MANAGING MENOPAUSE WHILE MINIMIZING RISKS

NEW DATA TO INFORM HORMONE PRESCRIBING

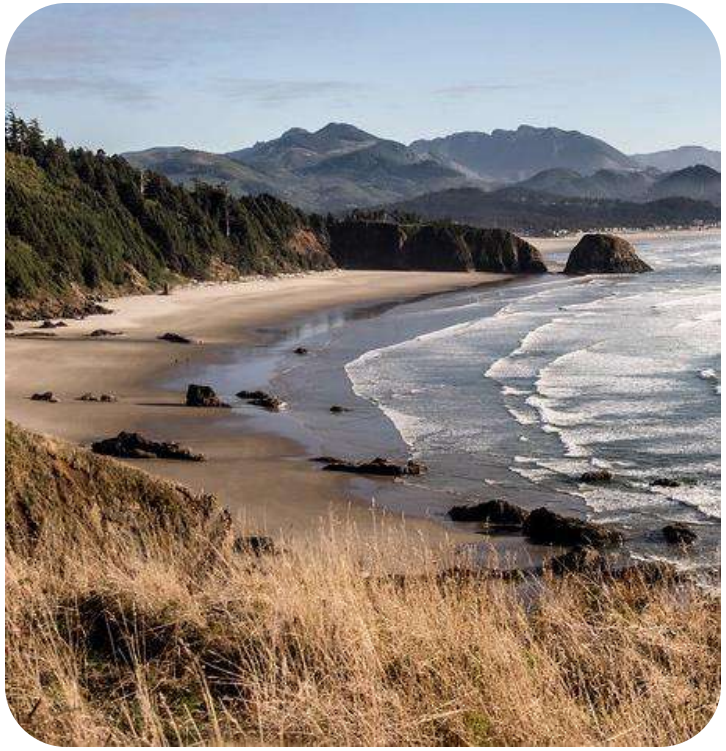
HEATHER HYDZIK, ND

Disclosure

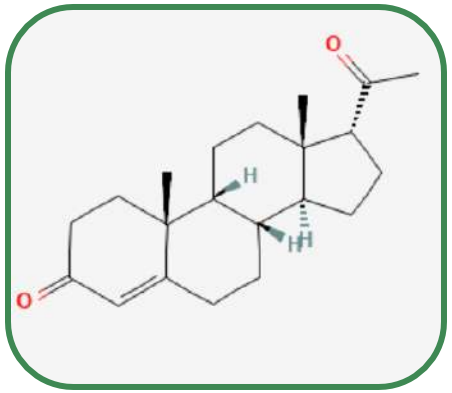
I am a staff physician at Doctor's Data Inc

Learning Objectives

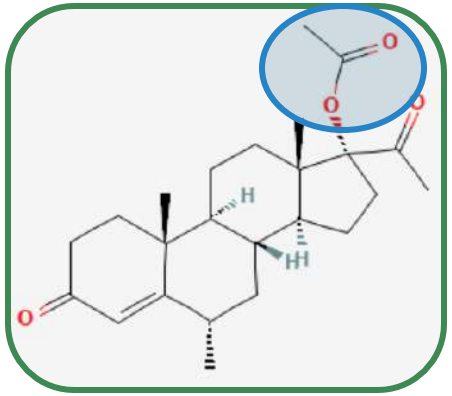
- Update your knowledge on the evolving conventional perspective on menopausal hormone therapy and risk to the breast
- Gain awareness of the reanalysis of the Women's Health Initiative showing different risks and benefits from estrogen supplementation than originally believed
- Devour the long-awaited findings of a new large-scale observational study regarding risk of hormone replacement after age 65 involving 10 million women and their risk of cancers, cardiovascular disease, dementia and mortality, which was just published in May 2024 in the journal Menopause
- Learn to choose the lowest risk hormone delivery formats and formulations
- Interpret urine hormone testing through the lens of breast health and risk reduction and discover therapeutic considerations to improve hormone metabolism and detoxification
- Review case example involving BHRT and the new non-hormonal medication fezolinetant



Vocab



Progesterone



MPA (a progestin)

- **Progestogen**: a hormone that can bind progesterone receptors, this encompasses progestins and progesterone
  - **Progestin**: synthetic medication similar to progesterone, but the molecular structure has been altered
  - **Progesterone**: the progestogen made by the body or the bioidental/isomolecular equivalent
- **Bioidentical**: a hormone with the same molecular structure as the endogenous hormone
- **Isomolecular**: bioidentical, but a more up to date term currently being used by the conventional medical community
- **MHT**: menopausal hormone therapy, BHRT or HRT
  - **ET**: estrogen only; **EPT**: estrogen + progestogen, aka combination therapy
  - **BHRT**: bioidentical hormone replacement therapy
  - **HRT**: hormone replacement therapy, usually refers to oral conjugated equine estrogens with or without a progestin
    - **CEE**: conjugated equine estrogens
    - **MPA**: medroxyprogesterone acetate

Hormone History

1998 – **Women's Health Initiative** started

- Largest randomized study thusfar, studied the effect of HRT on cardiovascular disease, cancer, and osteoporosis
- 16,608 postmeno females with a uterus randomized to 0.625mg CEE + 2.5mg MPA or placebo
- 10,739 postmeno females without a uterus randomized to 0.625mg CEE or placebo

Cagnacci A, Venier M. The Controversial History of Hormone Replacement Therapy. Medicina (Kaunas). 2019 Sep 18;55(9):602. doi: 10.3390/medicina55090602. PMID: 31540

WHI discontinued early

- 2002 – Estrogen/Progestin trial d/c because those receiving CEE+MPA had an increased incidence of **coronary heart disease** and **breast cancer**, and a reduction of osteoporotic fractures and colorectal cancer
- 2004 – CEE only trial d/c dt small increased incidence of **ischemic stroke** with HRT vs placebo

- This news resulted in a 46% decline in HRT use in US; 28% decline in Canada; similar decreases in Europe

WHI - Flaws

- 2004 - Statistical significance being questioned because nearly half of participants had dropped out of the study
- In 2018, discovered that the placebo group had a lower than expected risk of breast cancer likely because some women in this group had previously taken estrogen
- The original conclusions were wrong:
  - **Excluding women with history of estrogen use from the placebo group resulted in no increased risk of breast cancer in the CEE+MPA group**
  - 2004 reanalysis found no effect on risk of coronary disease

Hodis HN, Sarrel PM. Menopausal hormone therapy and breast cancer: what is the evidence from randomized trials?. Climacteric. 2018;21(6):521-528. doi:10.1080/13697137.2018.1514008

WHI – Age bias

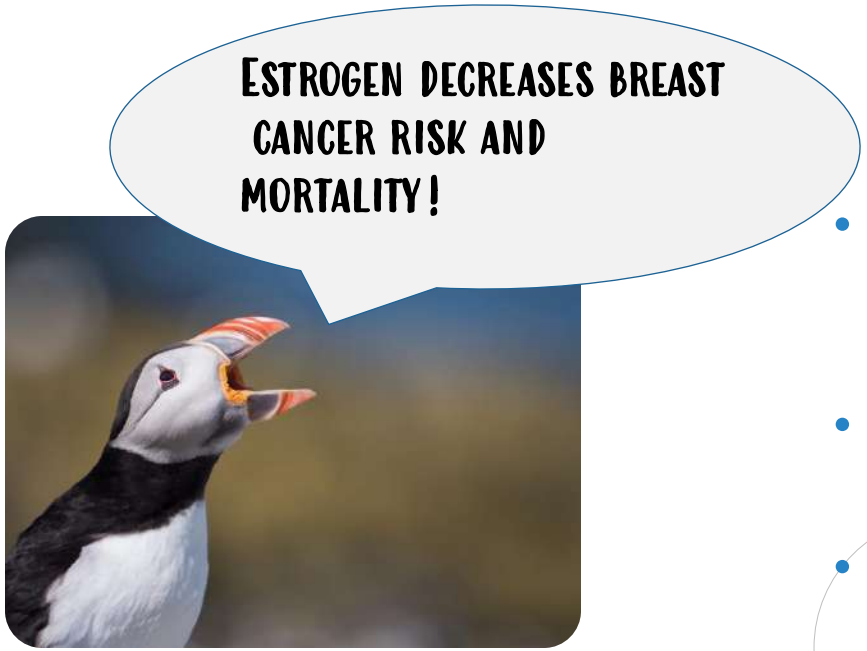
- Most participants were 10 yrs or more post-menopause
- Reanalysis and age stratification of the results found reduced cardiovascular risk and all-cause mortality among younger HRT users (ages 50 – 59 or within 10 yrs of menopause)
  - slower growth of calcification in their arteries

WHI Long Term f/u (2017) - Mortality

Conclusion: "Among postmenopausal women, hormone therapy with CEE plus MPA for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years."

Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. *JAMA*. 2017;318(10):927–938. doi:10.1001/jama.2017.11217

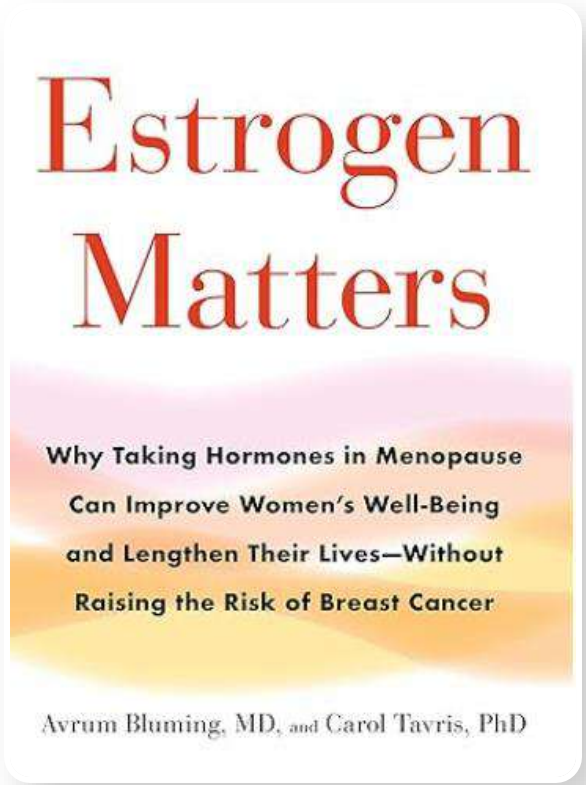
WHI Reanalysis in 2019



- Re-analysis of the WHI, sponsored by 12 cancer centers showed that if women took estrogen therapy, they had a **23% reduction in risk of getting breast cancer for the next 20 yrs**, even if only on it for a short while.
- Estrogen statistically **reduced ovarian, uterine, lung, and colorectal cancer risk by 33%**, if one had been on estrogen for at least 5 years.
- Participants on estrogen therapy who then developed breast cancer had a **44% less risk of dying from it**!
- No other therapy has ever shown this level of protection in breast cancer fatality before.

- 2019 SABCS Abstracts Home Print Page Session GS5 - GS5. General Session 5 GS5-00. Long-term influence of estrogen plus progestin and estrogen alone use on breast cancer incidence: The Women's Health Initiative randomized trials December 13, 2019, 9:30 AM - 9:45 AM Authors/Cancer Centers
- 2019 SABCS Abstracts Home Print Page Session GS5 - GS5. General Session 5 GS5-00. Long-term influence of estrogen plus progestin and estrogen alone use on breast cancer incidence: The Women's Health Initiative randomized trials December 13,
- 2019, 9:30 AM - 9:45 AM Authors/Cancer Centers

Does estrogen cause recurrence?



- Avrum Bluming MD, oncologist, gave Premarin to 248 women with breast cancer and found no increased risk of recurrence 14 years later compared to case-control breast cancer patients not given estrogen
- High dose estrogen was actually used to treat metastatic breast cancer from the 1940s to the 1970s

Bluming AZ. Safety of systemic hormone replacement therapy in breast cancer survivors. Breast Cancer Res Treat. 2022;191(3):685-686. doi:10.1007/s10549-021-06479-y

HABITS and Stockholm Trial (E2 + progestin)

- In 1997 two independent randomized clinical trials, Hormonal Replacement Therapy After Breast Cancer—Is It Safe? (HABITS; 434 patients) and the Stockholm trial (378 patients), were initiated in Sweden to compare MHT users with non-users after diagnosis of early-stage breast cancer.

- HABITS trial was prematurely stopped in December 2003, because, at follow-up of 2.1 years, the risk for recurrence of breast cancer among MHT patients was statistically significantly higher (relative hazard [RH] = 3.3) than among those not on hormones.

- In the Stockholm trial, however, at a follow-up of 4.1 years, the risk of breast cancer recurrence was not associated with MHT

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TABLE 1. Summary of 25 Studies of Breast Cancer Survivors Given HRT

Authors	Year	Study Type	No. on HRT/No. Controls	Median Duration of HRT/Range, y	Median Duration of Follow-up, y	Results	Reference
1a. Palshof et al.	1980	**Prospective randomized**	37/95	2	3	**Reduced recurrence***	61
1b. Palshof et al.	1985	Updates of the original study	51/103	2	6.5	**Reduced recurrence** **Reduced mortality**	62
2. Stoll and Parbhoo	1988	Prospective single-arm	14/	0.25–0.5	2	No recurrence	63
3. Powles et al.	1993	Retrospective observational	35/	1.2/0.1–3.7	3.6	2 of 35 developed recurrence No breast cancer deaths	64
4. Eden et al.	1995	Retrospective case-control	90/811	1.5/0.25–12	3	**Reduced recurrence**	65
5. Vassilopoulou-Sellin et al. (feasibility study)	1997	Prospective single-arm	43/	2.6/2–12	12	1 of 43 developed recurrence No breast cancer deaths	66
6. Dew et al.	1998	Retrospective cohort	167/1305	1.6/0.25–22	4	No difference†	67
7. Espie et al.	1999	Retrospective cohort	120/240	2.4/1–10.6	2.4	No difference	68
8. Guidozzi	1999	Prospective single-arm	20/	2.7/2–3.7	5.7	No recurrence	69
9. Natrajan et al.	1999	Retrospective cohort	50/26	5.5/0.5–32	7	No difference	70
10. Uršič-Vrščaj and Bebar	1999	Prospective cohort	21/42	2.3/0.25–6	2.3	No difference	71
11. Vassilopoulou-Sellin et al.	1999	Prospective cohort	39/280	4/2–6	3.8	No difference	72
12. Disaia et al.	2000	Retrospective cohort	125/362	1.8/0.1–30		**Reduced mortality**	73
13. Marsden et al.	2000	**Prospective randomized**	51/49	0.5		No difference	74
14. Peters et al.	2001	Prospective cohort	56/551	6.4/1–20.9	12.8	No difference	75
15. Marttunen et al.	2001	Prospective cohort	88/43	2.6	2.6	No difference	76
16. Beckmann et al.	2001	Retrospective cohort	64/121	3.5/3	5	No difference	77
17. O'Meara et al.	2001	Retrospective case-control	174/695	1.25	4.6	**Reduced recurrence** **Reduced mortality**	78
18. Vassilopoulou-Sellin et al.	2002	**Prospective randomized**	56/243	5	6	No difference	79
19. Durna et al.	2002	Retrospective observational	286/836	1.75/0.17–34	6	**Reduced recurrence** **Reduced mortality**	80
20. Decker et al.	2003	Prospective cohort	277/554		3.7	No difference	81
21. Gorins et al.	2003	Prospective cohort	230/	2.5		No difference	82
22a. Holmberg and Anderson (HABITS)	2004	**Prospective randomized**	174/171	2	2.1	**Increased risk of local or contralateral tumors only** **No increased risk of metastases or death**	83
22b. Holmberg et al. (HABITS)	2008	Updates of the original study	221/221	2	5	**No increased mortality**	84
23a. von Schoultz and Rutqvist (Stockholm)	2005	**Prospective randomized**	175/184	4.1/0.2–7	4.1	No difference	85
23b. Fahlén et al. (Stockholm)	2013	Updates of the original study	188/190	2.6	10.8	No difference	86
24. Bluming	2008	Prospective cohort	117/63	7.5/1–15	7.5	**Reduced recurrence**	87
25. Figueiredo et al.	2008	Retrospective case-control	708/1399			No difference	88

Boldface is employed to identify the prospective randomized trials and to identify significant positive or negative findings.

*Reduced recurrence = breast cancer survivors given HRT had *fewer* recurrences of breast cancer, or *lower* risk of death, than control group not on HRT.

†No difference in recurrence of breast cancer between survivors on HRT and the controls.

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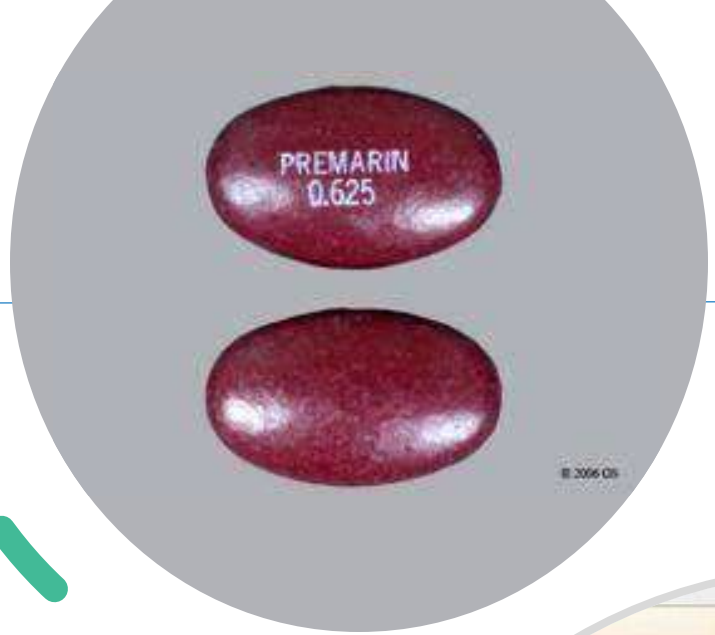
Bluming AZ. Hormone Replacement Therapy After Breast Cancer: It Is Time. Cancer J. 2022 May-Jun 01;28(3):183-190. doi: 10.1097/PPO.0000000000000595. PMID: 35594465.

Vaginal estrogen may decrease breast cancer recurrence vs no HRT

- To relieve the symptoms of urogenital atrophy, local estrogen therapy is commonly used.
- Comparing vaginal estrogen user breast cancer survivors and non-HRT user breast cancer survivors, Durna and colleagues found **9.1% recurrence in vaginal estrogen users versus 29.5% in non-HRT users.**
- Fahlen and colleagues compared the use of oral and local estrogen HRT in breast cancer survivors. Recurrence was detected in 7.4 % vs. 2.1 % of the two groups, respectively. Mortality between the two groups, however, was not significantly different.
- Local estrogen application is contraindicated during adjuvant aromatase inhibitor therapy, since the serum estrogen level has to be kept strictly at zero.

Deli T, Orosz M, Jakab A. Hormone Replacement Therapy in Cancer Survivors - Review of the Literature. Pathol Oncol Res. 2020 Jan;26(1):63-78. doi: 10.1007/s12253-018-00569-x. Epub 2019 Jan 8. PMID: 30617760; PMCID: PMC7109141.

CEE and hx of breast cancer - 5 yr prospective trial



- N=299
- Premarin 0.625 mg days 1-25 of the month x 5 yrs or no HRT
- Two of 56 women on ERT (3.6%) developed a contralateral, new breast carcinoma.
- In the group that was not on ERT, 33 of 243 women (13.5%) developed new or recurrent breast carcinoma.
- ERT did not compromise disease free survival in select patients who were treated previously for localized breast carcinoma.

Vassilopoulou-Sellin R, Cohen DS, Hortobagyi GN, et al. Estrogen replacement therapy for menopausal women with a history of breast carcinoma: results of a 5-year, prospective study. *Cancer*. 2002;95(9):1817-1826. doi:10.1002/cncr.10913

CONVENTIONAL CONSENSUS ON MHT

ACOG (2021) - Tx for GSM after Estrogen-dependent Breast Cancer

- **Increased recurrence was not seen in seven studies totaling more than 4,000 breast cancer survivors [using vaginal estrogen] over a median follow-up of 2–7 years**. These studies included women taking tamoxifen and women taking AIs and had varied follow-up time. Additionally, no change in breast density or Bi-RADS scores was observed in a cohort study of menopausal women after 1 year of [vaginal] estrogen use
- If nonhormonal treatments have failed to adequately address symptoms, after discussion of risks and benefits, **low-dose vaginal estrogen may be used in individuals with a history of breast cancer, including those taking tamoxifen**. For individuals taking aromatase inhibitors (AIs), low-dose vaginal estrogen can be used after shared decision making between the patient, gynecologist, and oncologist.

Treatment of Urogenital Symptoms in Individuals With a History of Estrogen-dependent Breast Cancer: Clinical Consensus. *Obstet Gynecol*. 2021;138(6):950-960. doi:10.1097/AOG.0000000000004601

Nonhormonal options for GSM

Table 1. Nonhormonal and Hormonal Treatment Options

Formulation	Composition	Dosages
Nonhormonal options		
Lubricants	Water-, silicone-, and polycarbophil-based products	See product labeling
Moisturizers	Hyaluronic acid Polyacrylic acid Polycarbophil-based vaginal moisturizer	5 mg daily for 2 weeks, then 3–5 times per week 3 g daily 2.5 g 3 times/week
Vaginal suppositories	Vitamin E Vitamin D	30–200 international units 1,000 international units
Lidocaine	4% aqueous lidocaine	Fully saturated cotton ball applied to the vulvar vestibule for 3 minutes

Treatment of Urogenital Symptoms in Individuals With a History of Estrogen-dependent Breast Cancer: Clinical Consensus. *Obstet Gynecol*. 2021;138(6):950-960. doi:10.1097/AOG.0000000000004601

ACOG (2021) - Non-estrogen options for GSM

- **Testosterone vaginal cream** - 150mcg or 300mcg x 14 days then twice per week
- **Prasterone (DHEA) suppositories** - 6.5mg, same regimen
- **Ospemifene**, an oral SERM
  - May be considered for individuals with a history of estrogen-dependent breast cancer
  - 60mg once per day

https://www.acog.org/clinical/clinical-guidance/clinical-consensus/articles/2021/12/treatment-of-urogenital-symptoms-in-individuals-with-a-history-of-estrogen-dependent-breast-cancer. Accessed 6/17/2024

NAMS (North American Menopause Society) 2022 Hormone Therapy Position Statement

- Contraindications for oral and transdermal hormone therapy:
  - unexplained vaginal bleeding; liver disease; prior estrogen sensitive cancer (including breast cancer); prior CHD, stroke, MI, or VTE; or personal history or inherited high risk of thromboembolic disease
- Observational evidence suggests that hormone therapy use does not further increase risk of breast cancer in women at high risk because of a family history of breast cancer or after bilateral salpingo-oophorectomy (BSO) for BRCA 1 or 2 genetic variants. (Level II)

https://www.menopause.org/docs/default-source/professional/nams-2022-hormone-therapy-position-statement.pdf
Loizzi V, Dellino M, Cerbone M, et al. The Role of Hormonal Replacement Therapy in BRCA Mutated Patients: Lights and Shadows. Int J Mol Sci. 2023;24(1):764. Published 2023 Jan 1. doi:10.3390/ijms24010764

NAMS 2022 Position Continued

- Systemic hormone therapy is generally not advised for survivors of breast cancer, although hormone therapy use may be considered in women with severe VMS unresponsive to nonhormone options, with shared decision-making in conjunction with their oncologists. (Level III)
- For survivors of breast cancer with GSM, low-dose vaginal ET or DHEA may be considered in consultation with their oncologists if bothersome symptoms persist after a trial of nonhormone therapy. There is increased concern with low-dose vaginal ET for women on AIs. (Level III)

- There is no general rule for stopping systemic hormone therapy in a woman aged 65 years

https://www.menopause.org/docs/default-source/professional/nams-2022-hormone-therapy-position-statement.pdf

NAMS 2023 -Nonhormonal therapies for Vasomotor Symptoms

Recommended nonhormonal treatments:

- **Weight loss**
- **CBT**
- **Hypnosis**
- **Rx:**
  - **SSRI/SNRI:**
    - Brisdelle (paroxetine) 7.5mg/day
      - Contraindicated with tamoxifen
    - Citalopram 10mg QD x 1 week, then increase to 20mg if needed, possibly up to 30mg
  - **Gabapentin** 100 mg 1 hr before bed, increase by 100 mg every 3 nights until relief of hot flashes, side effects, or max of 900 mg
  - **Oxybutynin** 5 to 10mg QD; causes dry mouth
  - **Fezolinetant** 45mg QD; follow up liver enzyme testing needed

- **Stellate Ganglion Block**

TABLE 2. *Treatment recommendations for nonhormone therapies for vasomotor symptoms with levels of evidence*

Category	Treatment	Recommended	Not recommended
Lifestyle			
	Cooling techniques		Level II
	Avoiding triggers		Level II
	Exercise		Level II
	Yoga		Level II
	Dietary modifications		Level III
	Weight loss	Levels II-III	
Mind-body techniques			
	Cognitive-behavioral therapy	Level I	
	Mindfulness-based interventions		Level II
	Clinical hypnosis	Level I	
	Paced respiration		Level I
	Relaxation		Level II
Prescription therapies			
	SSRIs/SNRIs	Level I	
	Gabapentin	Level I	
	Pregabalin		Level III
	Clonidine		Levels I-III
	Oxybutynin	Levels I-II	
	Suvorexant		Level II
	Fezolinetant	Level I	
Dietary supplements			
	Soy foods and soy extracts		Level II
	Soy metabolites equol		Level II
	Supplements/Herbal remedies[a]		Levels I-III
	Cannabinoids		Level II
Acupuncture, other treatments, and technologies			
	Acupuncture		Level II
	Stellate ganglion block	Levels II-III	
	Calibration of neural oscillations		Level II
	Chiropractic intervention		Level II

Level I, good and consistent scientific evidence; Level II, limited or inconsistent scientific evidence; Level III, consensus and expert opinion.
SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.
[a]Pollen extract, ammonium succinate, *Lactobacillus acidophilus*, rhubarb, black cohosh, wild yam, dong quai, evening primrose oil, maca, ginseng, *labisia pumila/eurycoma longifolia*, chasteberry, milk thistle, omega-3 fatty acids, vitamin E.

https://www.menopause.org/docs/default-source/professional/2023-nonhormone-therapy-position-statement.pdf

DO WE HAVE TO STOP HORMONES AFTER AGE 65?

Press release from the Menopause Society (formerly NAMS) - 2024

Women Aged Older Than 65 Years May Be Able to Safely Continue Taking Hormone Therapy

- Compared with never use or discontinuation of HT before the age of 65 years, the use of **estrogen monotherapy** beyond age 65 years was associated with significant risk reductions:
  - Mortality
  - Cancer – Breast, Lung, and Colorectal
  - Congestive heart failure
  - Venous thromboembolism
  - Atrial fibrillation
  - Acute myocardial infarction
  - Dementia

- https://www.menopause.org/docs/default-source/press-release/use-of-ht-beyond-age-65-and-its-effects-by-type.pdf
- Baik SH, Baye F, McDonald CJ. Use of menopausal hormone therapy beyond age 65 years and its effects on women's health outcomes by types, routes, and doses. Menopause. 2024;31(5):363-371. doi:10.1097/GME.0000000000002335

Results - estrogen and progestogen combo-therapy

- E+ any progestogen were associated with
  - Increased risk of breast cancer by 10%-19%,
  - But such risk can be mitigated using **low dose of transdermal or vaginal** E+ progestogen.
- E+ *progestin* exhibited significant risk reductions in
  - Endometrial cancer (45% or adjusted hazards ratio, 0.55; 95% CI, 0.50-0.60),
  - Ovarian cancer (21%),
  - Ischemic heart disease (5%),
  - CHF (5%), and
  - Venous thromboembolism (5%)
- E+ *progesterone* exhibited risk reduction only in CHF (4%)

Note: this study only included oral progestogens

Full text: https://journals.lww.com/menopausejournal/fulltext/2024/05000/use_of_menopausal_hormone_therapy_beyond_age_65.3.aspx

Details on routes and formulations

- Transdermal and vaginal estrogen preparations exhibited small (<10%) but significant risk reductions for stroke and dementia
- Mortality risk reduction of E2 was significantly greater than that of CEE (21% vs 13%)
- Progesterone monotherapy was associated with a 10% reduction in breast cancer risk
- Progestin monotherapy increased breast cancer risk by 21%

Full text: https://journals.lww.com/menopausejournal/fulltext/2024/05000/use_of_menopausal_hormone_therapy_beyond_age_65.3.aspx

Conclusion

Risk reductions appear to be greater with:

- **Low doses** rather than medium or high doses
- **Vaginal or transdermal** rather than oral preparations
- **E2** rather than conjugated estrogen

Baik SH, Baye F, McDonald CJ. Use of menopausal hormone therapy beyond age 65 years and its effects on women's health outcomes by types, routes, and doses. *Menopause*. 2024;31(5):363-371. doi:10.1097/GME.0000000000002335

Estrogen only for women without a uterus?

- 20 years of follow-up on WHI participants, **ovarian cancer incidence doubled among the estrogen only** group, a difference that reached statistical significance at 12 years' follow up.
- **Ovarian cancer mortality was also significantly increased** (HR = 2.79 95% CI 1.30-5.99, *P* = .006). Absolute numbers were small, however, with 35 cases of ovarian cancer compared with 17 in the placebo group.
- Combined therapy recipients saw no increased risk for ovarian cancer and significantly lower endometrial cancer incidence (106 cases vs. 140)

Chlebowski RT, Aragaki AK, Pan K, et al. Menopausal hormone therapy and endometrial and ovarian cancer outcomes: long-term follow-up of the Women's Health Initiative randomized trials. J Clin Oncol. 2024;42(suppl 16):10506. doi:10.1200/JCO.2024.42.16_suppl.10506

RISK STRATIFICATION BY TYPES OF HORMONES

Isomolecular vs molecularly-altered

ACOG (2024) - updated perspective on MHT based on review of WHI and other large studies

Conjugated Equine Estrogens (CEE)

- Binds primarily to beta receptors, leading to more potent clinical effects
- Increases **inflammatory** markers such as C-reactive protein
- Induces matrix metalloproteinase 9, an enzyme that **breaks down collagen**.
- Early WHI cardiovascular events are attributed to resulting plaque destabilization and rupture.

Estradiol (E2)

- Binds to alpha and beta estrogen receptors
- Tablets, patches, and gels have been shown to **improve vasomotor sx, GSM and improve BMD**

Levy B, Simon JA. A Contemporary View of Menopausal Hormone Therapy. Obstet Gynecol. Published online March 14, 2024. doi:10.1097/AOG.0000000000005553

ACOG (2024)

Progestins

- Can bind to receptors for P, androgens, and glucocorticoids
- Can increase IGF-1 and promote insulin resistance
- Increase breast cancer risk
- MPA enhances thrombotic risk of estrogen therapy

Micronized progesterone

- Has not been implicated in risk of thrombosis or increased incidence of breast cancer

Levy B, Simon JA. A Contemporary View of Menopausal Hormone Therapy. Obstet Gynecol. Published online March 14, 2024. doi:10.1097/AOG.0000000000005553

ACOG (2024)

CEE + MPA and breast cancer risk

- WHI re-evaluated by *Hoddis and Sarrel* in 2018 and found that CEE + MPA had a null effect on breast cancer risk in the 11 yrs of follow up
- 25% of the placebo group had used hormones up to 3 months prior to the trial!
  - This subset had the lowest breast cancer risk
- Current CEE+MPA users and never users had equal breast cancer incidence

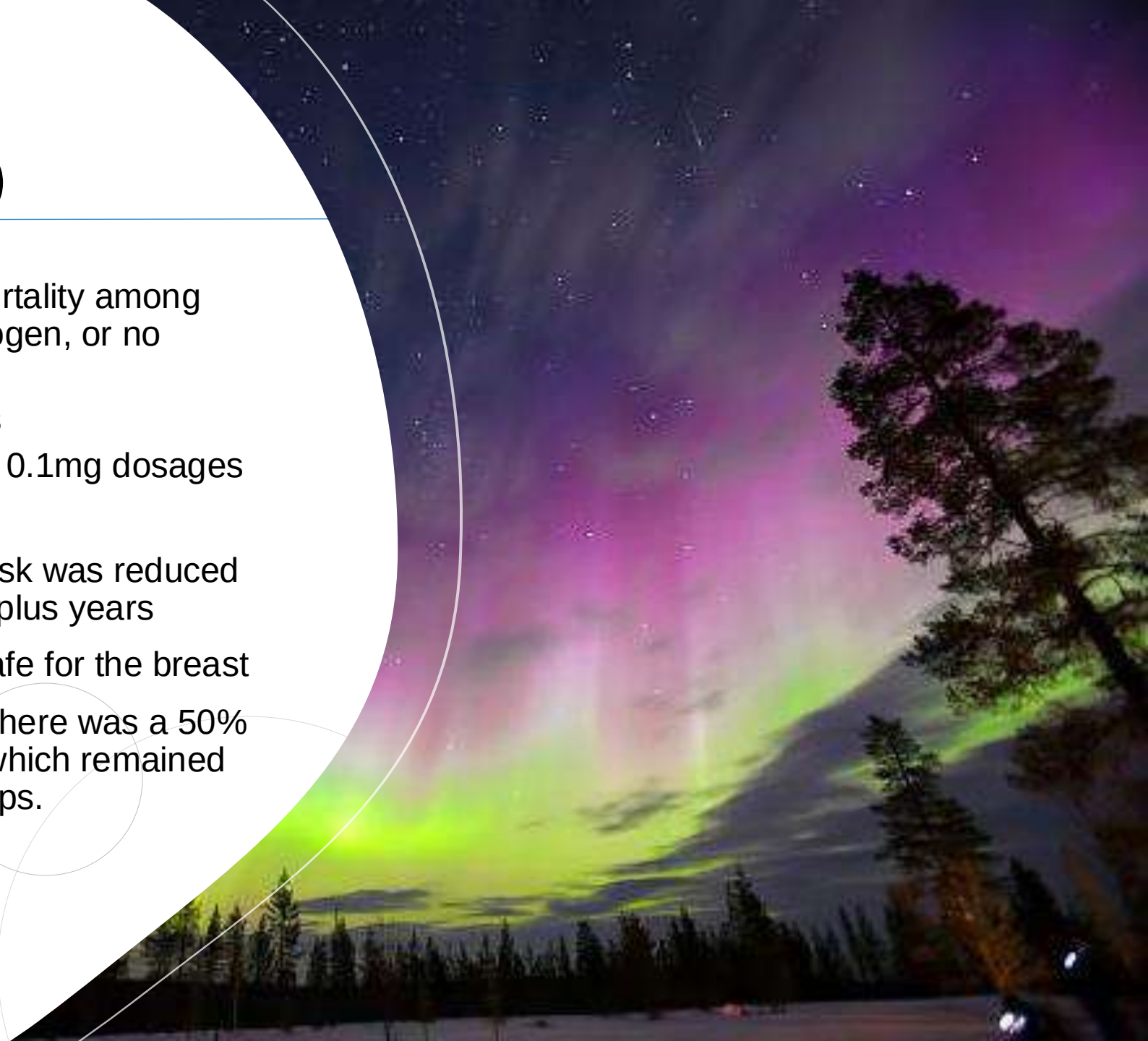
CEE only risk

- 45% statistically significant reduction in breast cancer mortality after 18 years of follow up.
- Among the 10,739 women without a uterus randomized to CEE .0625mg vs placebo (WHI)

- Levy B, Simon JA. A Contemporary View of Menopausal Hormone Therapy. Obstet Gynecol. Published online March 14, 2024. doi:10.1097/AOG.0000000000005553
- Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-333. doi:10.1001/jama.288.3.321
- Hodis HN, Sarrel PM. Menopausal hormone therapy and breast cancer: what is the evidence from randomized trials?. Climacteric. 2018;21(6):521-528. doi:10.1080/13697137.2018.1514008

Nationwide Finnish Comparative study (2016)

- Observational trial on breast cancer mortality among 489,105 women using E2, E2+progestogen, or no hormones
  - Oral E2 in 1 mg and 2 mg dosages
  - Transdermal E2 patches in 0.025 - 0.1mg dosages
  - E2 gels 0.5-1.5 mg.
- Researchers concluded that mortality risk was reduced in all HT users, with exposure up to 10 plus years
- E2 when used more than 10 years is safe for the breast
- Even with (E2 + progestin) vs placebo there was a 50% breast cancer mortality risk reduction, which remained more than 10 years across all age groups.



Mikkola, Tomi S. MD, PhD; Savolainen-Peltonen, Hanna MD, PhD; Tuomikoski, Pauliina MD, PhD; Hoti, Fabian PhD; Vattulainen, Pia MSc; Gissler, Mika M.SocSci, PhD; Ylikorkala, Olavi MD, PhD. Reduced risk of breast cancer mortality in women using postmenopausal hormone therapy: a Finnish nationwide comparative study. Menopause 23(11):p 1199-1203, November 2016. | DOI: 10.1097/GME.0000000000000698

WHAT IS THE LOWEST RISK FORM OF HORMONE SUPPLEMENTATION?

Conventional low dose vaginal estradiol options for GSM

Estradiol vaginal inserts

- 4 mcg (Imvexxy caps)
- 7.5 mcg (Estring ring)
- 10 mcg (Imvexxy caps, Vagifem tabs, Yuvafem tabs)
- 25 mcg (Vagifem tabs – not avail in US anymore)

Dosing instructions:

- Tablets or capsules - 1 daily for 2 weeks, then twice weekly
- Ring - insert and replace every 90 days

Estradiol vaginal cream, USP, 0.01% (Estrace) 0.1mg/gm

- The usual dosage range is 2 to 4 g (marked on the applicator) daily for one or two weeks, then gradually reduced to one half initial dosage for a similar period. A maintenance dosage of 1 g, one to three times a week, may be used after restoration of the vaginal mucosa has been achieved.

Moderate dose vaginal estradiol rings to treat vasomotor symptoms

Femring

- 12.4mg/ring (releases 0.05mg/24hr for 3 months)
- 24.8mg/ring (releases 0.1mg/24hr for 3 months)

- Dosing instructions:
  - 1 ring intravaginally for 90 days; replace with new ring at 90 days if continuing therapy

OVER THE COUNTER?! VAGINAL HORMONES

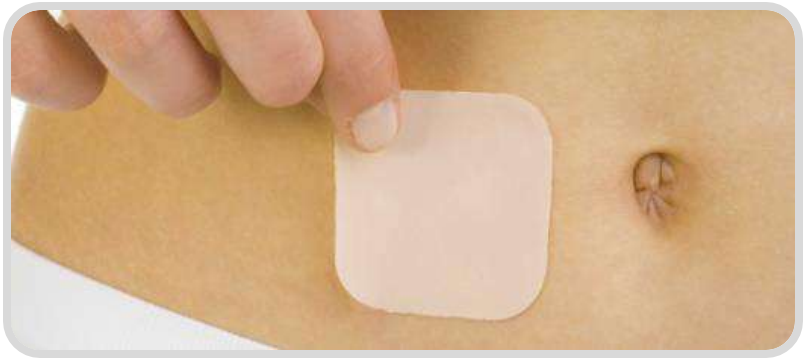
Hydration Ovals

- Hormone options:
  - E3
  - E3, DHEA
  - E3, P
  - E3, P, DHEA
- Other ingredients: cocoa butter, vitamin E, beeswax

- Dose per suppository
  - Estriol:1mg or 2mg
  - Progesterone: 20mg
  - DHEA: 3.25mg
- Instructions: 1 suppository daily for 14 days then 1 to 3x per week prn
- Note: Can stain clothing, recommend a liner

Conventional low dose estradiol patches

- 14mcg/24hr
  - Menostar
  - 1 patch to lower abdomen per week
- 0.025mg/24hr (25mcg/day)
  - Alora, Dotti, Estradiol, Lylana, Minivelle
  - Twice per week



- Moderate and high doses available:
  - 0.0375, 0.05, 0.075 or 0.1 milligrams/day

Conventional oral progesterone options

- Prometrium (oral micronized progesterone) capsules
  - Contains peanut, you can compound it to avoid this ingredient if needed
  - 100mg progesterone sufficient with 0.025-0.05mg E2 patch
  - 200mg progesterone sufficient with 0.075mg E2 patch or higher

- 90% of oral progesterone is enzymatically inactivated in the gut and liver
  - A portion is converted into allopregnanolone
  - Allopregnanolone stimulates GABA receptors and has anti-anxiety effects

Elshafie MA, Ewies AA. Transdermal natural progesterone cream for postmenopausal women: inconsistent data and complex pharmacokinetics. *J Obstet Gynaecol*. 2007;27(7):655-659. doi:10.1080/01443610701582727179992 87

Transdermal/vaginal progesterone and the endometrium

- **100mg vaginal progesterone twice per week was sufficient to prevent endometrial stimulation from a 25mcg estradiol patch twice per week** in 64 postmenopausal females, but this delivery method was associated with more episodes of bleeding compared to oral P4.
- In this study of 35 postmenopausal women, twice-weekly administration of a progesterone vaginal gel (45mg P4/ day) for 1 year sufficiently protected the endometrium in women receiving transdermal estradiol (0.05mg/day) as revealed by endometrial thickness and histology
- **20mg of transdermal progesterone twice per day combined with 0.625mg CEE had similar effects on the endometrium as CEE plus 2.5mg oral MPA**. Endometrial biopsies before and after 6 months showed no endometrial hyperplasia. (PMID: 16320858)

- Sriprasert I, Mert M, Mack WJ, Hodis HN, Shoupe D. Use of oral estradiol plus vaginal progesterone in healthy postmenopausal women. *Maturitas*. 2021;154:13-19. doi:10.1016/j.maturitas.2021.09.002
- Fernández-Murga L, Hermenegildo C, Tarín JJ, García-Pérez MÁ, Cano A. Endometrial response to concurrent treatment with vaginal progesterone and transdermal estradiol. *Climacteric*. 2012;15(5):455-459. doi:10.3109/13697137.2011.644360
- Cincinelle E, de Ziegler D, Galantino P, Pinto V, Barba B, Morgese S, Schonauer S. Twice-weekly transdermal estradiol and vaginal progesterone as continuous combined hormone replacement therapy in postmenopausal women: a 1-year prospective study. Am J Obstet Gynecol 2002 Sep; 187(3):556-60.

Transdermal progesterone effects on breast

- 25mg of transdermal progesterone applied to the breast was shown to decrease cell proliferation in women scheduled for a benign lesion biopsy in a placebo-controlled study involving 40 premenopausal women.
- Among 1150 premenopausal French women diagnosed with benign breast disease, there was no association noted between progesterone cream use and breast cancer risk. Furthermore, women who had used both progesterone cream and an oral progestogen had a significant decrease in breast cancer risk (RR= 0.5) as compared to women who did not use progesterone cream

- Chang KJ, et al. Influences of Percutaneous Administration of Estradiol and Progesterone on Human Breast Epithelial Cell Cycle In Vivo. Fertil Steril (1995) 63(4):785-91.
- Leonetti HB, et al. Topical progesterone cream has an antiproliferative effect on estrogenstimulated endometrium.Fertility and Sterility (2003) 79:221-2.
- Plu-Bureau G, Lê MG, Thalabard JC, Sitruk-Ware R, Mauvais-Jarvis P. Percutaneous progesterone use and risk of breast cancer: results from a French cohort study of premenopausal women with benign breast disease. Cancer Detect Prev. 1999;23(4):290-296. doi:10.1046/j.1525-1500.1999.99032.x

Transdermal and vaginal progesterone cream dosing

- Divided (BID) dosing can be more effective for hot flashes and mental/emotional sx
- For females weighing over 150lb
  - 40 to 60mg per day
- For females weighing under 150lb:
  - 20 to 30mg per day

Transdermal Bi-est

- 80:20; E3:E2 cream
  - Typical dose: 1 mg transdermal daily to areas of thin skin, rotating sites
  - Range: 0.5mg to 2mg
- 50:50; E3:E2 cream
  - 0.5mg to 1mg
  - Good for transitioning off of higher dose oral or patch

Don't forget to add progesterone!

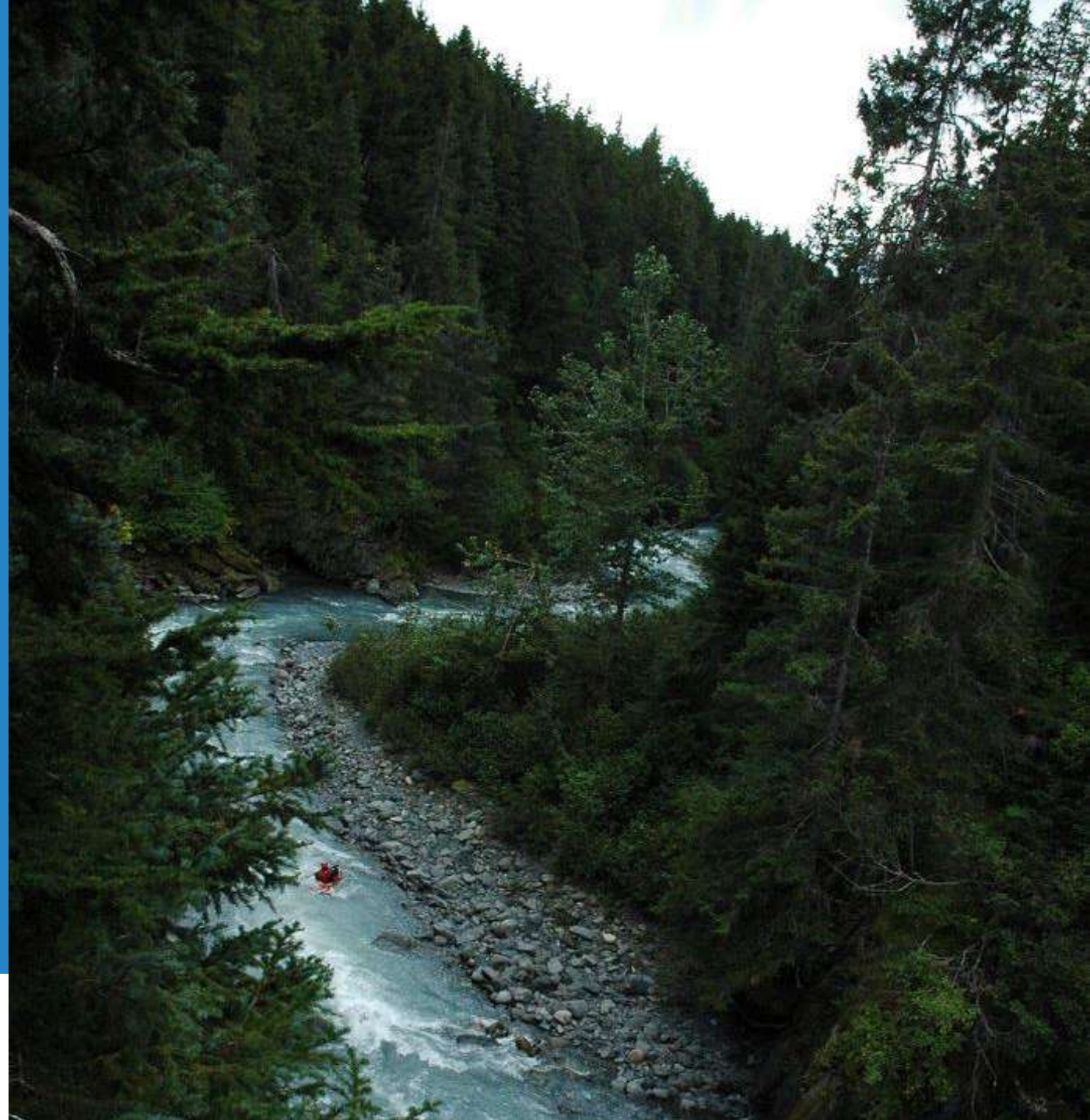
Why include estriol?

Estriol is a weaker estrogen than estradiol that has particular benefits for vaginal health, anti-inflammatory properties, and can also address vasomotor symptoms to some extent. It is not known to be harmful to the breast or endometrium and it cannot convert into harmful metabolites like other estrogens.

Androgens

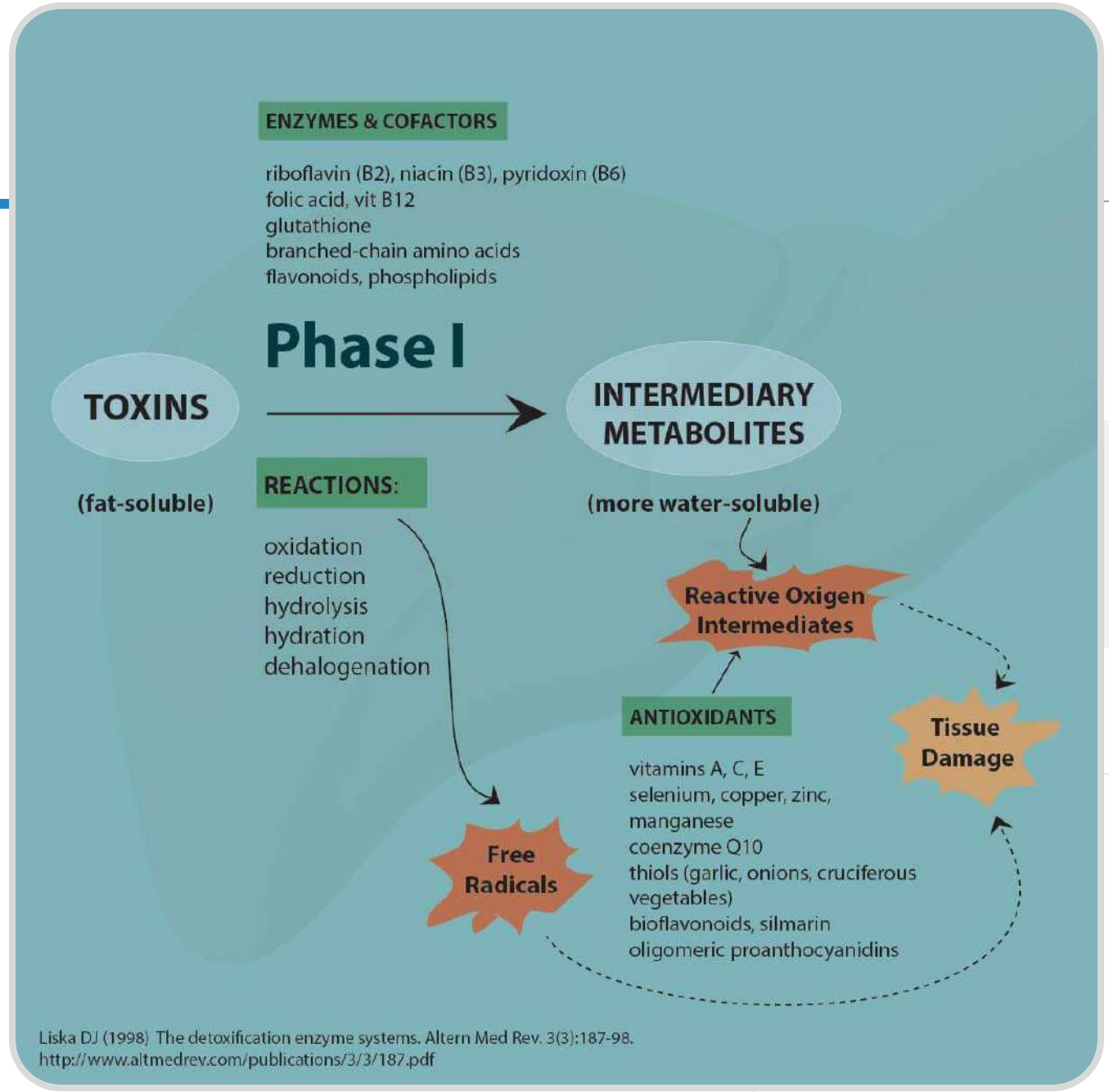
- Testosterone
  - Transdermal preferred because oral is liver toxic
  - Benefits include sexual function, bone health, mood, muscle strength
  - 0.25 to 1.5 mg per day, rotate sites
  - Can compound with other hormones in a cream
  - Avoid in premenopausal females interested in conception.
- DHEA
  - Benefits include better energy, cognitive function, bone and skin health
  - Oral preferred because topical may interact with other hormones in combination creams
  - 2 to 10mg to start for females with low levels

HOW CAN WE SUPPORT HORMONE METABOLISM TO REDUCE RISK AND IMPROVE HORMONE TOLERABILITY?



Assessing Estrogen Metabolism with Urine Testing

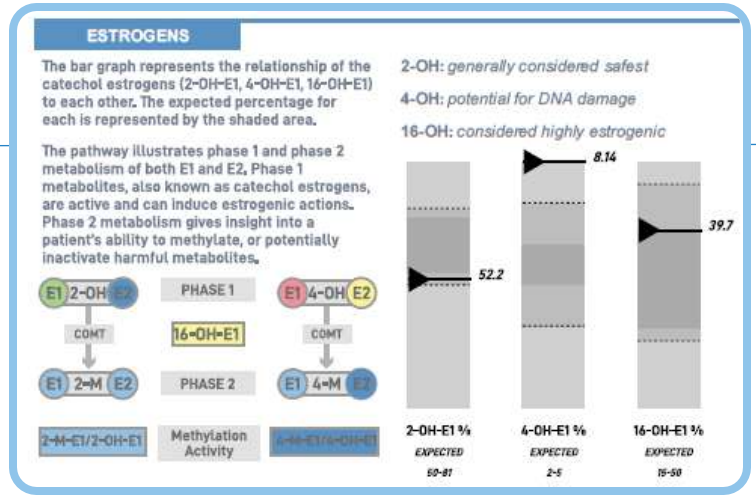
- **E1, E2, E3** – abundance of unconjugated hormones being cleared (both endogenous and supplemented)
- **Phase 1**: Tendency towards safe or risky pathways?
    - 2-OH vs 4-OH or 16-OH estrogens
- **Phase 2**: Are –OH metabolites being rendered inactive?
    - Methylation Activity (COMT)
- **Phase 3**: Hormone elimination via stool or urine...or deconjugation via beta glucuronidase and reabsorption?
    - Look for elevated methylation ratios and possibly estrogens
    - Evaluate diet, hydration, digestive health/bowel regularity
    - Consider beta glucuronidase testing in stool

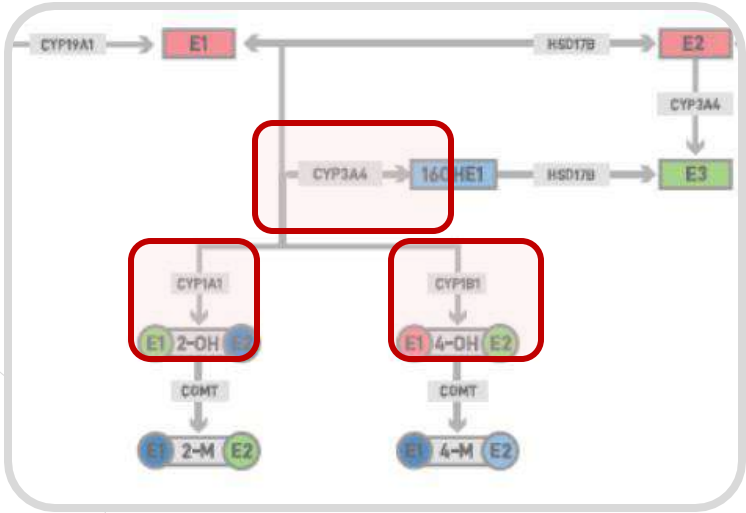


Phase 1 Detox

Phase 1 Detox- Estrogen Metabolism

- **“Catechol Estrogens”**
  - 2-OH E1,E2- “safe” estrogen (CYP1A1)
  - 4-OH E1,E2- DNA damage potential (CYP1B1)
  - 16-OH E1-highly estrogenic (CYP3A4)
- Ratios
  - 4-OH-E1: 2-OH-E1 – lower is better
  - 2-OH-E1: 16-OH-E1 – higher is better

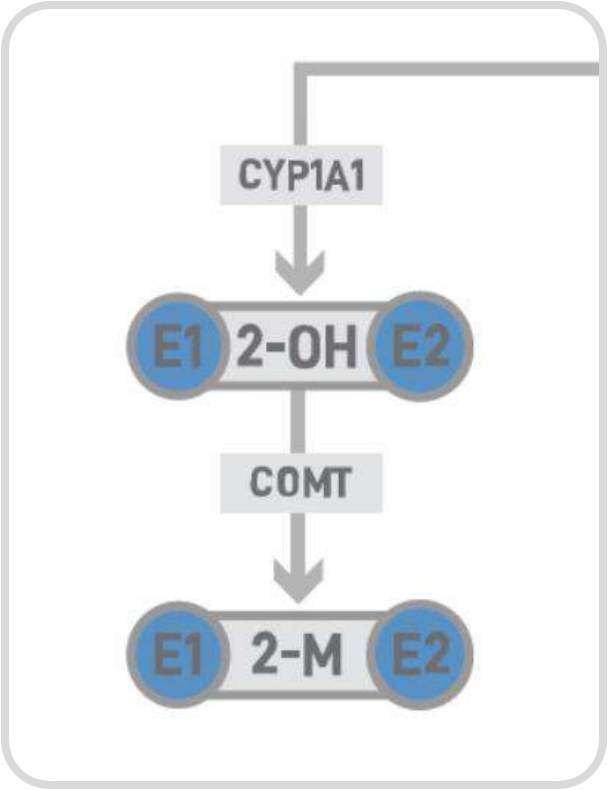




Fuhrman BJ, Schairer C, Gail M, et al., Estrogen Metabolism and Risk of Breast Cancer in Postmenopausal Women, *JNCI: Journal of the National Cancer Institute*, Volume 104, Issue 4, 22 February 2012, Pages 326–339, https://doi.org/10.1093/jnci/djr531

CYP1A1

- Healthy pathway of phase 1
  - Hydroxylates E1 to 2-OH E1
- Mainly involved in detoxification PMID: 19531241
- Can also activate carcinogens (polycyclic aromatic hydrocarbons, aflatoxin B1, and tobacco) PMID: 19531241 PMID: 28074113



CYP1A1 *"A = Awesome!"*

And charred meat, smoking, BPA, phthalates, xenoestrogens, PAH, PCBs, Xyflamend

CYP1A1

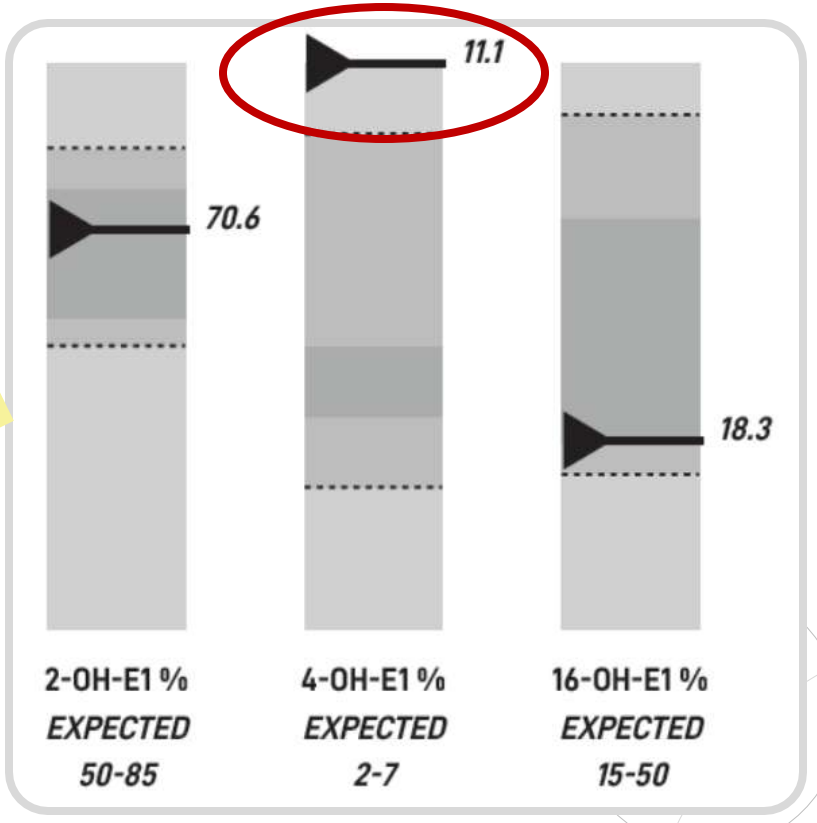
(-) Resveratrol, EGCG, berries, St. John's wort, lycopene, propolis, grapefruit

(+) DIM, rosemary, fish oil, tea, coffee, hops

and cruciferous vegetables, andrographis, shrimp, and garlic oil

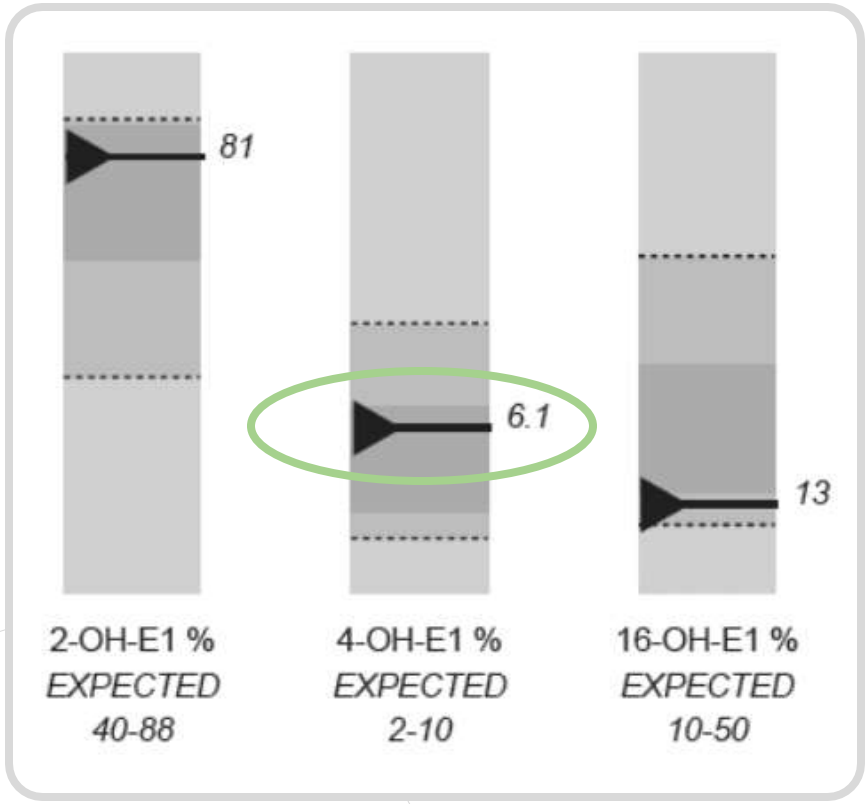
Is the DIM working?

BEFORE



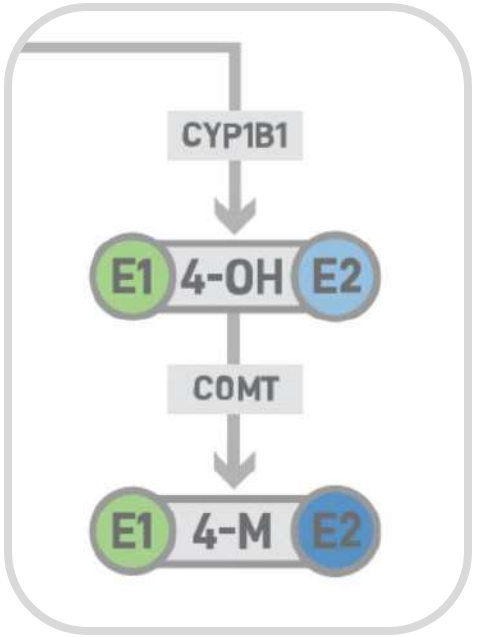
E 4-OH-E1:2-OH-E1

AFTER 6 months on DIM



E 4-OH-E1:2-OH-E1

CYP1B1 *"B = Bad"*



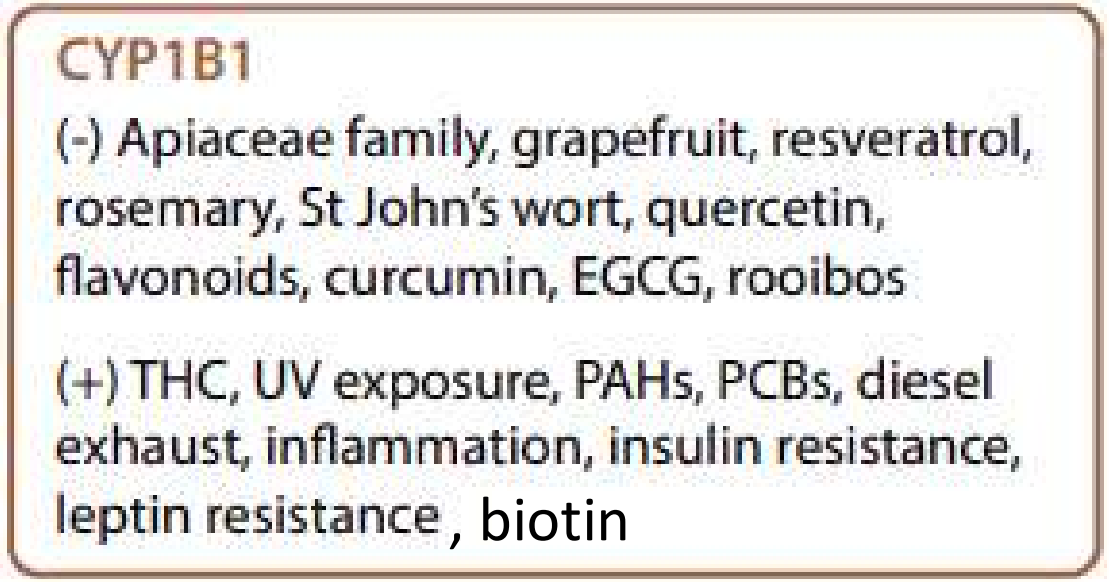
- Hydroxylates E1 to 4-OH E1 (and E2 to 4-OH E2).
- **High CYP1B1 expression in breast cancer and prostate cancer** tissues - positively correlated with Gleason score and associated with lower survival rates
- Also metabolizes: cortisol, aldosterone, FAs, fat-soluble vitamins, melatonin, retinol, plant flavonoids, many environmental toxins.
- Can activate cancer promoting compounds
- **Increases fat** uptake and can lead to factors of metabolic syndrome
- Modulation of CYP1B1 can decrease adipogenesis and tumorigenesis, and prevent obesity, hypertension, atherosclerosis, and cancer. PMID: 28322972

Lin, Q., Cao, J., Du, X. *et al.* CYP1B1-catalyzed 4-OHE2 promotes the castration resistance of prostate cancer stem cells by estrogen receptor α-mediated IL6 activation. *Cell Commun Signal* **20**, 31 (2022). https://doi.org/10.1186/s12964-021-00807-x

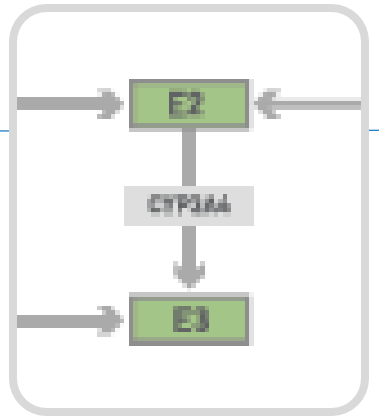
CYP1B1

Downregulate ☺

- Apiacea family: carrots, cumin, anise, celery, caraway PMID: 26381237
- Ginseng PMID: 11901090
- Lycopene (tomatoes, carrots, and watermelon) PMID: 20400267
- A polyherbal formulation (rosemary, turmeric, ginger, holy basil, green tea, hu zhang, Chinese goldthread, barberry, oregano, and Baikal skullcap) PMID: 22374940

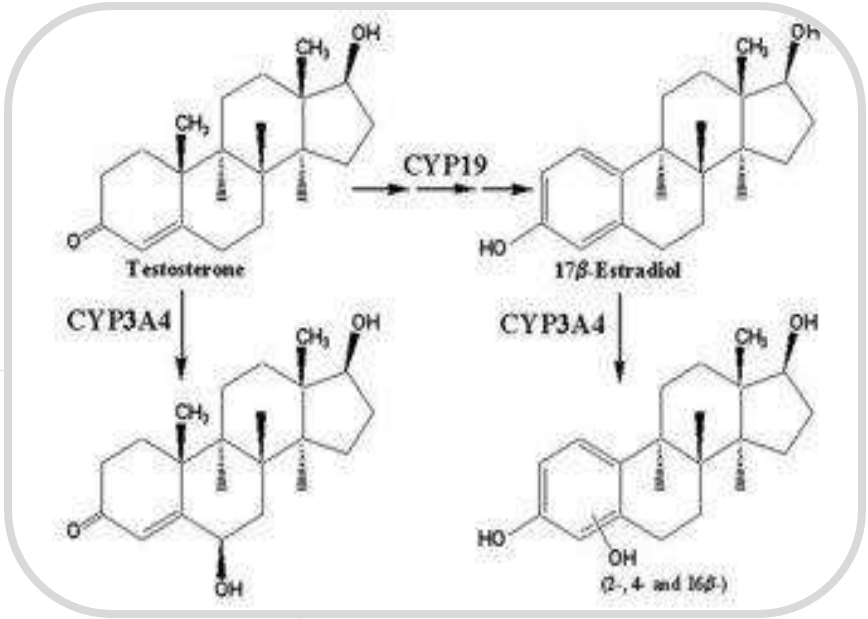


CYP3A4



Converts E2 to E3 and E1 to 16OHE1
(and metabolizes testosterone)

- Metabolizes about half of all drugs on the market
- Mostly found in the liver, but most active in the gut
- Metabolizes cholesterol, fatty acids, prostaglandins, leukotrienes, retinoids and biogenic amines PMID: 25332983.
- Detoxifies bile acids PMID: 25332983
- Partially degrades vitamin D PMID: 22985909



CYP3A4

Increased activity associated w/:

- UV exposure PMID: 22985909
- Being female PMID: 23333322
- Diabetes PMID: 24739263
- Polycyclic aromatic hydrocarbons (PAH) found in cigarettes PMID: 23845848
- Aflatoxin B1 PMID: 21641981
- Medications: carbamazepine, phenytoin, modafanil, dexamethasone, phenobarbitol

Decreased activity associated w:

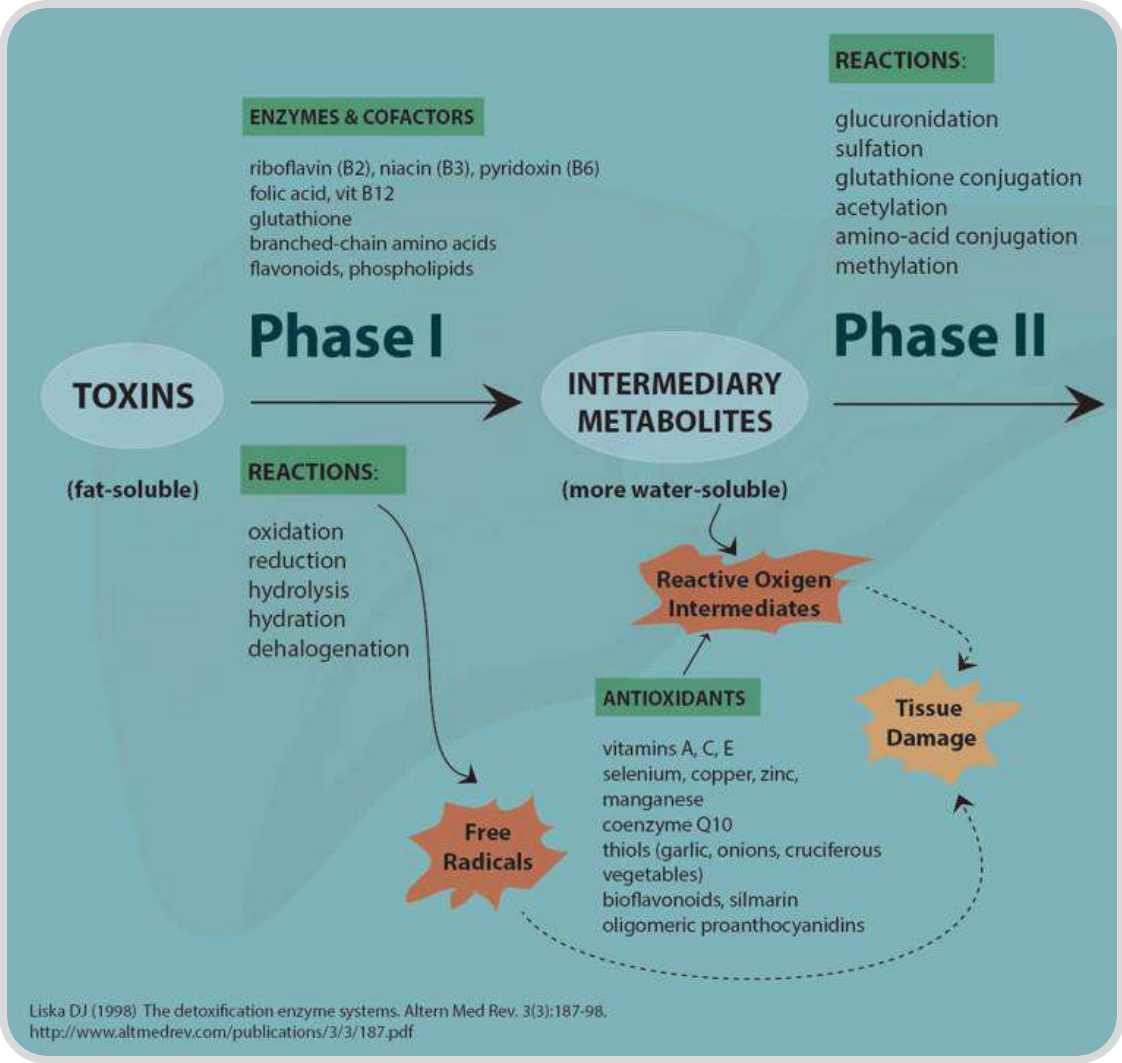
- Iron Deficiency
- Vitamin D deficiency

Therapeutics

CYP3A4

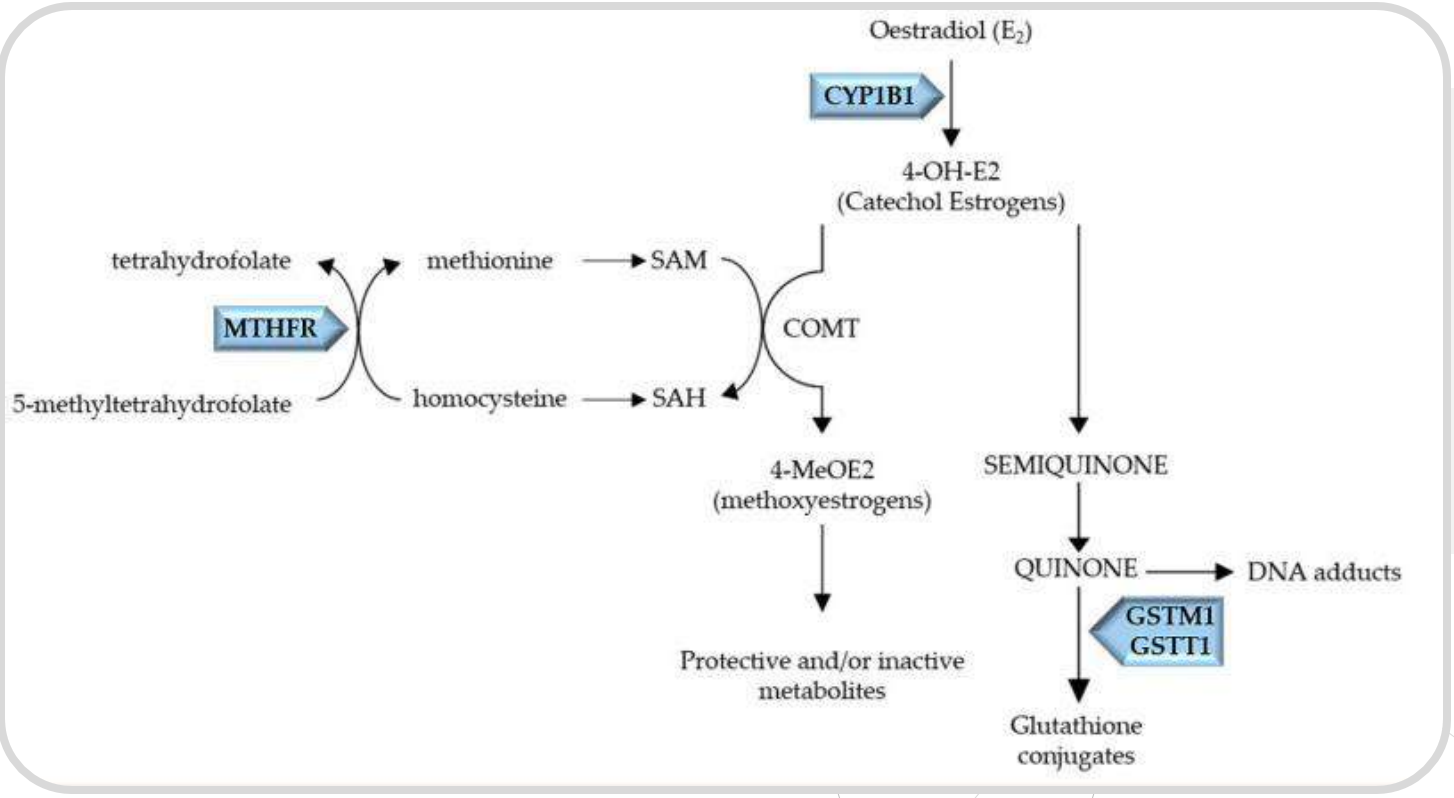
(-) Grapefruit, aloe, polyphenols (i.e. resveratrol), flavonoids, ECGC, coffee, fennel, black pepper, licorice, chrysin, quercetin

(+) St. John's wort, capsaicin, valerian, gingko biloba, fatty acids, Vit D



Phase 2 Detoxification

Phase II - Inactivation of catechol estrogens



Methylation by COMT or glutathione conjugation inactivate the catechol estrogens and mark them for elimination

CYP1B1, a Phase I enzyme, leads to 4-OH-E2 production. The Phase II enzymes, COMT and GSTM1/GSTT1 inactivate the estrogen catechol, semiquinone and quinone, diminishing DNA adducts formation. MTHFR, an enzyme of the folate metabolism, catalyzes 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which allows the remethylation of homocysteine to methionine, a precursor of S-adenosylmethionine (SAM). SAM is the methyl donor for COMT catalyzed reactions, allowing the inactivation of catechol estrogens.

Brooks J, et al. “Promotor methylation and the detection of breast cancer.” Cancer Causes Control. 2009;20(9):1539-50.

Evaluation of methylation potential

- Look at ratios of methylated estrogens to hydroxylated estrogens

2-M-E1:2-OH-E1‡	(COMT/Methylation activity)	0.29	0.08 – 0.50
2-M-E2:2-OH-E2‡	(COMT/Methylation activity)	0.14	0.07 – 0.86
4-M-E1:4-OH-E1‡	(COMT/Methylation activity)	0.34	0.09 – 1.0
4-M-E2:4-OH-E2‡	(COMT/Methylation activity)	0.03	0.02 – 0.50

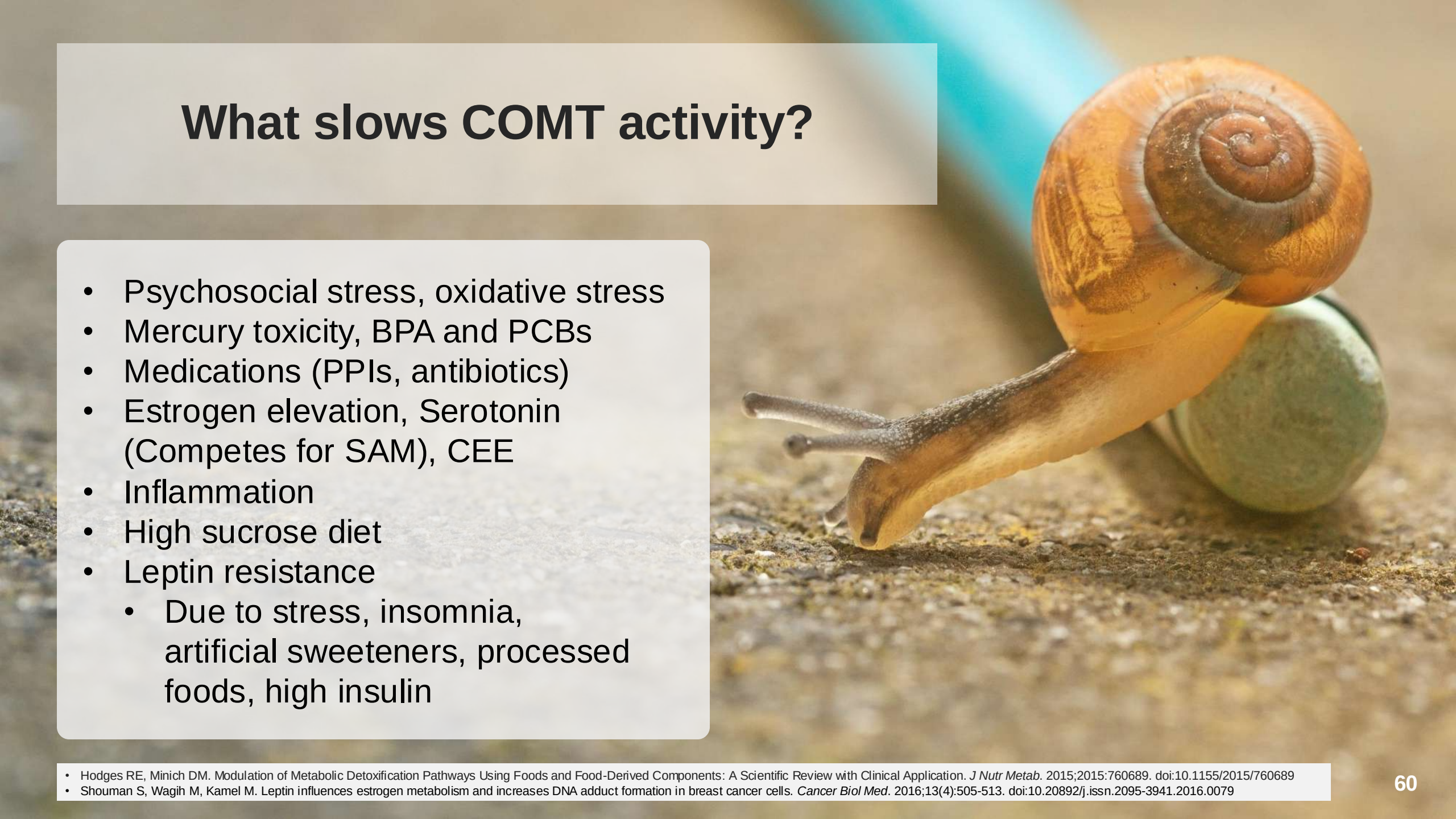
Phase II Support (COMT, MTHFR, GSTM/GSTT)

- Methyl- / hydroxy-/ adenosyl- cobalamin 50mcg - 1500mcg
- MTHF (folate) - 400 – 5000mcg or folinic acid 800mcg
- P5P: 20 – 50 mg
- SAMe: 100 – 500mg (endogenous levels can be supported with MTHF, Mag, Methyl-B12)
- Magnesium: 150 - 500mg
- DIM: 100 to 300mg per day
- Betaine (aka trimethylglycine) - from beets, can decrease homocysteine levels
- To support glutathione-s-transferases (GSTM and GSTT): Cruciferous vegetables, Citrus, Soy, Curcumin, Resveratrol, Rooibos, Rosemary, Dandelion, Garlic

- Hodges RE, Minich DM. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. J Nutr Metab. 2015;2015:760689. doi:10.1155/2015/760689
- Reding, K. W., Weiss, N. S., Chen, C.,et al. (2009). Genetic polymorphisms in the catechol estrogen metabolism pathway and breast cancer risk. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 18(5), 1461–1467. https://doi.org/10.1158/1055-9965.EPI-08-0917

What slows COMT activity?

- Psychosocial stress, oxidative stress
- Mercury toxicity, BPA and PCBs
- Medications (PPIs, antibiotics)
- Estrogen elevation, Serotonin (Competes for SAM), CEE
- Inflammation
- High sucrose diet
- Leptin resistance
  - Due to stress, insomnia, artificial sweeteners, processed foods, high insulin



- Hodges RE, Minich DM. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. *J Nutr Metab*. 2015;2015:760689. doi:10.1155/2015/760689
- Shouman S, Wagih M, Kamel M. Leptin influences estrogen metabolism and increases DNA adduct formation in breast cancer cells. *Cancer Biol Med*. 2016;13(4):505-513. doi:10.20892/j.issn.2095-3941.2016.0079

Estrogen Quinones and Breast Cancer

- Unmethylated 2-OH and 4-OH metabolites can oxidize into quinones / semi-quinones, which can bond to DNA forming DNA-adducts
- This can lead to DNA damage and mutations (depurinated DNA)
- DNA adducts can disrupt the functioning of genes involved in cell growth regulation, leading to uncontrolled cell proliferation and tumor formation
- “Increased amounts of estrogen-DNA adducts are found not only in people with several different types of cancer but also in women at high risk for breast cancer, indicating that the formation of adducts is on the pathway to cancer initiation. ”

- Yager JD. Mechanisms of estrogen carcinogenesis: The role of E2/E1–quinone metabolites suggests new approaches to preventive intervention – A Review. *Steroids*. 2015;99:56-60. doi:10.1016/j.steroids.2014.08.006
- Cavalieri E, Rogan E. The 3,4-quinones of estrone and estradiol are the initiators of cancer whereas resveratrol and N-acetylcysteine are the preventers. *International Journal of Molecular Sciences*. 2021;22(15):8238. doi:10.3390/ijms22158238

QUINONE REDUCTION

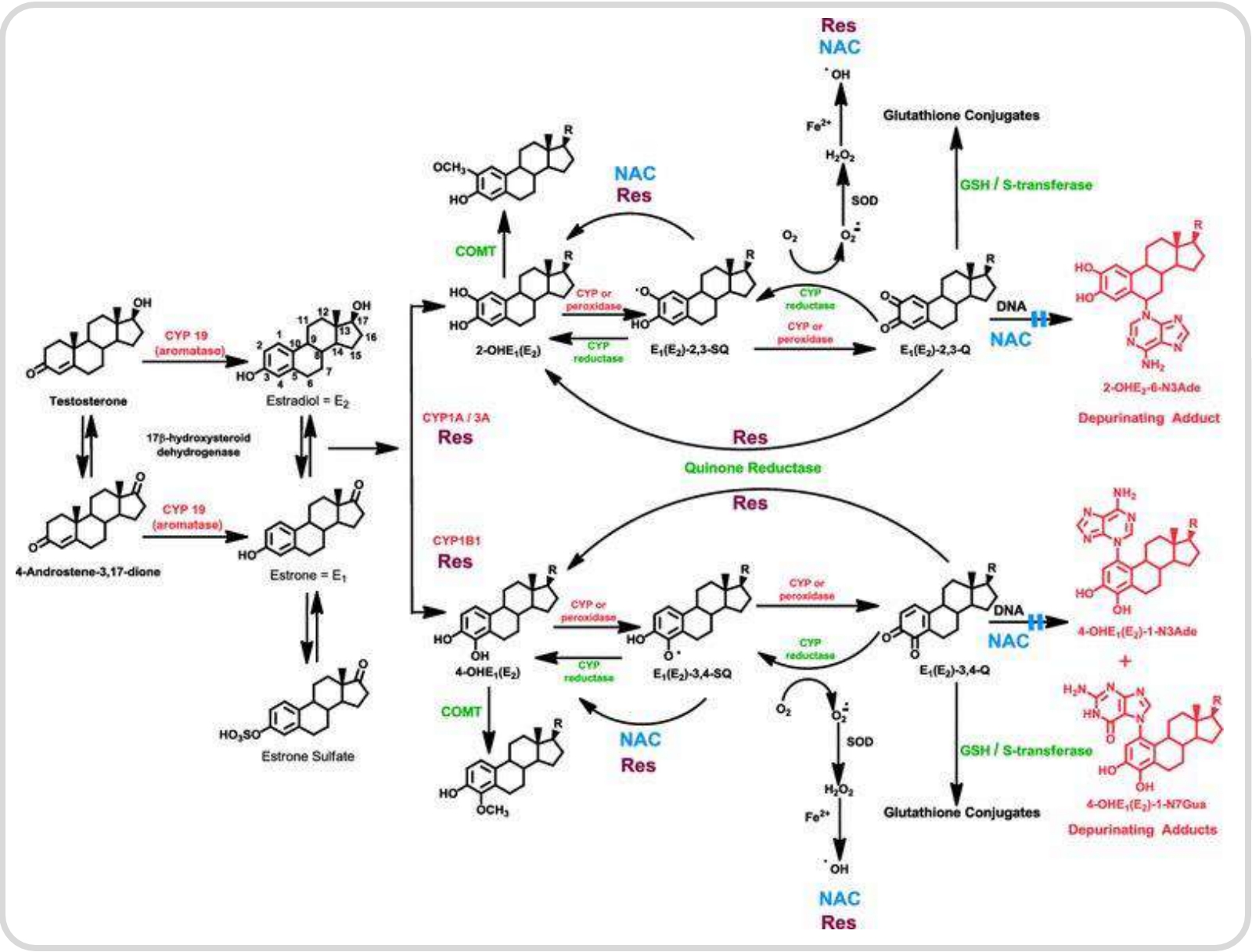
NAC

- Reduce estrogen semiquinones back to catechol estrogens
- Reacts with quinones to form conjugates preventing the formation of estrogen-DNA adducts.

Resveratrol

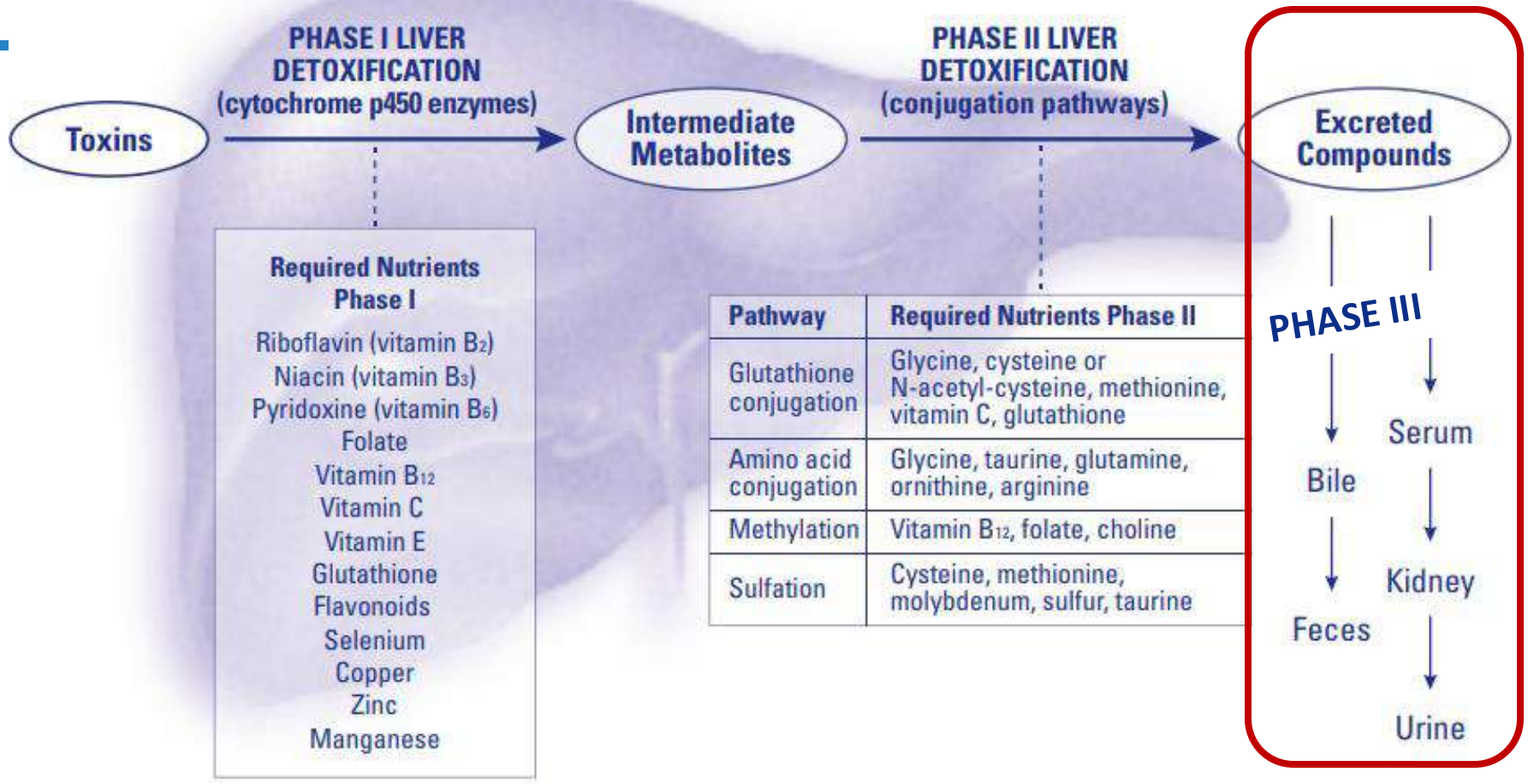
- Reduce estrogen semiquinones back to catechol estrogens
- Induce the protective enzyme quinone reductase
- Reduced CYP1B1 activity

- Shrivastava N, Parikh A, Dewangan RP, et al. Solid Self-Nano Emulsifying Nanoplatform Loaded with Tamoxifen and Resveratrol for Treatment of Breast Cancer. Pharmaceutics. 2022;14(7):1486. Published 2022 Jul 18. doi:10.3390/pharmaceutics14071486
- Cavalieri E, Rogan E. The 3,4-quinones of estrone and estradiol are the initiators of cancer whereas resveratrol and N-acetylcysteine are the preventers. *International Journal of Molecular Sciences*. 2021;22(15):8238. doi:10.3390/ijms22158238

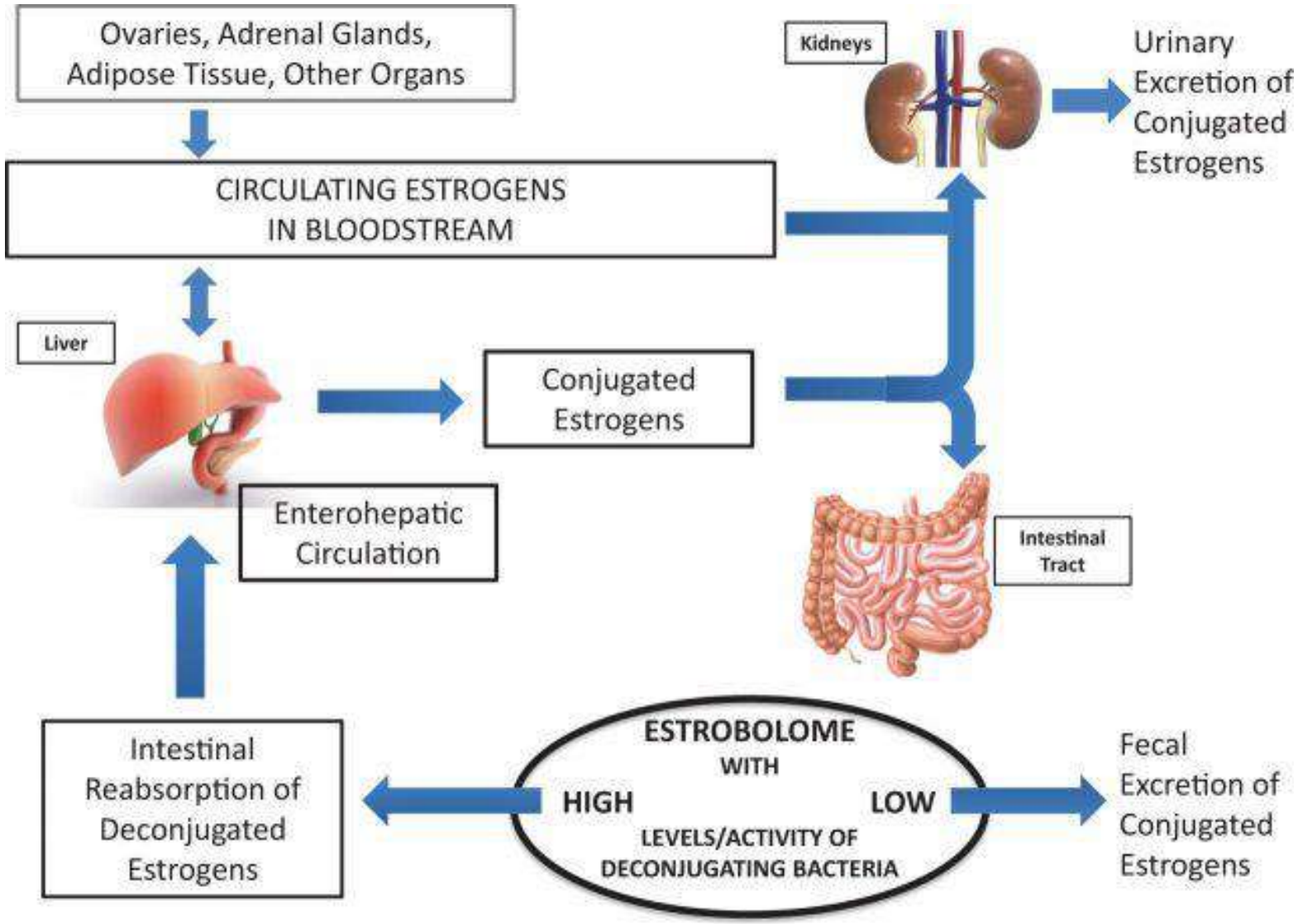


Resveratrol and NAC preventing estrogen-DNA adduct formation

Cavalieri EL, Rogan EG. Depurinating estrogen-DNA adducts, generators of cancer initiation: their minimization leads to cancer prevention. *Clin Transl Med*. 2016;5(1):12. doi:10.1186/s40169-016-0088-3



https://www.pureencapsulationspro.com/media/brch_Detox.pdf



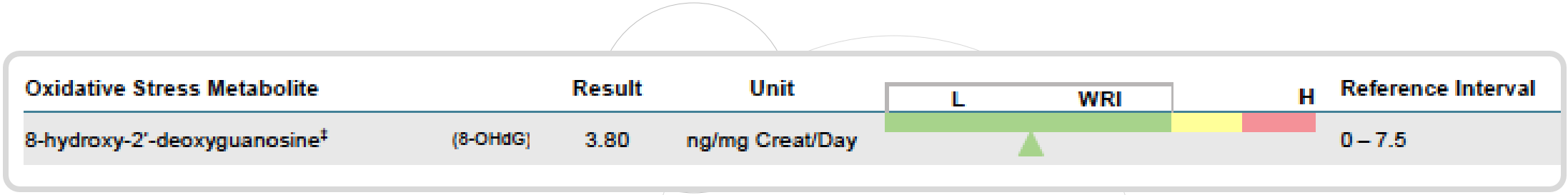
Kwa M, Plottel CS, Blaser MJ, Adams S. The Intestinal Microbiome and Estrogen Receptor-Positive Female Breast Cancer. *J Natl Cancer Inst*. 2016;108(8):djw029. Published 2016 Apr 22. doi:10.1093/jnci/djw029

Phase 3/Estrobolome Support Considerations

- Address dysbiosis and constipation, if applicable
- 8 to 12 grams soluble fiber per day (oats, peas, beans, lentils, apples, bananas, citrus fruits, carrots, Jerusalem artichokes, onions, garlic, leeks, barley and psyllium)
- 30 different plant foods per week improves microbiome diversity
- Reduce/avoid charred meat and carcinogens which increase B-glucuronidase activity
- In cases of high b-glucuronidase activity, reduce meat and fat in diet and increase plants and fiber
- Inulin (leeks, asparagus, onions, wheat, garlic, chicory, oats, soybeans, and Jerusalem artichokes)
- Lactobacillus rhamnosus GG lowers B-glucuronidase activity
- Calcium d glucarate 500mg TID with food to inhibit beta glucuronidase and increase excretion of xenobiotics and deconjugated estrogens PMID 2346674
- Address underlying causes - blood sugar, alcohol, oral health, stress, medications (especially antibiotics, OCPs) and environmental exposures

Assessing oxidative damage: 8-hydroxy-2-deoxyguanosine(8-OHdG)

- Lipids of cellular membranes, proteins, and DNA can incur permanent oxidative damage.
- In nuclear and mitochondrial DNA, 8-OHdG is one of the predominant forms of free radical-induced oxidative lesions and widely used as a biomarker for oxidative stress and carcinogenesis.
- 8-OHdG may indicate DNA damage from harmful metabolites (quinones and DNA adducts)



Oxidative Stress Metabolite		Result	Unit	L WRI H	Reference Interval
8-hydroxy-2'-deoxyguanosine‡	(8-OHdG)	3.80	ng/mg Creat/Day		0 – 7.5

VALAVANIDIS ATHANASIOS, VLACHOGIANNI THOMAIS, FIOTAKIS CONSTANTINOS. 8-hydroxy-2′ -deoxyguanosine (8-ohdg): A critical biomarker of oxidative stress and carcinogenesis. *Journal of Environmental Science and Health, Part C*. 2009;27(2):120-139. doi:10.1080/10590500902885684

OXIDATIVE STRESS AND DISEASE STATES

- Chronic stress, Cortisol elevation
- Inflammation
- Insomnia in postmenopausal women
- Degenerative diseases (rheumatoid arthritis, parkinson's disease, huntington's disease, alzheimer's disease)
- Chronic fatigue syndrome
- Major depression
- Hypertension, Cardiovascular disease
- Diabetes type II
- Cystic fibrosis
- Psoriasis
- Chronic hepatitis
- Gastritis
- Irritable bowel disease
- Pancreatitis
- Cancer
- Acute viral infection
- Copper implants
- Toxic exposures (tobacco smoke, methamphetamines, asbestos, heavy metals, polycyclic hydrocarbons).

TREATMENT FOR ELEVATED 8-OHDG

Address the cause of oxidative stress ☺

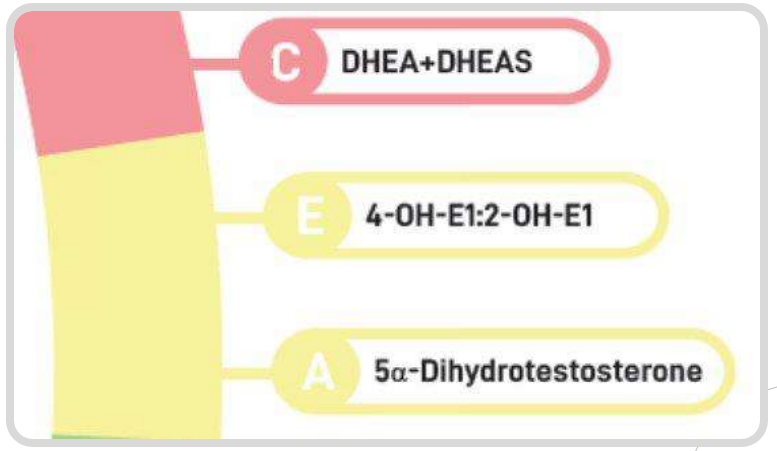
- Glutathione
- NAC
- Green tea
- CoQ10
- Onion
- Garlic
- Alpha lipoic acid
- Vitamins C and E
- Melatonin
- Folate
- Berberine
- EPA/DHA
- Fermented papaya powder
- Increase fruit and veggies
- Yoga

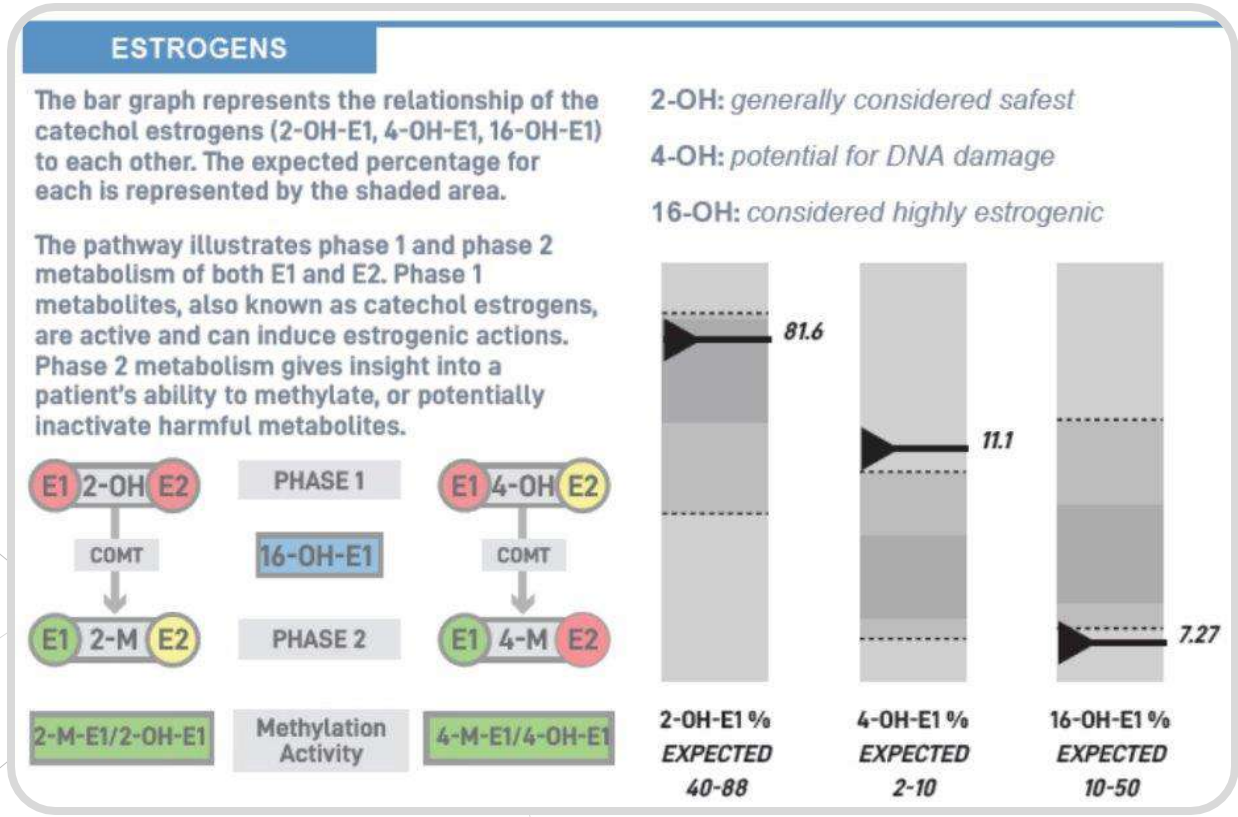

CASE STUDIES

Case #1: Hormone metabolite testing to help a postmenopausal patient on hormones

- 50yo F on E2 patch (0.05mg/day) once per week and 60 mg oral P4 each day
- Hot flashes, night sweats, and mood are under control
- Still experiencing unwanted facial hair and weight gain in the waist

50yo postmenopausal F on estradiol and progesterone with unwanted hair and central adiposity





WRI = Within Reference Interval RI = Reference Interval

Below RI | WRI Low | WRI Optimal | WRI High | Above RI

Therapeutic Options to Improve Phase 1 Estrogen Detox and Lower DHEA and DHT

- Treat the cause: stress, blood sugar dysregulation, inflammation
- **EGCG** 250 to 500mg per day to downregulate 4-hydroxylation and 5 alpha reductase
- **Curcumin** decreases 4-hydroxylation, is anti-inflammatory, and can decrease the conversion of pregnenolone to DHEA
- Stress Management
- Stabilize blood sugar
  - High fiber diet with adequate protein and healthy fat
  - Regular resistance training
  - Optimizing sleep

Case # 2: 42yo F

- Hysterectomy for endometriosis 2 yrs ago
- Insomnia caused by terrible night sweats
- Irritable mood
- Low libido
- Decreased muscle strength and motivation
- Sensation of racing heart rate
- On 2mg oral estradiol. Started at 1mg and increased dose.
  - Her doctor tried Gabapentin for the night sweats – couldn't sleep and felt confused
  - Did not like estrogen patch in the past because was uncomfortable with swimsuits

Saliva labs showed very high E2, low Pg, low DHEA

Analyte	Result	Unit	L	WRI	H	Reference Interval	Supplementation Range**
Estradiol (E2)	71	pg/mL			↑	0.5 – 3.2	1.0 – 6.0
Progesterone (Pg)	18	pg/mL		◆		18 – 130	400 – 4000
Pg/E2 Ratio†	0.3						≥ 200
Testosterone	12	pg/mL		◆		6 – 49	25 – 60
DHEA*	72	pg/mL	↓			106 – 300	

Cortisol AM30	15	nmol/L		◆		14.0 – 25.0	7.0 – 30.0
Cortisol Noon	3.1	nmol/L	◆			5.0 – 10.0	2.1 – 14.0
Cortisol Evening	1.5	nmol/L	◆			2.0 – 5.0	1.5 – 8.0
Cortisol Night	0.91	nmol/L	◆			1.0 – 4.0	0.33 – 7.0

42yo F - Initial treatment

- Decrease estradiol to 1.5mg per morning
- 100mg oral micronized progesterone at night
- 5mg oral DHEA each morning
- Adrenal support supplement 3 per day

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1 month follow up:

- DHEA has been helping exercise tolerance, muscle strength
- At first on lower E2 dose (1.5mg) better sleep, less night sweats, waking up maybe once a night sweaty but not soaked, mood more even, not having racing heart
- After ~ 3 weeks all sx returned and tapered dose down to 1mg – same thing, everything got better

Supplement Facts

Serving Size 3 Capsules, 30 Servings per Container

Amount per Serving		% Daily Value
Vitamin C, buffered (as calcium ascorbate)	500 mg	555
Vitamin B6 (as pyridoxal-5-phosphate)	50 mg	2940
Pantothenic acid (Vitamin B5) (as calcium pantothenate)	100 mg	2000
Calcium (as calcium ascorbate)	57 mg	4
Magnesium (as magnesium bisglycinate chelate)	50 mg	12
Zinc (as zinc bisglycinate chelate)	10 mg	61
Rhodiola rosea root extract	200 mg	†
Astragalus *(Astragalus membranaceus)* root	150 mg	†
Maca *(Lepidium meyenii)* root	125 mg	†
Ashwagandha *(Withania somnifera)* root extract	100 mg	†
Holy basil *(Ocimum sanctum)* leaf extract	100 mg	†
American Ginseng *(Panax quinquefolius)* root extract	100 mg	†
Schisandra *(Schisandra chinensis)* berry	75 mg	†
Eleuthero *(Eleutherococcus senticosus)* root extract	50 mg	†

† Daily Value not established

Other ingredients: Vegan capsule (HPMC, water), calcium laurate.

Treatment adjustments and follow up

Treatment changes:

- Added a vitamin/herbal product to support hormone detoxification and receptor sensitivity
- Decrease E2 dose to 0.5mg after 2 weeks on 1mg
- Then retest saliva in 8 weeks

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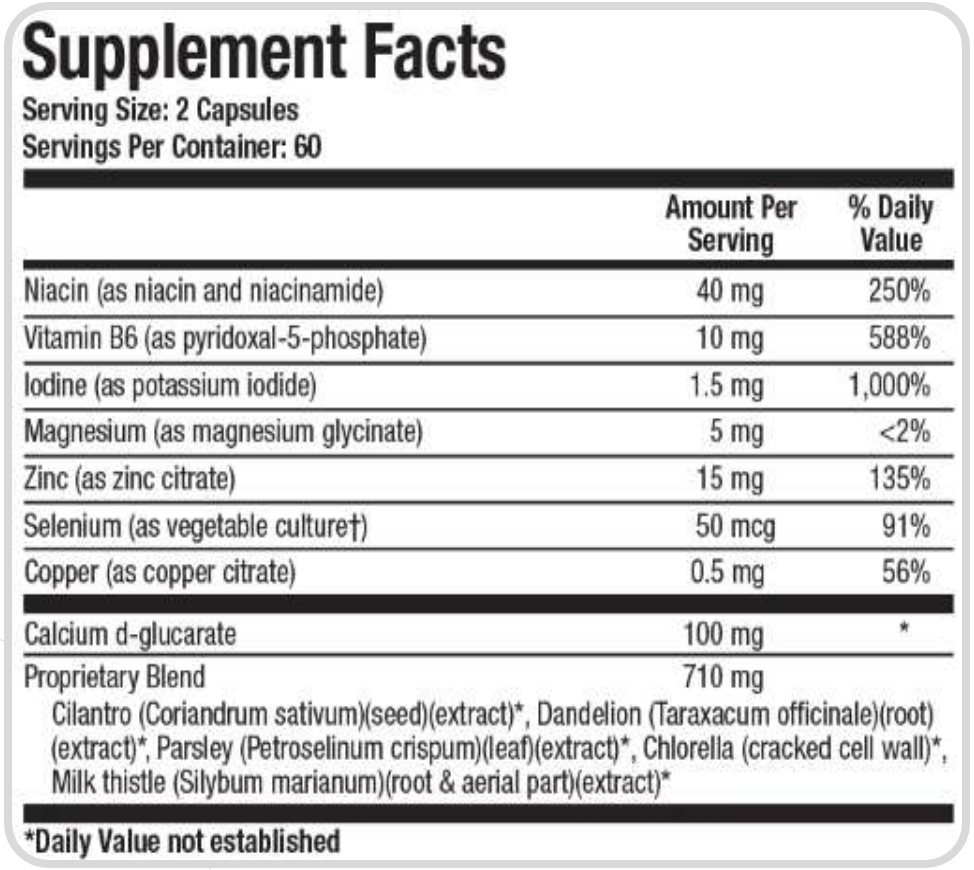
1 month later:

- Headaches from vitamin/herbal detox product – stopped and headaches went away
- E2 at 0.5 - vasomotor sx returned, and hormonal headaches
- She had increased her E2 dose to 1mg, improved the headaches. Still not sleeping well enough
- Felt progesterone is helping mood and somewhat helping sleep



Supplement Facts

Serving Size: 2 Capsules
Servings Per Container: 60

	Amount Per Serving	% Daily Value
Niacin (as niacin and niacinamide)	40 mg	250%
Vitamin B6 (as pyridoxal-5-phosphate)	10 mg	588%
Iodine (as potassium iodide)	1.5 mg	1,000%
Magnesium (as magnesium glycinate)	5 mg	<2%
Zinc (as zinc citrate)	15 mg	135%
Selenium (as vegetable culture†)	50 mcg	91%
Copper (as copper citrate)	0.5 mg	56%
Calcium d-glucarate	100 mg	*
Proprietary Blend	710 mg	
Cilantro (Coriandrum sativum)(seed)(extract)*, Dandelion (Taraxacum officinale)(root)(extract)*, Parsley (Petroselinum crispum)(leaf)(extract)*, Chlorella (cracked cell wall)*, Milk thistle (Silybum marianum)(root & aerial part)(extract)*		

*Daily Value not established

1 month later

Treatment changes:

- Changed to topical biest (E3:E2; 50:50) 3mg/ml 0.25 ml BID,
- Increased progesterone to 200mg qhs
- Added veozah (fezolinetant) 45mg
- Talked about frequently fluctuating estradiol dose possibly triggering sx
- Warned her that switching from oral to topical estrogen may temporarily worsen vasomotor symptoms
- Referred to acupuncture to help with hot flashes

1 month follow up:

- Initially headache x 4 days, hot flashes day and night
- Once on the veozah in the AM, daytime hot flashes stopped, switched to nighttime and virtually no night sweats until 4am

Final treatment plan

- **Veozah (fezolinetant) 45 mg oral tablet**
  - 1 tablet(s) once a day with meals, oral route. take at the same time each day.
  - Liver enzymes at 3, 6, 9 months into treatment and if sx suggest liver injury
- **Bi-Est 50:50 Transdermal Cream (topiclick) 3 mg/mL transdermal cream with applicator**
  - Apply 0.25 ml (1 click) 2 times a day to areas of thin skin, rotating sites
- **progesterone 200 mg oral capsule**
  - 1 cap po qd
- **DHEA 5mg po qd**
- **Adrenal support (vitamins and adaptogens)**


THANK YOU!