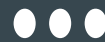


# Supplements for Menopause



Mark Owolabi MD  
Integrative Medicine Fellow  
Department of Family Medicine

# Disclosures

None

# Roadmap

- Basic overview of menopause
- Non-pill therapies
- Quick primer for supplement prescribing
- Supplements used for menopausal symptoms

# Goals for Talk

- Learn which non-pharmaceutical treatments are safe and beneficial for menopausal symptoms.
- Learn what supplements to avoid

# Menopause - Overview

- Transition generally begins in mid 40s
- Average age menopause: 51
- Eventual decrease in estrogen as follicle count diminishes
- Menopause negatively affects CNS, Lipids, Bone mass, Connective tissue
- Symptoms - hot flashes, depression, insomnia, vaginal dryness
  - Symptoms affected by BMI, Ethnicity, SES, Anxiety/Depression, and PTSD status

# Conventional treatments

- Hormone Replacement Therapy
- SSRI/SNRI (Venlafaxine, Paxil)
- Gabapentin
- Clonidine
- Vaginal estrogen & lubricants

# Unconventional treatments *(It's not all about pills)*

- Start with holistic lifestyle counseling
  - Mediterranean diet template reduces CVD, DM, Depression, and Cancer incidence & morbidity
  - Regular Exercise reduces CVD, DM, Osteoporosis, Weight gain, Breast Cancer, and Dementia Risk.
  - Weight loss can be beneficial for hot flash frequency
  - Cognitive Behavioral Therapy beneficial for hot flashes, mood and sleep
    - MENOS II trial revealed Group & self guided CBT decreased hot flashes by 2 pts on a 10pt scale
    - Benefits maintained at 26 week follow up

1. Lassale et al. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. *Molecular Psychiatry*. 2018.
2. Gabriel et al. Recent evidence exploring the associations between physical activity and menopausal symptoms in midlife women: perceived risks and possible health benefits. *Womens Midlife Health*. 2015.
3. Wu et al. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Research and Treatment*. 2013
4. Thurston. Behavioral Weight Loss for the Management of Menopausal Hot Flashes: A Pilot Study. *Menopause*. 2015
5. Huang. An intensive behavioral weight loss intervention and hot flushes in women. *Archives of Internal Medicine*. 2010
6. Ayers B, Smith. Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flashes and night sweats (MENOS 2): a randomized controlled trial. *Menopause* 2012

# Unconventional treatments *(It's not all about pills)*

- Acupuncture

- Meta-analysis of 8 RCTs (~800 subjects): Decreased hot flash severity & frequency over a three month duration
- Benefit sharply decreased when compared to sham acupuncture
- Few risks. Can be especially beneficial if there is comorbid chronic pain (back, neck, HA)

- Yoga

- Meta-analysis of 5 RCTs (~500 subjects): Benefit for vasomotor & psychological symptoms versus a waitlist control
- Low quality, short term evidence. Heterogenous types of yoga. Low risk intervention that can be done at home.

- Hypnosis

- Elkins trial showed a 75% reduction in hot flashes over 12 wks via self-hypnosis
- Adoption hampered by lack of widely available resources



# What to consider before prescribing supplements

- Dietary Supplement:
  - “Vitamin, mineral, amino acid, herb, or other substance that can be used to supplement the diet”
- Herbs differ based on plant part isolated and amount of active compound
- Stick with supplements with studies verifying safety at a particular dose
- Choose brands with 3rd party testing to avoid risk of adulterants
  - **ConsumerLab** - Helpful for choosing safe brand
  - **Natural Medicines** - Helpful for identifying interactions, side effects, and indications
  - **National Center for Complementary and Integrative Health**
  - **‘About Herbs’** phone app - quick reference guide for most supplements

# Supplements Cheat Sheet

## Small benefit:

- Phytoestrogens
  - Soy isoflavone extracts containing 30-60mg genistein daily *(avoid in breast CA)*
  - S-Equol 10mg daily *(avoid in breast CA)*
  - Siberian Rhubarb 4mg daily *(avoid in breast CA)*
- Maca 3g powdered root daily in food *(avoid in breast CA)*
- Pycnogenol 60-200mg daily

## No benefit:

- Black Cohosh
- Phytoestrogens: dietary soy, flax, hops *(avoid supplements made up of these sources in breast CA)*
- Evening Primrose Oil
- Vitamin E
- Wild Yam
- Dong Quai *(avoid in breast CA)*

# Phytoestrogens

- Specific type of Phytoestrogens
  - Isoflavones (soy & red clover)
  - Lignans (flax)
  - Hops (humulus Lupulus)
  - Siberian Rhubarb (Rheum Raponticum)
- Isoflavone breakdown in soy: 50% **genistein**, 40% **daidzein**
- Mechanism: agonist/antagonist properties at the Beta Estrogen Receptor
- Safety: Found to be safe up to 1yr. Avoid use in breast CA survivors
- Side effects: Hypersensitivity, GI upset
- Drug/Herb Interactions:
  - Avoid use w/ MAO-I due to tyramine-induced HTN
  - Caution w/ anti-platelets & anticoagulants

1. Roberts. Safety of herbal medicinal products in women with breast cancer.
2. Lethaby. Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database of Systemic Reviews. 2013.
3. Biglia. Non-hormonal strategies for managing menopausal symptoms in cancer survivors: an update. E Cancer Medical Science. 2019
4. Johnson. Complementary and Alternative Medicine for Menopause. Journal of Evidence Based Integrative Medicine. 2019
5. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. Menopause. 2015

# Phytoestrogens

- Efficacy
  - Dietary soy: no benefit beyond placebo
  - Red Clover: no benefit beyond placebo
  - Hops: no benefit beyond placebo
  - Soy extracts: mixed, overall no conclusive evidence for benefit
    - 4 trials of extracts containing 30-60mg Genistein better than placebo
  - Siberian Rhubarb (Rheum Raponticum Extract - ER 731)
    - One study showing benefit beyond placebo in a menopausal rating scale
    - 42% of subjects completed trial
    - Post market surveillance from 1993-2014 revealed only mild SE's (mostly GI)

1. Lethaby. Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database of Systemic Reviews. 2013.
2. Johnson. Complementary and Alternative Medicine for Menopause. Journal of Evidence Based Integrative Medicine. 2019
3. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. Menopause. 2015
4. Chang. Rheum rhaponticum Extract (ERr 731): Postmarketing Data on Safety Surveillance and Consumer Complaints. Integrative Medicine (Encinitas). 2016

# Phytoestrogens - S-Equol

- Daidzein metabolized by gut bacteria to produce → S-Equol
- Asians produce Equol at twice the rate of non-asian (50% vs 25% respectively)
- Observational study:
  - Sample of perimenopausal women regularly consuming dietary soy → Decreased VMS in Equol-producers vs no change in non-producers.
- Clinical Trials:
  - Japanese study → 10mg of S-Equol x12wk decreased VMS by 60% vs 35% in placebo arm
  - US study → 40mg of S-Equol vs 50mg soy isoflavone control x8wk.
    - 43% of responders in the S-Equol arm vs 16% in the isoflavone arm. (Responder = 50% decrease in VMS)

# Phytoestrogens: S-Equol

- No major side effects reported. Must still avoid use in breast cancer survivors
- Currently no commercial test to determine S-Equol producer & non-producers
- Setchell and colleagues found vegetarians to be Equol producers 50% of the time vs 25% in a non-vegetarian sample
  - Sample of 41 healthy adults. Ethnicity of subjects & Diet compositions unknown
- One commercial S-Equol product exists on the market, but unclear whether it is the exact product used in clinical trials
- Differences in S-Equol production may underlie the mixed benefit seen with soy supplements for menopausal symptoms!

1. Utian et al. S-equol: A Potential Nonhormonal Agent for Menopause-Related Symptom Relief. *Journal of Womens Health*. 2015
2. Setchell. The Clinical Importance of the Metabolite Equol—A Clue to the Effectiveness of Soy and Its Isoflavones. *The Journal of Nutrition*. 2002.
3. Setchell. Method of defining equol-producer status and its frequency among vegetarians. *The Journal of Nutrition*. 2006

# Maca (*Lepidium Meyenii*)

- Peruvian root vegetable grown high up in the andes mountains
- Traditionally regarded as an ‘adaptogen’ for improving vitality & libido
- Mechanism: Contains Beta Sitosterol. Possible modulation of sex steroid receptors.
- Safety: Safe in food doses. 3g up to 4 months safe.
- Side effects: None. Avoid use in breast cancer survivors due to estrogen stimulation
- Drug/Herb Interactions: none
- Efficacy
  - Four low quality trials (N: 202) compiled in a systematic review
  - Dose of 2-3.5g daily of powdered or a “pre-gelatinized” product for two months
  - Statistical significant benefit seen compared to placebo in two menopausal symptom rating scales (Green Climacteric Scale & Kupperman Index)

# Pycnogenol (*Pinus Pinaster*)

- *Pinus Pinaster* is from a pine tree native to Mediterranean countries
- Most studies performed using a commercial product → '*Pycnogenol*'
- Evidence for benefit in asthma, venous insufficiency, and athletic performance
- Mechanism: Standardized to 65-75% Proanthocyanidin → potent antioxidant
- Safety: Safe up to 450 mg daily for 1 year
- Side effects: GI upset, HA, dizziness.
- Drug/Herb Interactions:
  - Be cautious with antiplatelets, anticoagulants, and diabetic drugs as pycnogenol can reduce blood sugar and inhibit platelet aggregation.
- Efficacy
  - Three small trials available
  - Dose of 60-200mg daily of *Pycnogenol* showed benefit in two menopausal symptom rating scales
  - Cannot extrapolate benefit to other pine bark extracts



# No conclusive evidence of benefit (*SAFE*)

## Black Cohosh (*Actaea or Cimicifugae Racemosae*)

- North American perennial plant.
- Used for centuries by Native American herbalist for various ailments
- Mechanism: modulation of serotonin receptors centrally
- Safety: Found to be safe up to 1yr, including breast CA patients
- Side effects: Abdominal pain, N/V, rash, rare liver toxicity (not confirmed)
- Drug/Herb Interactions: none
- Efficacy: Large cochrane article found inconclusive benefit in terms of hot flashes
- Recent large placebo-controlled trials generally show no benefit beyond placebo
- Early studies (80s & 90s) showed some benefit with *Remifemin* 40-80mg daily

# No conclusive evidence of benefit (*SAFE*)

- Evening Primrose Oil (*Oenothera Biennis*)
  - Rich source of gamma linoleic acid.
  - Used for multiple inflammatory, autoimmune, and gynecologic conditions
  - No benefit for hot flashes beyond placebo using up to a 4g dose daily for 6 months
  - Safe up to 6 grams for 1yr
- Vitamin E
  - Safe at a max of 400 IU daily
  - Just has 1 small crossover trial of 50 subjects that showed a benefit. Two other trials negative. .

1. Johnson. Complementary and Alternative Medicine for Menopause. Journal of Evidence Based Integrative Medicine. 2019
2. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. Menopause. 2015
3. <https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/>

# No conclusive evidence of benefit (NOT SAFE)

- Wild Yam (Dioscorea)
  - Rhizome grown in tropical climates
  - Contains diosgenin a steroid precursor. In vitro, converts to progesterone (not in vivo)
  - Topical cream ineffective for menopausal symptoms. No evidence for oral use.
  - Large amounts consumed orally can lead to nausea/vomiting
  - Due to lack of sufficient safety data, avoid oral supplements
- Dong Quai (Angelica Sinensis)
  - Traditional Chinese Medicine root used for multiple gynecologic complaints
  - May have some estrogen stimulation effects.. Avoid use in breast cancer survivors.
  - Constituents Bergapten & Safrole are known carcinogens

# Case

## Subjective:

- 50y/o F p/w several months hx of 3-5 daily episodes of flushing, diaphoresis, and dizziness
- Often occur at night and disrupt her sleep
- Feeling more Irritable and having trouble functioning at work due to “brain fog”
- Last menses 10 months ago
- Patient prefers “natural” medicines and actively avoids pharmaceuticals
- PMHx: obesity, pre-HTN, mild generalized anxiety
- Social Hx: Busy executive. Mostly eats fast food. Intimidated by gyms, so avoids exercise.
- Meds: none

## Objective:

- BMI: 32, BP 135/88, other labs wnl
- Exam: unremarkable

# Case

Assessment: N95.1 - Menopausal & Female Climacteric States

Plan:

- Modify diet to model a mediterranean diet template
- Start walking program and gradually work towards 150 min/wk
- Start group yoga course for beginners; continue practice at home via youtube
- Refer to psychology for individual or group cognitive behavioral therapy (CBT)
- Add 3g maca root powder to breakfast oatmeal or smoothie (*ConsumerLab approved brand*)
- Trial soy isoflavone extract containing 30mg genistein for at least 2 month
- Trial Pycnogenol starting at 60mg daily, but titrating up to a max of 200mg if needed
- Discuss all supplement usage with PCP or specialist before starting new medications in the future
- Refer to acupuncture or clinical hypnotherapy at follow up if needed
- Follow up in 3mo

Q&A