
- **Ashwagandha:** In an RCT, pre-menopausal women who took 600mg ashwagandha for 8 weeks had improved Female Sexual Function Index scores (desire, arousal, lubrication, orgasm, sexual satisfaction, and pain) (5)
- **Panax Ginseng:** In a double blind RCT, post menopausal women who took 500 mg Panax Ginseng twice daily for 4 weeks had improved sexual function, quality of life and menopausal symptoms (6). (caution: may increase blood pressure in some individuals)

1. <https://pubmed.ncbi.nlm.nih.gov/34602943/>
2. <https://pubmed.ncbi.nlm.nih.gov/29066307/>
3. <https://pubmed.ncbi.nlm.nih.gov/34311679/>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5949309/>
5. <https://pubmed.ncbi.nlm.nih.gov/36447681/>
6. <https://pubmed.ncbi.nlm.nih.gov/31331583/>
7. [Lady Prelox® improves sexual function in generally healthy women of reproductive age. - Abstract - Europe PMC](#)
8. [Effect of ArginMax on sexual functioning and quality of life among female cancer survivors: results of the WFU CCOP Research Base Protocol 97106 - PubMed \(nih.gov\)](#)
9. <https://pubmed.ncbi.nlm.nih.gov/18323413/>
10. <https://jamanetwork.com/journals/jamaoncology/fullarticle/2580714>
11. <https://academic.oup.com/jcem/article/103/11/4146/5096789?login=false>
12. <https://pubmed.ncbi.nlm.nih.gov/30239842/>
13. <https://pubmed.ncbi.nlm.nih.gov/30598928/>
14. <https://pubmed.ncbi.nlm.nih.gov/29172782/>
15. <https://pubmed.ncbi.nlm.nih.gov/19781624/>


Sexual Dysfunction

- **L Arginine combinations** in the general population: In a systematic review of 5 RCT's and 2 non-randomized CT's, L arginine containing combinations were effective for hypoactive arousal disorder in women [eg. ArginMax, Lady Prelox]. Lady Prelox® -2 tabs BID for eight weeks (7). ArginMax 3 caps BID for 12 weeks improved QOL in cancer survivors but did not improve sexual function (8)]
- **Testosterone:** controversial in breast cancer survivors;
 - higher baseline testosterone levels not associated with risk of recurrence in the WHEL study (9)
 - High dose vaginal testosterone (5000 µg 3 times/week) raised serum estradiol temporarily in 12% of breast cancer survivors on AI's and longer term in 12% of breast cancer survivors taking AI's (10)
 - Low dose vaginal testosterone (150-300 µg daily) did not significantly elevate estradiol or serum testosterone at 13 weeks in breast cancer survivors on AI's (11)
 - 300 µg intravaginal testosterone daily for 2 weeks and then three times weekly for 24 weeks improved sexual satisfaction and reduced dyspareunia without affecting estradiol levels (12)

1. <https://pubmed.ncbi.nlm.nih.gov/34602943/>
2. <https://pubmed.ncbi.nlm.nih.gov/29066307/>
3. <https://pubmed.ncbi.nlm.nih.gov/34311679/>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5949309/>
5. <https://pubmed.ncbi.nlm.nih.gov/36447681/>
6. <https://pubmed.ncbi.nlm.nih.gov/31331583/>
7. [Lady Prelox® improves sexual function in generally healthy women of reproductive age. - Abstract - Europe PMC](#) (20 mg Pycnogenol® pine bark extract, 200 mg L-arginine, 200 mg L-citrulline and 50 mg Rosvita® rose hip extract).
8. [Effect of ArginMax on sexual functioning and quality of life among female cancer survivors: results of the WFU CCOP Research Base Protocol 97106 - PubMed \(nih.gov\)](#) (proprietary blend L arginine, Asian Ginseng, Damiana and Ginkgo)
9. <https://pubmed.ncbi.nlm.nih.gov/18323413/>
10. <https://jamanetwork.com/journals/jamaoncology/fullarticle/2580714>
11. <https://academic.oup.com/jcem/article/103/11/4146/5096789?login=false>
12. <https://pubmed.ncbi.nlm.nih.gov/30239842/>
13. <https://pubmed.ncbi.nlm.nih.gov/30598928/>
14. <https://pubmed.ncbi.nlm.nih.gov/29172782/>

15. <https://pubmed.ncbi.nlm.nih.gov/19781624/>

Cardiac Effects of ET

- In breast cancer patients taking ET, pooled analysis of 25 studies showed prevalence rate of cardiovascular disease was **6.08 per 100 persons** (1)
- In older breast cancer patients, the leading cause of death 10 yrs after cancer diagnosis is cardiovascular disease/CVD rather than cancer (2)
- Presence of any of the following risk factors in addition to a history of lower-dose anthracycline or trastuzumab treatment increases CVD; Older age (≥ 60 y.o. if cardiology guidelines vs > 65 if oncology guidelines), History of myocardial infarction, moderate valvular disease, or low-normal left ventricular function (50%–55%) before or during cancer treatment, OR ≥ 2 CVD risk factors during or after cancer treatment: diabetes mellitus, dyslipidemia, hypertension, obesity, smoking (3,4)
- Online calculator for CVD: <http://www.reynoldsriskscore.org/> 

1. <https://pubmed.ncbi.nlm.nih.gov/36826103/>
2. <https://pubmed.ncbi.nlm.nih.gov/21689398/>
3. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol* 2012;23 Suppl 7:vii155-66.
4. <https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000556>

Cardiac Effects of ET

<https://pubmed.ncbi.nlm.nih.gov/36848014/>

Table 1 Comparative Effects of Hormonal Therapy on Specific Cardiovascular Outcomes

Endocrine Breast Cancer Therapies	SEAMs	Aromatase Inhibitors	GnRHs
Mechanism of action	Estrogen receptor ligands with tissue specific agonists or antagonist activity	Inhibit aromatase, which converts androstenedione into estrone, leading to decreased estradiol levels.	Suppress estrogen synthesis through ovarian suppression
Myocardial infarction	↓	↑ ↔	↓ ○
Heart failure	↓	↑	○
LDL	↓	↑ ↔	↑ ○
TG	↔ ○	↔ ○	↑ ○
Venous Thromboembolism	↑	↓	↑
Stroke	↑	↔	○

- ↑ Trend towards/associated with increase incident.
- ↓ Trend towards/associated with decrease incident.
- ↔ Equivocal data /results or no change.



Cardiac Effects of ET

Tamoxifen;

- cardioprotective during active treatment (lowers MI, arrhythmia, coronary heart disease) but not over the long term (1)
- increases lipids & inflammation, increases risk of stroke and venous thromboembolism (eg. 2.8% with tamoxifen vs 1.6% with aromatase inhibitor) (2)

AI's;

- People taking AI's vs Tam have more frequent dysrhythmia, valvular dysfunction, pericarditis and heart failure (3,4).
- In women with **preexisting heart disease**, the incidence of cardiovascular events was **17%** with anastrozole vs **10%** with Tam (5)
- AI's occasionally cause hypercholesterolemia

GnRH agonists - not been studied yet. In men, GnRH agonists resulted in a 38% increased risk of any CVD, 57% more myocardial infarction & 51% more stroke (6)

Recall that Tamoxifen raises serum estrogen (while blocking ER receptors selectively in breast tissue), so this may account for the CVD benefit and increased clotting risk. Consider screening for hypercoagulability and inflammation level.

It has been theorized that when compared to tamoxifen, the increased risk of developing cardiovascular events associated with AI use are due to the cardioprotective effects of tamoxifen. However, this author thinks that AI's increasing risk of CVD is consistent with the understanding that when women lose estrogen and become menopausal, their CVD risk

increases to approximate the rate for men.

<https://pubmed.ncbi.nlm.nih.gov/36848014/>

1. Amir E, Seruga B, Niraula S, Carlsson L, Ocaña A. Toxicity of Adjuvant Endocrine Therapy in Postmenopausal Breast Cancer Patients: A Systematic Review and Meta-analysis. *JNCI J Natl Cancer Inst.* 2011;103(17):1299-1309.

2. <https://pubmed.ncbi.nlm.nih.gov/36848014/>

3. Khosrow-Khavar F, Filion KB, Bouganim N, et al. Aromatase inhibitors and the risk of cardiovascular outcomes in women with breast cancer: a population-based cohort study. *Circulation.* 2020;141:549–559. <https://doi.org/10.1161/CIRCULATIONAHA.119.044750>

4. <https://pubmed.ncbi.nlm.nih.gov/27100398/>

5. <https://pubmed.ncbi.nlm.nih.gov/16887480/>

6. Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating NL, Van Hemelrijck M. Quantifying Observational Evidence for Risk of Fatal and Nonfatal Cardiovascular Disease Following Androgen Deprivation Therapy for Prostate Cancer: A Meta- analysis. *Eur Urol.* 2015;68(3):386-396.

CVD Prevention

Universal Naturopathic approaches;

- Exercise + avoid sedentary lifestyle (“sitting is the new smoking”)
- Ensure 7-8 h sleep (1)
- Manage stress (2)
- Mediterranean Diet (3,4)
- Optimize body weight
- Quit smoking
- Avoid drugs that stress on the heart, including cocaine, diet pills, ephedra/ma huang, performance-enhancing drugs, caffeinated energy drinks (5)

Clinical Tips

- Tamoxifen – consider hsCRP, lipids, fasting insulin, fibrinogen. CoQ10 supplementation in everyone (6-12). Watch for clotting issues.
- AI’s – consider hsCRP, lipids, carotid artery ultrasound
- Crossover supports: L carnitine 3g, fish oil, magnesium, CoQ10, astragalus, grape seed extract, taurine
- See Cardio-oncology lecture notes on oncANP website



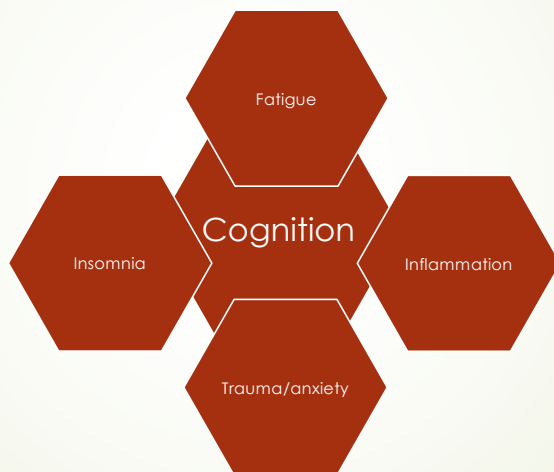
1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5442407/>
2. <https://pubmed.ncbi.nlm.nih.gov/32791843/>
3. <https://www.ncbi.nlm.nih.gov/pubmed/26365989>
4. <https://www.ncbi.nlm.nih.gov/pubmed/28133855>
5. <https://www.ncbi.nlm.nih.gov/pubmed/28189188>
6. <https://www.ncbi.nlm.nih.gov/pubmed/17268082>
7. <https://www.ncbi.nlm.nih.gov/pubmed/17425952>
8. <https://www.ncbi.nlm.nih.gov/pubmed/17668211>
9. <https://www.ncbi.nlm.nih.gov/pubmed/18427979>
10. <https://www.ncbi.nlm.nih.gov/pubmed/18377693>
11. <https://www.ncbi.nlm.nih.gov/pubmed/17516992>
12. <https://www.ncbi.nlm.nih.gov/pubmed/19096111>
13. <https://pubmed.ncbi.nlm.nih.gov/12817526/>

Cognitive Issues in ET

- Rates of cognitive impairment in women on ET vary from **32% to 64%** (1)
- While global measures of cognitive function rarely change with ET, **verbal memory and executive function** are main areas that tend to show deficits (3)
- According to TailorRx, receiving chemotherapy before ET significantly increased risk of cognitive changes at 3 and 6 months but abates with time - no differences at 12 months and beyond (2) Idea: Heal leaky BBB after chemo
- Women who took Tam followed by exemestane had more cognitive decline than controls. Meanwhile there was no cognitive decline in the exemestane-only group compared with controls (4). Consistent with a mouse study that showed that exemestane was the only AI that didn't cause hippocampal-dependent memory impairments (5)
- Screen for contributing factors; unmanaged pain (6), sleep apnea, PTSD, anemia, inflammation, high cortisol, diabetes, B12 deficiency, and vitamin D deficiency

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10121332/>
2. <https://pubmed.ncbi.nlm.nih.gov/32271671/>
3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10121332/>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10121337/>
5. <https://pubmed.ncbi.nlm.nih.gov/29128813/>
6. <https://www.explorationpub.com/Journals/em/Article/1001138>

Cognitive Issues in ET





Cognitive Support for ET

- **Stress management or MBSR program** first and always. Stress management/ psychotherapy can improve cognitive function in cancer survivors (1) Also has a **survival benefit** in breast cancer (2,3)
- **Restorative yoga** in BC survivors improved cognitive function more than vigorous yoga (4) (role of anxiety in cognitive changes?)
- In women with BC, **higher vegetable, fruit and fish** intake, supplementation with vitamin B and vitamin E, and **tea drinking** were associated with higher cognitive scores, while alcohol drinking was associated with lower cognitive scores at 36 months post-diagnosis (5)
- **CoQ10**: In a double blind RCT, women taking Tamoxifen who received CoQ10 100mg for 8 weeks had improved cognitive function as well as improved physical and emotional functioning (6)

1. <http://www.curetoday.com/articles/new-psychotherapy-may-help-fight-chemobrain-in-cancer-survivors?p=2>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5752103>
3. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2661422/>
4. <https://pubmed.ncbi.nlm.nih.gov/35861215/>
5. <https://www.ncbi.nlm.nih.gov/pubmed/29744676>
6. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7039424/>



Cognitive Support for BC chemo

- **Melatonin 5-20mg:**
 - In an RCT, women who took 20mg melatonin nightly alongside chemotherapy for breast cancer had improved cognition, sleep and depression (2)
 - In an RCT, women with breast cancer who took 20mg melatonin during chemotherapy for breast cancer had better neuroplasticity and improved pain perception (3)
 - In a phase II study, women with advanced breast cancer who took melatonin 5mg alongside hormone therapy or trastuzumab had improved cognition, sleep, fatigue, and quality of life (4)
- **Curcumin phytosome 500mg TID:** In an RCT of 160 people with solid tumors receiving chemotherapy or radiation, those who took Meriva curcumin for 2 months during treatment experienced less memory/cognitive impairment, constipation/diarrhea, nausea, vomiting, fatigue and malnutrition/weight loss (5)
- **Cognitive training, exercise:** In a systematic review on cognitive alterations after chemotherapy for BC, five studies on “cognitive training interventions” (eg. Tibetan sound meditation, CBT-based stress management, computer memory based training or executive function training) showed benefits. Two studies on **physical activity** interventions also effective (6)

1. <https://journals.sagepub.com/doi/10.1177/15347354211019470>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164654/>
3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6883914/>
4. <https://pubmed.ncbi.nlm.nih.gov/26260726/>
5. <https://pubmed.ncbi.nlm.nih.gov/23775598>
6. <https://pubmed.ncbi.nlm.nih.gov/25623439/>
7. [The use of Ginkgo biloba for the prevention of chemotherapy-related cognitive dysfunction in women receiving adjuvant treatment for breast cancer, N00C9 - PMC \(nih.gov\)](#)
8. [Phase II study of Ginkgo biloba in irradiated brain tumor patients: effect on cognitive function, quality of life, and mood | SpringerLink](#)

An aside: Cognitive Support for Radiation

- **Homeopathy:** In a double blind RCT, women undergoing radiation for breast cancer post surgery and chemotherapy who received homeopathics for 8 weeks had improved attention performance. They received **Carc 30 C – 1 granule/d and a combination of Phos acidum 30C, Rad-br 30C, X-ray 6C and Cadm-s 30C– 1 granule TID (1)**
- Ginkgo failed to improve chemo brain (7) but improved cognition during brain radiation (8)




1. <https://journals.sagepub.com/doi/10.1177/15347354211019470>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164654/>
3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6883914/>
4. <https://pubmed.ncbi.nlm.nih.gov/26260726/>
5. <https://pubmed.ncbi.nlm.nih.gov/23775598>
6. <https://pubmed.ncbi.nlm.nih.gov/25623439/>
7. [The use of Ginkgo biloba for the prevention of chemotherapy-related cognitive dysfunction in women receiving adjuvant treatment for breast cancer, N00C9 - PMC \(nih.gov\)](#)
8. [Phase II study of Ginkgo biloba in irradiated brain tumor patients: effect on cognitive function, quality of life, and mood | SpringerLink](#)

Cognitive Supports in General Population

- **Bacopa** (1) Unknown effects on CYP metabolism
- **Saffron 30mg** (14) Unknown effects on CYP metabolism
- **Ashwagandha 600mg** (3,4) Unknown effects on CYP metabolism
- **Inhaled Rosemary essential oil** (5)
- Resveratrol 150mg (2)
- Rosemary 1000mg (also lowered anxiety/depression) (6)
- Green Tea Extract and l-Theanine (7), Theracurmin (8), American ginseng/Panax quinquefolius (9,10), Citicoline (CDP-choline) 500mg (11), Avena Sativa 430 mg and 1290 mg (12)
- Hyperbaric oxygen (13)
- Clinical pearls: Chewable GABA calms anxiety while increasing focus. Don't forget to treat the gut because Short Chain Fatty Acids affect gut-brain communication (leaky gut = leaky brain)

1. <https://pubmed.ncbi.nlm.nih.gov/12093601/> and <https://pubmed.ncbi.nlm.nih.gov/23788517/>
2. [Long-term effects of resveratrol on cognition, cerebrovascular function and cardio-metabolic markers in postmenopausal women: A 24-month randomised, double-blind, placebo-controlled, crossover study - PubMed \(nih.gov\)](#)
3. <https://pubmed.ncbi.nlm.nih.gov/28471731/>
4. [Efficacy and Safety of Ashwagandha \(Withania somnifera \(L.\) Dunal\) Root Extract in Improving Memory and Cognitive Functions - PubMed \(nih.gov\)](#)
5. <https://www.ncbi.nlm.nih.gov/pubmed/23983963>
6. <https://pubmed.ncbi.nlm.nih.gov/29389474/>
7. <http://www.ncbi.nlm.nih.gov/pubmed/21303262>
8. [Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial - PubMed \(nih.gov\)](#)
9. <https://pubmed.ncbi.nlm.nih.gov/34396468/>
10. <https://pubmed.ncbi.nlm.nih.gov/32896022/>
11. <https://pubmed.ncbi.nlm.nih.gov/33978188/>
12. <https://pubmed.ncbi.nlm.nih.gov/32485993/>

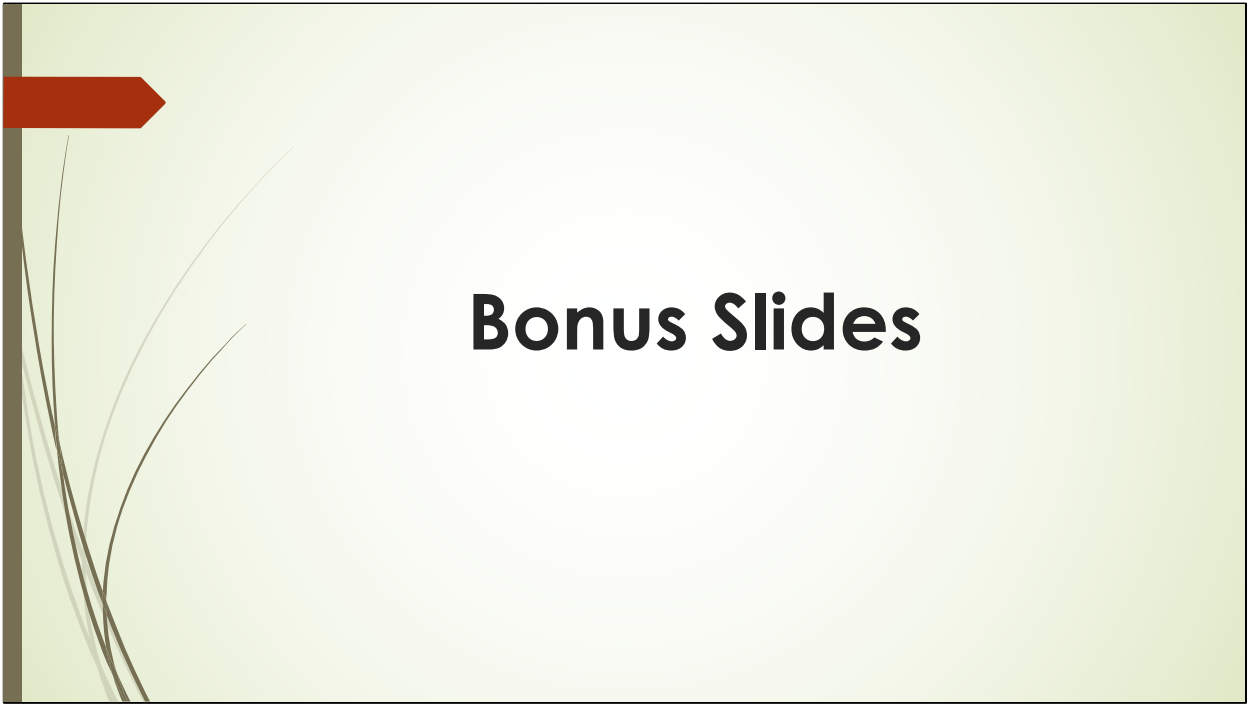
13. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8533945/>
14. <https://pubmed.ncbi.nlm.nih.gov/32445136/>



A reminder from shaman and poet María Sabina...

Cure yourself with the light of the sun and the rays of the moon.
With the sound of the river and the waterfall.
With the swaying of the sea and the fluttering of birds.
Heal yourself with mint, with neem and eucalyptus.
Sweeten yourself with lavender, rosemary, and chamomile.
Hug yourself with the cocoa bean and a touch of cinnamon.
Put love in tea instead of sugar, and take it looking at the stars.
Heal yourself with the kisses that the wind gives you and the hugs of the rain.
Get strong with bare feet on the ground
and with everything that is born from it.
Get smarter every day by listening to your intuition,
looking at the world with the eye of your forehead.
Jump, dance, sing, so that you live happier.
Heal yourself, with beautiful love, and always remember:
you are the medicine.





Bonus Slides



Fatigue

- In a cross sectional study of stage 1-3 breast cancer, 60% had fatigue during ET
- BMI, clinical stage, menopausal status, duration of endocrine therapy/ET, physical activity, and diet were associated with fatigue (1)
- **Fatigue Reduction Diet/FRD:** In an RCT, women with fatigue who had completed breast cancer treatment (except for ET and/or Herceptin), those who followed a 3-month FRD high in whole grains, vegetables, fruit and omega-3 fatty acids, had improved fatigue and sleep quality compared to controls (3)
- **Reishi:** In an RCT, women with fatigue during endocrine therapy for breast cancer who took Reishi/Ganoderma 1 g TID for 4 weeks had improved fatigue, less anxiety, less depression and better quality of life (4)
- **Shiitake:** In an uncontrolled trial, women undergoing ET who took 1800mg of shitake/Lentinula extract for 8 weeks had improved QOL and vitality scores (5)

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2939549/>
2. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8776586/>
3. <https://pubmed.ncbi.nlm.nih.gov/27913933>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3236089/?tool=pmcentrez&report=abstract>
5. http://journal.waocp.org/article_27809_396dca1a98ee71b19e749956206c50d6.pdf



Fatigue

- **Panax Ginseng:** In an uncontrolled trial, patients with cancer related fatigue took Panax Ginseng 400mg twice daily for 29 days safely and had improvements in their fatigue, quality of life, appetite and sleep (2)
- **Melatonin:** In a phase II study, women with advanced breast cancer who took melatonin 5mg alongside ET or trastuzumab had improved sleep, fatigue, cognition and quality of life (3). In an RCT, out of 78 women with breast cancer who received adjuvant chemotherapy and radiotherapy, those who took oral melatonin 18 mg/night starting one week before chemotherapy until one month after completion of radiotherapy had lowered levels of fatigue vs placebo (4)
- **IVC:** In an RCT, women with stage 2 and 3 breast cancer who received 25 g per week of intravenous vitamin C (IVC) for one month alongside standard of care (chemotherapy, radiation or hormone therapy) had significantly improved scores for nausea, loss of appetite, tumor pain, fatigue, and insomnia compared to their baseline levels (5)
- **Clinical tip:** Sleep apnea super common! HYDRATION

1. http://journal.waocp.org/article_27809_396dca1a98ee71b19e749956206c50d6.pdf
2. <https://pubmed.ncbi.nlm.nih.gov/25873296>
3. <https://pubmed.ncbi.nlm.nih.gov/26260726/>
4. <https://doi.org/10.1177/1534735420988343>
5. <https://www.cureus.com/articles/58349-impact-of-intravenous-vitamin-c-administration-in-reducing-severity-of-symptoms-in-breast-cancer-patients-during-treatment>



Chemotherapy Related Fatigue

- In an RCT, women who had received chemotherapy prior to ET had worse fatigue at 3 & 6 months compared to the no chemotherapy group, but the difference between groups evened out at 12, 24, and 36 months (8)
- **L carnitine** 1.5-3g: Common deficiency induced by chemo. 76-83% of advanced cancer patients deficient in carnitine (10). Supplementation decreases fatigue (9) Ask about muscle weakness in large muscles eg. Are legs like jello walking up stairs?
- **Yoga**: In an RCT, women with breast cancer undergoing chemotherapy or radiation who did yoga had reduced fatigue and inflammation levels (IL-1 β , IL-10) (1)
- **Exercise and dietary counselling**: In an RCT, women with breast cancer received either 3x weekly exercise session with nine face-to-face individual diet counseling sessions during chemotherapy and radiotherapy or usual care. People receiving exercise and dietary counseling had significantly improved psychological, physiological and behavioral outcomes at the end of intervention, and better fatigue and quality of life outcomes at long term follow up (2)
- **Coconut oil**: In an RCT, women with breast cancer who received virgin coconut oil 10 ml twice a daily starting 1 week after chemotherapy cycle three through six had improved global quality of life and functional status, including improved symptom scores for fatigue, dyspnea, sleep difficulties, sexual function and loss of appetite (3)

1. <https://pubmed.ncbi.nlm.nih.gov/36512140/>
2. <https://pubmed.ncbi.nlm.nih.gov/31345179/>
3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4965196/pdf/epj-08-2475.pdf>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4176590/>
5. <https://pubmed.ncbi.nlm.nih.gov/23142798/>
6. <https://www.ncbi.nlm.nih.gov/pubmed/15015612>
7. <https://link.springer.com/article/10.1007/s00520-022-06921-x>
8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8776586/>
9. <https://pubmed.ncbi.nlm.nih.gov/29456846/>
10. <https://pubmed.ncbi.nlm.nih.gov/17157757/>



Chemotherapy Related Fatigue

- **Royal Jelly:** In a double blind RCT, people with various cancers who received royal jelly in honey 5 mL twice daily for their cancer-related fatigue had significantly less fatigue after 2 and 4 weeks of treatment vs pure honey control (3)
- **Ashwagandha/Withania:** In a controlled trial, women undergoing chemotherapy for breast cancer who took 2g ashwagandha 3x daily during chemotherapy had reduced fatigue and improved QOL (5)
- **Viscum album/Mistletoe:**
 - In an RCT, people with breast, ovarian and NSCLC who used mistletoe extract alongside chemotherapy had increased QOL, functioning and decreased side effects (pain, nausea, fatigue, anorexia, and insomnia) vs control(6)
 - In two meta-analysis, one involving 1494 people from 12 RCTs, and one involving 2668 people from 7 retrospective studies, use of mistletoe therapy improved cancer fatigue. Heterogeneity between the studies was high in both meta-analyses and most studies had a high risk of bias. Treatment with mistletoe extracts shows a moderate effect on cancer-related fatigue of similar size to physical activity (7)

1. <https://pubmed.ncbi.nlm.nih.gov/36512140/>
2. <https://pubmed.ncbi.nlm.nih.gov/31345179/>
3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4965196/pdf/epj-08-2475.pdf>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4176590/>
5. <https://pubmed.ncbi.nlm.nih.gov/23142798/>
6. <https://www.ncbi.nlm.nih.gov/pubmed/15015612>
7. <https://link.springer.com/article/10.1007/s00520-022-06921-x>
8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8776586/>



Mood Changes & ET

- ▶ Research is mixed as to whether AI's increase, are neutral or even decrease incidence of anxiety and depression (1)
- ▶ Empirically mood changes on ET are a common reason for breast cancer survivors to seek naturopathic treatment.
- ▶ Important mood comorbidities to screen for include; hypothyroidism, low ferritin, zinc deficiency, magnesium deficiency, vit D deficiency. Note that mood changes from hormone blockers can sometimes be resistant to both conventional and integrative mood supports.

1. <https://pubmed.ncbi.nlm.nih.gov/36288635/>
2. <https://pubmed.ncbi.nlm.nih.gov/32214378/>



Mood Changes & ET

- First and always – referral to a **stress management or MBSR program**.
 - In an RCT, breast cancer survivors did a 10 wk group based Cognitive Based Stress Management Class vs. 1 day psychosocial seminar. After 11 years, the stress management group had 75% reduced risk of death from breast cancer, and 79% lower risk of dying from any cause (1)
 - In a second RCT, breast cancer survivors did a 26 session stress management class or assessment only. After 11 years, the stress management group had 56% reduced risk of death from breast cancer, and 49% reduced risk of death from all causes (2)
- **Vit D deficiency** is associated with anxiety and depression in breast cancer survivors receiving endocrine therapies (3)
- Prevention at time of breast surgery: In a double blind RCT, women with breast cancer who took **melatonin 6mg** pre and post surgically had lower risk of depression. For every 3 women treated, an expected one woman would avoid depression (NNT=3) (4)

1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5752103>
2. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2661422/>
3. <https://pubmed.ncbi.nlm.nih.gov/35933326/>
4. <https://www.ncbi.nlm.nih.gov/pubmed/24756186>

Anxiety in BC

- ASCO Recommendations: **Meditation, particularly MBSR, Relaxation, Yoga** (grade A recommendations), **Massage, Music Therapy** (grade B recommendations), **Acupuncture, healing touch, stress management** (grade C recommendations) (1)
- Logotherapy (therapy aimed at discovering meaning) plus nutrition counseling greatly reduced anxiety and depression in breast cancer survivors (2) as did Smart phone psychotherapy (3)
- **Chamomile tea:** In women with breast cancer undergoing chemotherapy, chamomile 500mg twice for 5 days before after chemotherapy improved chemotherapy-induced nausea (9) In a double blind RCT, people with generalized anxiety disorder who took chamomile 240mg capsules in escalating doses up to 5 caps daily had improved anxiety (10)
- **Reishi/Ganoderma:** In an RCT, women with fatigue during ET who took Reishi/Ganoderma 1 g TID for 4 weeks had improved fatigue, less anxiety, less depression and better quality of life (4)
- **Ashwagandha/Withania:** In a controlled trial, women undergoing chemotherapy for breast cancer who took 2g ashwagandha 3x daily during chemotherapy had reduced fatigue and improved quality of life (5). In a double blind RCT, adults without cancer who had stress who took Ashwagandha 240mg for 2 months had less anxiety and lower cortisol (6)

1. Greenlee H, Balneaves LG, Carlson LE, et al. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. 2017 <https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21397>
2. <https://pubmed.ncbi.nlm.nih.gov/35759049/>
3. <https://pubmed.ncbi.nlm.nih.gov/36322882/>
4. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3236089/?tool=pmcentrez&report=abstract>
5. <https://pubmed.ncbi.nlm.nih.gov/23142798/>
6. [An investigation into the stress-relieving and pharmacological actions of an ashwagandha \(Withania somnifera\) extract: A randomized, double-blind, placebo-controlled study - PubMed \(nih.gov\)](#)
7. <https://pubmed.ncbi.nlm.nih.gov/28326753/> ,
<https://pubmed.ncbi.nlm.nih.gov/23358464/>
8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938102/>
9. <https://pubmed.ncbi.nlm.nih.gov/27644672/>
10. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3600416/>

Anxiety with Insomnia

- In a meta-analysis of 5 RCT's on melatonin in breast cancer survivors, melatonin 3mg-20mg improved sleep quality, total sleep time and how often people awoke after falling asleep (14)
- In the general population, there are ≥ 6 RCTs showing benefit of the following for anxiety; Lavender EO capsules/Silexan Passionflower/Passiflora, and Crocus Sativus/Saffron (which showed benefits comparable to standard anxiolytics and antidepressants) (10)
- Multiple RCT's on inhaled lavender essential oil for anxiety & insomnia (1-4) Lavender is not estrogenic (11,12)
- Physical activity & mindfulness meditation (5)
- Passionflower tea: In a double blind crossover RCT, healthy adults who drank passionflower tea before bed had improved sleep quality (8)
- Cranio-electrical stimulation (eg. Alpha Stim, CES Ultra). In an uncontrolled trial, people with advanced cancer who used CES daily for 4 weeks had improved depression, anxiety, pain, and sleep scores (9)
- Clinical pearl: EMDR especially good for PTSD, Heartmath, Chewable GABA, Headspace "How to Sleep" on Netflix, Reduce alcohol and caffeine

1. [Aromatherapy: The Effect of Lavender on Anxiety and Sleep Quality in Patients Treated With Chemotherapy - PubMed \(nih.gov\)](#)
2. [Both lavender fleur oil and unscented oil aromatherapy reduce preoperative anxiety in breast surgery patients: a randomized trial - PubMed \(nih.gov\)](#)
3. [Effect of Lavender Oil on the Anxiety of Patients Before Breast Surgery - PubMed \(nih.gov\)](#)
4. [The Effect of Lavender Aroma on Anxiety of Patients Having Bone Marrow Biopsy - PubMed \(nih.gov\)](#)
5. [Physical activity, mindfulness meditation, or heart rate variability biofeedback for stress reduction: a randomized controlled trial - PubMed \(nih.gov\)](#)
6. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3600416/>
7. <https://pubmed.ncbi.nlm.nih.gov/27644672/>
8. <https://www.ncbi.nlm.nih.gov/pubmed/21294203>
9. [Cranial Electrotherapy Stimulation for the Management of Depression, Anxiety, Sleep Disturbance, and Pain in Patients With Advanced Cancer: A Preliminary Study - Journal of Pain and Symptom Management \(jpsmjournal.com\)](#)
10. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5938102/>

11. <https://pubmed.ncbi.nlm.nih.gov/28326753/>
12. <https://pubmed.ncbi.nlm.nih.gov/23358464/>
13. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10001052/>
14. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10001052/>



Anxiety with Poor Memory

Rosemary

- In an RCT, people with major depressive disorder who took 2 caps rosemary capsule daily had improved depression, anxiety and memory (1)
- In a double blind RCT, university students who took 1000mg rosemary for 1 month had reduced anxiety and depression, with improved sleep and memory (2)
- Makes a lovely tea (with sencha green tea, chamomile, passionflower etc)

1. <https://pubmed.ncbi.nlm.nih.gov/36343423/>
2. <https://pubmed.ncbi.nlm.nih.gov/29389474/>

Depression

- **Curcumin phytosome 1000mg:** In an RCT of people with major depression, either alone (1) or in conjunction with fluoxetine (2) improved depression (Safety note: max 1g with Tamoxifen because of 3.6g interaction with Tamoxifen)
- **Saffron 30mg:** In an RCT, women who took 30 mg/day of crocin during BC chemotherapy had improved anxiety, depression, with lower incidence of hypersensitivity reactions to chemotherapy (5). Also improves CIPN (6)
- Paroxetine (Paxil) not recommended with Tamoxifen due to increased risk of death from breast cancer (3). Fluoxetine (Prozac) similar interaction with Tamoxifen (94)
- Clinical pearls for depression: Black Cohosh, Saffron, chewable 5HTP, lithium orotate 10-20mg.

1. <http://www.ncbi.nlm.nih.gov/pubmed/25046624>

2. <https://www.ncbi.nlm.nih.gov/pubmed/23832433>

3. [Kelly CM¹](#), [Juurink DN](#), [Gomes T](#), et al. **Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study.** *BMJ*. 2010 Feb 8;340:c693

4. [Desmarais JE¹](#), [Looper KJ](#). Interactions between tamoxifen and antidepressants via cytochrome P450 2D6. *J Clin Psychiatry*. 2009 Dec;70(12):1688-97.

5. <https://pubmed.ncbi.nlm.nih.gov/34164855/>

6. <https://linkinghub.elsevier.com/retrieve/pii/S0378874121007406>

Phytoestrogens

- ▶ ER alpha is proliferative. ER beta is non proliferative. Phytoestrogens primarily bind to ER beta
- ▶ Flaxseed: In a double-blind RCT, breast cancer patients taking 25g of ground flaxseed meal between for 4 weeks) had reduced expression of HER-2/neu, slower proliferation rates (ki-67), and increased rates of tumor cell death (apoptosis) (15) Associated with decreased BC risk (16)
- ▶ Soy: Multiple large prospective trials demonstrating safety and benefit of soy in breast cancer survivors. “There is no proof from large studies that soy leads to poor cancer outcomes. Eating 3 or fewer servings of soy daily is safe” NCCN Guidelines: <https://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/pathology-reports-fact-sheet>
- ▶ Phytoestrogens in the diet are safe and beneficial for BR cancer survivors (isolated extracts are a different story)

ER Alpha proliferative

ERbeta which is non proliferative, phytoestrogens bind

1. <https://pubmed.ncbi.nlm.nih.gov/16611391/>
2. <https://pubmed.ncbi.nlm.nih.gov/14600287/>
3. <https://pubmed.ncbi.nlm.nih.gov/11739882/>
4. <https://pubmed.ncbi.nlm.nih.gov/14679019/>
5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4932855/>
6. <https://pubmed.ncbi.nlm.nih.gov/16080194/>
7. <https://pubmed.ncbi.nlm.nih.gov/19075592/>
8. <https://pubmed.ncbi.nlm.nih.gov/11168905/>
9. <https://pubmed.ncbi.nlm.nih.gov/28560655/>
10. <https://pubmed.ncbi.nlm.nih.gov/21254914/>
11. <https://pubmed.ncbi.nlm.nih.gov/15623462/>
12. <https://pubmed.ncbi.nlm.nih.gov/27312859/>
13. <https://pubmed.ncbi.nlm.nih.gov/17289903/>
14. <https://www.ncbi.nlm.nih.gov/pubmed/20432168>
15. <https://pubmed.ncbi.nlm.nih.gov/15897583/>
16. <https://pubmed.ncbi.nlm.nih.gov/24013641/>

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15. <https://pubmed.ncbi.nlm.nih.gov/15897583/>

Mild Natural Estrogen Blockers

- ▶ Not the same as endocrine therapy! Do not substitute!! Useful for patients who cannot tolerate hormone blockers or who have finished their course of treatment
- ▶ White button mushrooms seem to be AI's (3). High mushrooms consumption in the diet is associated with lower risk of breast cancer in premenopausal women (14)
- ▶ Green tea: estradiol levels were lower for people with higher EGCG intake (1) In a mouse model EGCG inhibited aromatase activity by 56% (2)
- ▶ Melatonin: aromatase inhibitor in mouse models (6) and SERM (7) but doesn't affect serum estradiol at 3mg nightly (8)
- ▶ Grape seed extract in vitro AI activity(4) but in a pilot study, 200, 400, 600 or 800 mg of GSE daily for 12 weeks did not decrease plasma estrogens (estrone, estradiol, estrone sulfate) in postmenopausal women (5)
- ▶ DIM: 300mg increased C2:C16 estrogen ratio in women (9,10) and increases SHBG (9). 108mg daily DIM increased the 2-hydroxylation of estrogen urinary metabolites (11) Avoid with Tam
- ▶ I3C: In mouse model anti-estrogenic effects (12) Avoid with Tam until more research

ERbeta which is bound by phytoestrogens does not have growth effects like ER Alpha

1. <https://pubmed.ncbi.nlm.nih.gov/16611391/>
2. <https://pubmed.ncbi.nlm.nih.gov/14600287/>
3. <https://pubmed.ncbi.nlm.nih.gov/11739882/>
4. <https://pubmed.ncbi.nlm.nih.gov/14679019/>
5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4932855/>
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