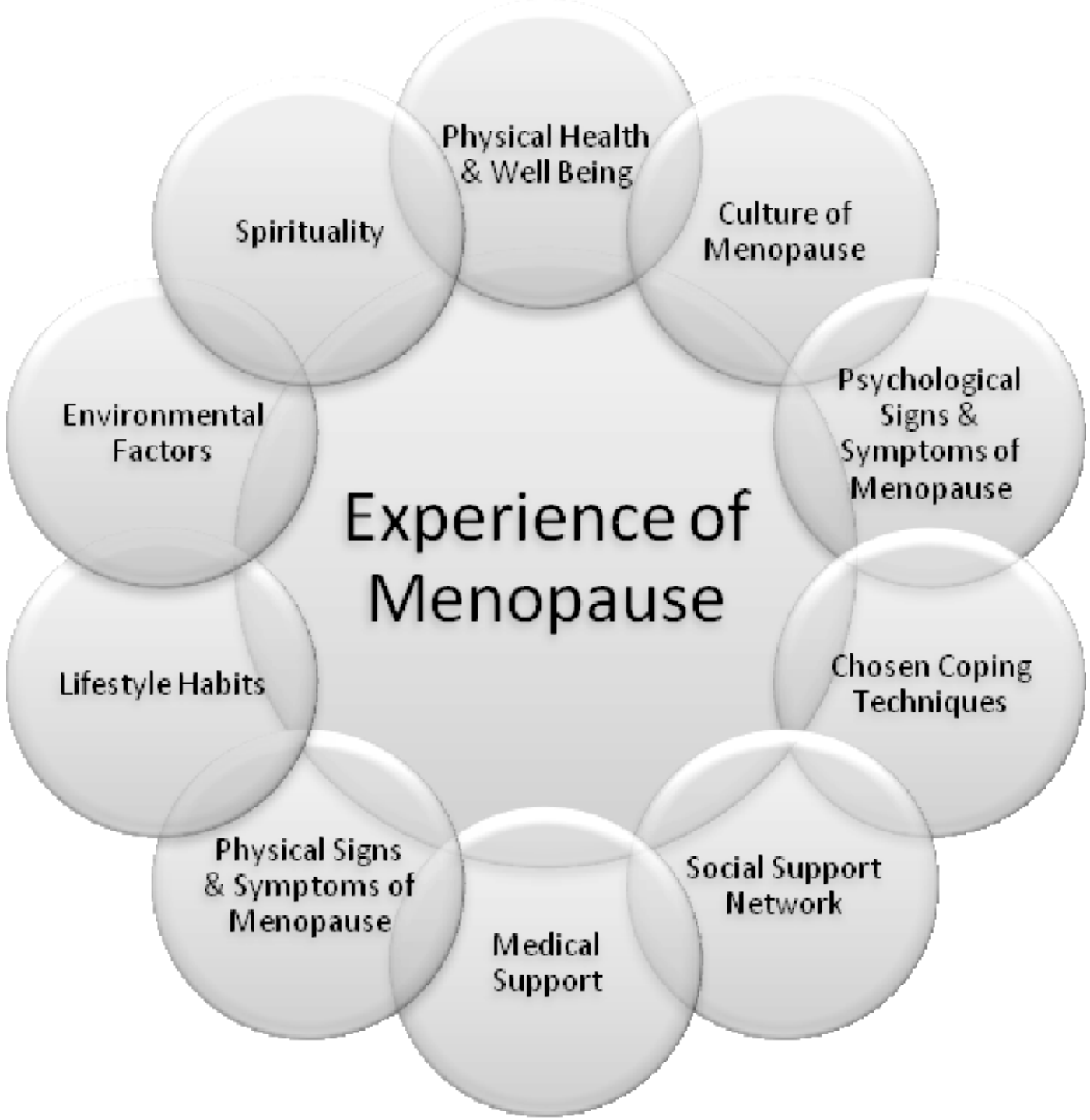
Lifestyle changes, herbal remedies & Non-Hormonal treatments: SSRIs, GABA : alternative care

Axelle Pintiaux, MD, PhD- ULg

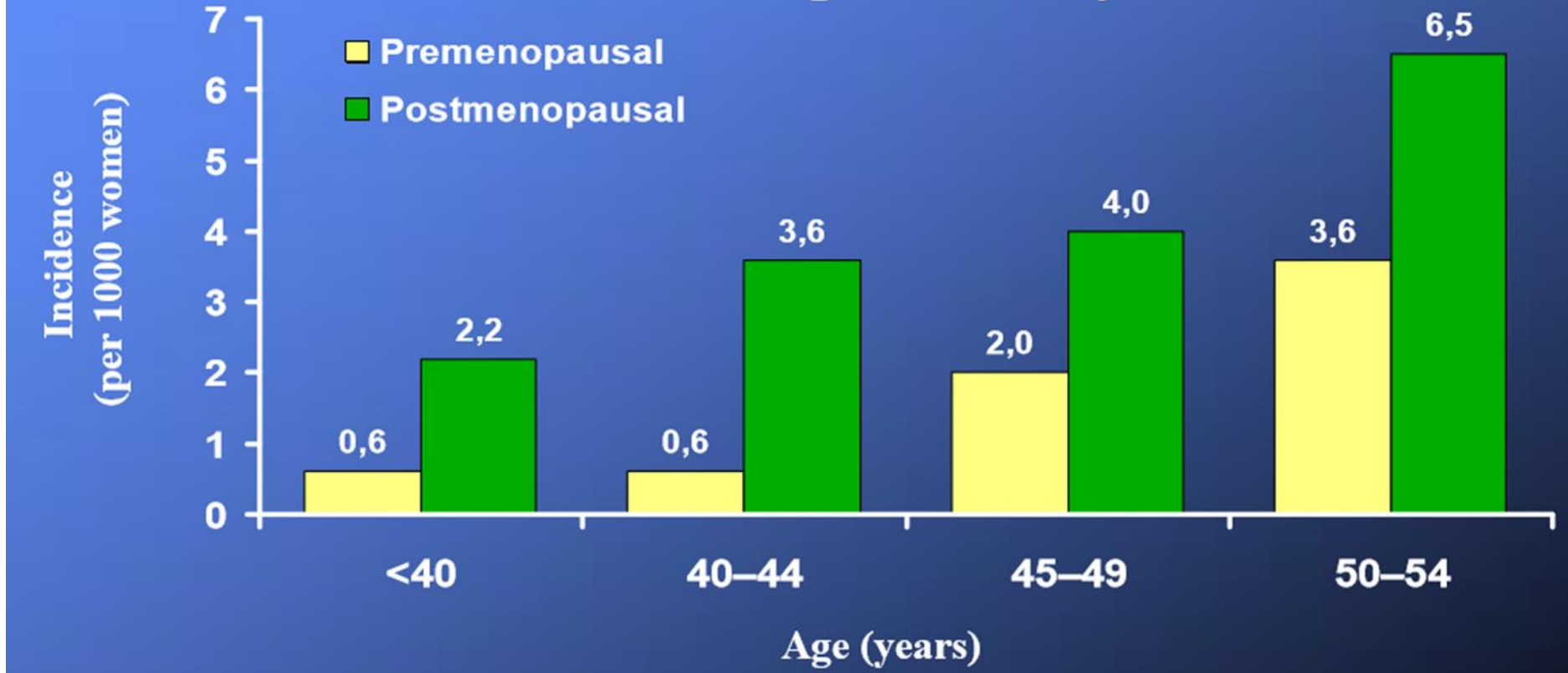
Citadelle
Centre de la ménopause

The Belgian Menopause Society


Experience of Menopause
Physical Health & Well Being
Culture of Menopause
Psychological Signs & Symptoms of Menopause
Chosen Coping Techniques
Social Support Network
Medical Support
Physical Signs & Symptoms of Menopause
Lifestyle Habits
Environmental Factors
Spirituality

Incidence of CVD: Relation to Menopause Status

The Framingham Study



n = 2873.

Kannel WB, et al. *Ann Intern Med.* 1976;85:447-52.

Cardiovascular risks

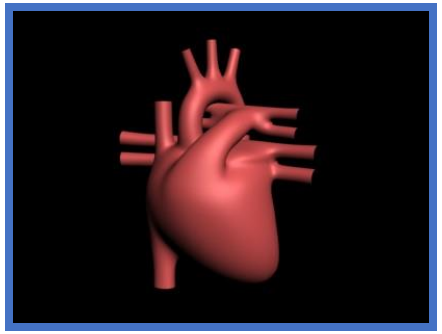
AGE-
MENOPAUSE

DIABETES- IR

NUTRITION

HTA,Hyperthyroidism,

COAGULATION



STRESS

TOBACCO
ALCOHOL

SEDENTARY
Lifestyle

CHOLESTEROL

ANDROID FAT MASS

Bone – osteoporosis risk factors

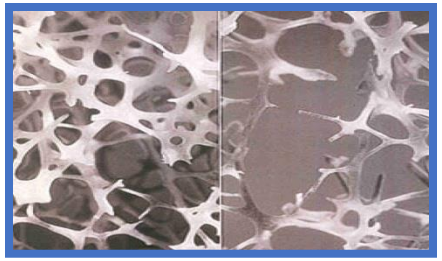
PREVIOUS FRACTURE

NUTRITION

AGE , MENOPAUSE

HYPOGONADISM

GENETIC



Hyperthyroidism

TOBACCO

ALCOHOL

CORTISONE

FALLS

SEDENTARITY

LOW FAT MASS

Breast risk factors

BREAST HIGH DENSITY

NUTRITION

METABOLIC S, IR

GENETIC

AGE

ALCOHOL

REPRODUCTIVE FACTORS

SEDENTARITY

HIGH FAT MASS

Bone Health

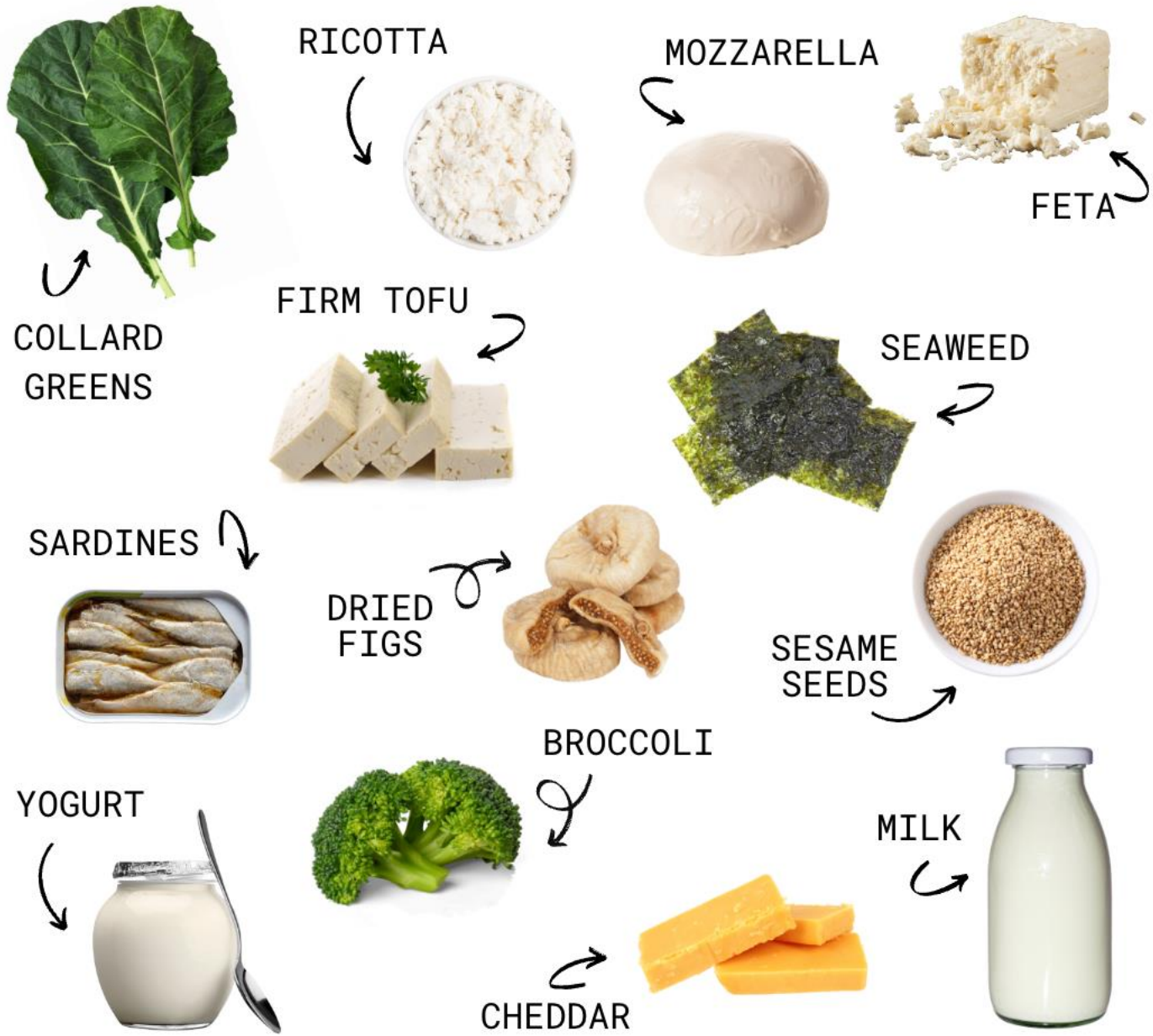
CALCIUM

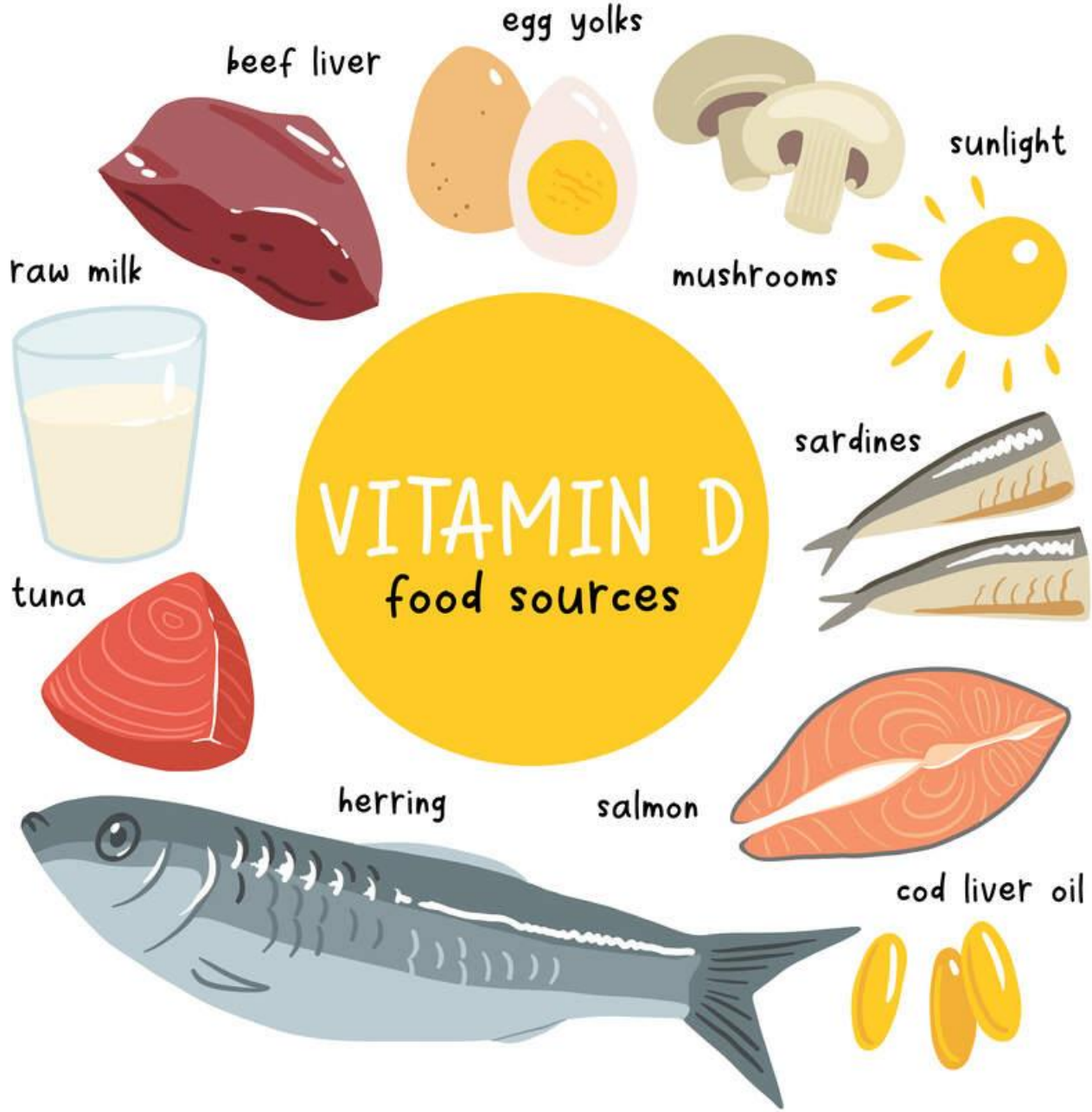
1200 - 1500 mg/D in postmenopausal women outside of meals

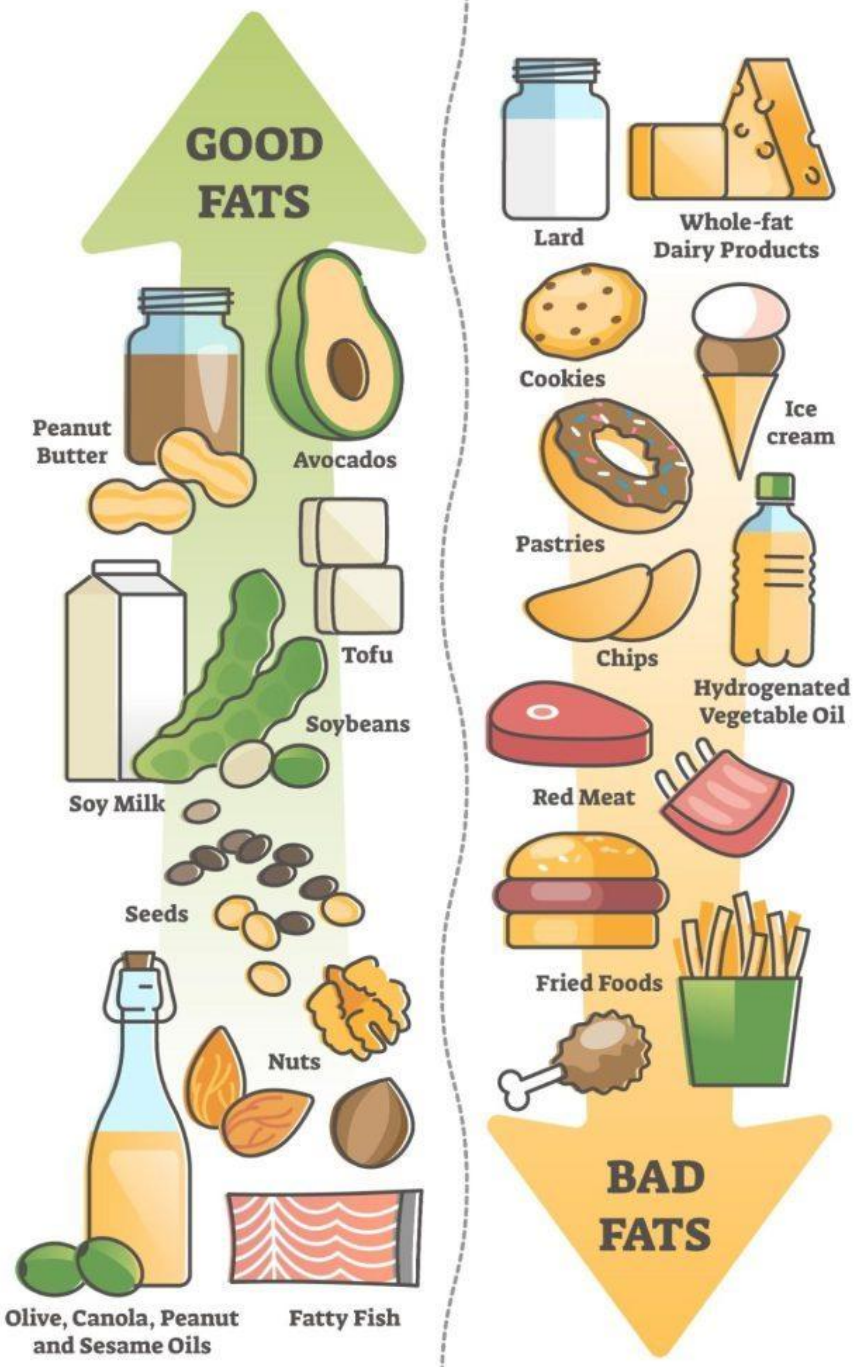
VIT D :

Minimum 800 UI /D- during a meal with lipids

How to know if the intake is sufficient ?


COLLARD GREENS
RICOTTA
MOZZARELLA
FETA
FIRM TOFU
SEAWEED
SARDINES
DRIED FIGS
SESAME SEEDS
BROCCOLI
YOGURT
MILK
CHEDDAR


VITAMIN D
food sources
beef liver
egg yolks
sunlight
raw milk
mushrooms
sardines
tuna
herring
salmon
cod liver oil


GOOD FATS
Peanut Butter
Avocados
Tofu
Soybeans
Soy Milk
Seeds
Nuts
Olive, Canola, Peanut and Sesame Oils
Fatty Fish
Lard
Whole-fat Dairy Products
Cookies
Ice cream
Pastries
Chips
Hydrogenated Vegetable Oil
Red Meat
Fried Foods
BAD FATS

LOW CARB FOODS

Foods to eat

Proteins
- Chicken breast
- Turkey breast
- Lean cuts of beef (e.g., sirloin, tenderloin)
- Pork tenderloin
- Fish (salmon, tuna, mackerel, trout)
- Shellfish (shrimp, crab, lobster)
- Eggs
- Tofu
- Tempeh
- Seitan

Healthy Fats
- Avocado
- Olive oil
- Coconut oil
- Butter (in moderation)
- Nuts (almonds, walnuts, pecans)
- Seeds (chia seeds, flaxseeds, pumpkin seeds)
- Fatty fish (salmon, sardines, mackerel)
- Full-fat cheese (in moderation)
- Greek yogurt (unsweetened)

Non-starchy Vegetables
- Leafy greens (spinach, kale, arugula)
- Cruciferous vegetables (broccoli, cauliflower, Brussels sprouts)
- Bell peppers
- Zucchini
- Cucumbers
- Asparagus
- Green beans
- Mushrooms
- Tomatoes (in moderation)
- Eggplant

Low Sugar Fruits (in moderation)
- Berries (strawberries, blueberries, raspberries)
- Avocado
- Lemons
- Limes
- Watermelon (in small portions)
- Cantaloupe (in small portions)
- Peaches (in moderation)
- Plums (in moderation)
- Kiwi (in moderation)

Nuts And Seeds
- Almonds
- Walnuts
- Pecans
- Macadamia nuts
- Hazelnuts
- Pistachios (in moderation)
- Cashews (in moderation)
- Sunflower seeds
- Pumpkin seeds
- Chia seeds

Herbs And Spices
- Basil
- Oregano
- Thyme
- Rosemary
- Cilantro
- Parsley
- Cumin
- Paprika
- Turmeric
- Ginger

Dairy (in moderation)
- Greek yogurt (unsweetened)
- Cottage cheese (low-fat)
- Cheese (hard cheeses like cheddar, mozzarella, parmesan)
- Heavy cream (in moderation)
- Sour cream (in moderation)
- Unsweetened almond milk
- Unsweetened coconut milk
- Butter (in moderation)
- Cream cheese (in moderation)
- Ricotta cheese (in moderation)

Legumes and Beans (in moderation)
- Lentils
- Chickpeas
- Black beans
- Kidney beans
- Edamame
- Green peas
- Pinto beans
- Black-eyed peas
- Navy beans
- Split peas

Beverages
- Water
- Unsweetened tea (green tea, herbal tea)
- Black coffee
- Sparkling water (plain or flavored, without added sugars)
- Bone broth
- Sugar-free almond milk or coconut milk
- Diet sodas (in moderation)
- Red wine (in moderation)
- White wine (in moderation)
- Spirits (gin, vodka, whiskey) without sugary mixers

Foods to avoid

High-Carb Grains and Grain Products
- Bread (white, whole wheat, multigrain)
- Pasta (spaghetti, fettuccine, penne)
- Rice (white rice, brown rice)
- Breakfast cereals (cornflakes, rice cereal, sugary granola)
- Oats
- Quinoa
- Barley
- Couscous
- Millet
- Crackers and crispbreads

Starchy Vegetables
- Potatoes (white potatoes, sweet potatoes)
- Corn
- Winter squash (butternut squash, acorn squash)
- Parsnips
- Plantains
- Beets
- Yams
- Turnips
- Cassava

Sugary Foods And Sweets
- Candy (chocolates, gummies, jelly beans)
- Cookies
- Pastries (cakes, pies, tarts)
- Ice cream
- Sugary drinks (sodas, fruit juices, energy drinks)
- Desserts (puddings, custards, sweetened yogurt)
- Sweetened sauces and toppings (chocolate sauce, caramel sauce)
- Honey
- Maple syrup
- Agave nectar

High Sugar Fruits
- Bananas
- Grapes
- Mangoes
- Pineapples
- Cherries
- Oranges
- Apples
- Pears
- Figs
- Dates

Processed Foods And Snacks
- Chips (potato chips, corn chips)
- Pretzels
- Crackers
- Packaged snack bars (granola bars, cereal bars)
- Sugary breakfast cereals
- Microwave popcorn
- Flavored rice cakes
- Packaged cookies and cakes
- Sugary yogurt
- Instant noodles and pasta dishes

Sugary Condiments And Sauces
- Ketchup
- BBQ sauce
- Teriyaki sauce
- Sweet chili sauce
- Hoisin sauce
- Honey mustard
- Sweet and sour sauce
- Pancake syrup
- Salad dressings with added sugars
- Fruit preserves and jams

Fried Foods And Fast Food
- French fries
- Onion rings
- Breaded chicken/fish sandwiches
- Fried chicken with breading
- Fast food burgers with buns

Baked Goods And Desserts
- Cakes
- Pies
- Cookies
- Donuts
- Muffins
- Cheesecake
- Rice pudding
- Banana bread
- Cinnamon rolls

High-carb Beverages (in moderation)
- Regular sodas
- Sweetened iced tea
- Fruit juices
- Energy drinks
- Flavored waters with added sugars

Alcoholic Beverages (in moderation)
- Beer
- Sweet wines
- Liqueurs
- Sweet cocktails
- Ciders
- Regular tonic water
- Sugary mixers (soda, juice)
- Dessert wines
- Flavored spirits (unless sugar-free)
- Fortified wines

Disclaimer: This list of low carb foods is for informational purposes only and should not replace medical advice. Individual responses may vary, and it's recommended to consult a healthcare professional before making dietary changes.

Our goal during menopause transition and after

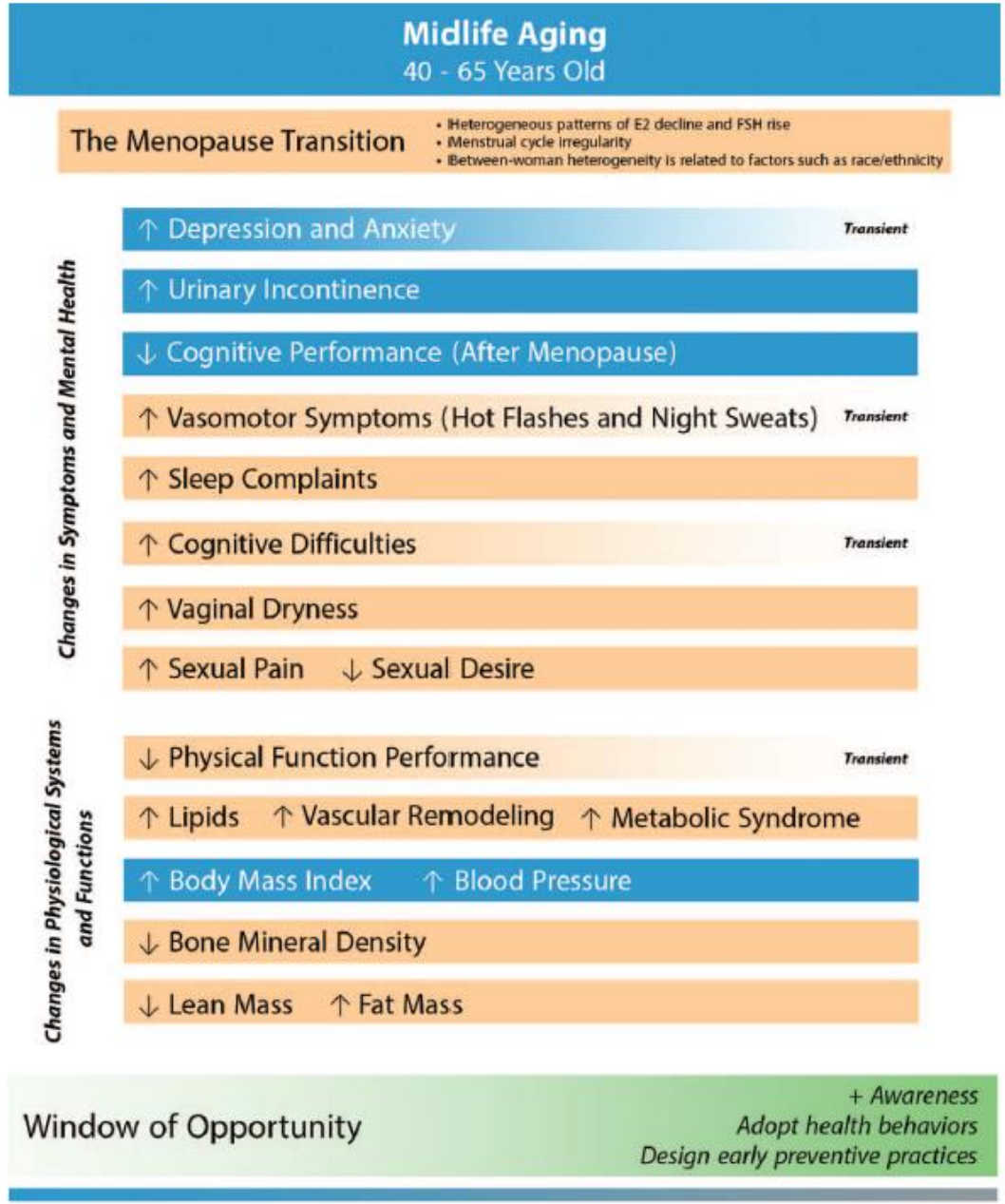
- The ultimate goal of health care is to restore or preserve functioning and well-being related to health.

The aim is maximal vigor in life rather than accepting linear senescence

Health-related quality of life (HRQoL) – issues in menopause and aging.

- Vasomotor symptoms
- Cognitive functioning
- Vaginal dryness
- Mood symptoms
- Urinary complaints
- Uterine bleeding
- Sleep
- Attractiveness
- Sexual activity
- Anxiety
- Depression
- HRQoL associated with chronic conditions

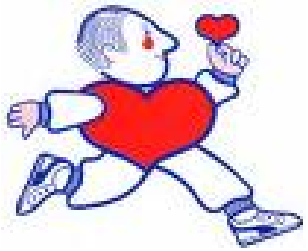
H. P. G. Schneider & M. Birkhäuser (2017) Quality of life in climacteric women, Climacteric, 20:3, 187-194,



Samar R. El Khoudary, Menopause, Vol. 26, No. 10, 2019

Therapeutic targets

- Vasomotor Symptoms
- Sleep, mood, brain fog
- Genito-Urinary Atrophy
- Cardiovascular risk factors (hypertension, diabetes, smoking)
- Bone demineralization: osteopenia, osteoporosis
- Sexual dysfunction



- Hormone therapy is considered the most effective treatment for hot flushes and climacteric syndrome
- Treatment is unsuitable for breast cancer survivors, some ovarian or endometrial cancer survivors and for patients with meningioma or patients with cardiovascular contraindications
- Accordingly, many patients with climacteric syndrome seek a complementary and alternative medicine to relieve their symptoms, such as special diets, yoga, herbal therapies, acupuncture, and others.

Agent	Number of studies in meta-analysis	Duration of treatment	Mean difference in number of hot flushes per day*
Oral 17-β-oestradiol and progestagen	5	12 to 24 weeks	−16·8 (−23·4 to −10·2)†
Transdermal 17-β-oestradiol	6	11 to 12 weeks	−22·4 (−35·9 to −10·4)†
Gabapentin	2	8 to 12 weeks	−2·05 (−2·80 to −1·30)
SSRI or SNRI (paroxetine, venalfaxine, citalopram)	6	4 weeks to 12 months	−1·13 (−1·70 to −0·57)
Clonidine	10	4 weeks 8 weeks	−0·95 (−1·44 to −0·47) −1·63 (−2·76 to −0·05)
Red-clover isoflavones	6	12 weeks to 12 months	−0·44 (−1·47 to 0·58)
Soy isoflavones	11	4 to 6 weeks 6 months 12 months	−1·15 (−2·33 to 0·03) −0·97 (−1·82 to −0·12) −1·22 (−2·02 to −0·42)

*Compared with control. †Per week. SSRI=selective serotonin reuptake inhibitors. SNRI=serotonin-norepinephrine reuptake inhibitors.

Table: Overview of treatments for hot flushes that have been included in recent meta-analyses[3,14]

Stearns V, Lancet 2007

Nonhormone pharmacologic agents

- Selective serotonin reuptake inhibitors (SSRIs)- low dose paroxetine non hormone treatment for VMS approved by the United States Food and Drug Administration (FDA)
- Serotonin and norepinephrine reuptake inhibitors (SSNRIs)
- Gabapentinoids,
- Clonidine
- Oxybutynin
- NK3R antagonists
- Racemosa cimifuga ou black cohosh, other herbal supplements

TABLE IX NONHORMONAL OPTIONS FOR MANAGEMENT OF VASOMOTOR SYMPTOMS (ADAPTED FROM (NORTH AMERICAN MENOPAUSE SOCIETY., 2023) WITH PERMISSION).

Agent	Dose	Comments
Pharmacological		
SNRIs		
Venlafaxine	37.5-150 mg/day	Commence with lowest dose then titrate upwards
Desvenlafaxine	100-150 mg/day	Commence with 50mg/day and titrate upwards
SSRIs		
Paroxetine	7.5 mg/day[1]	Do not use paroxetine concurrently with tamoxifen. Single dose, no titration needed
	10-25 mg/day	Commence with 5-10mg dose then titrate upwards
Escitalopram	10-20 mg/day	
Citalopram	10-20 mg/day	
Other		
Gabapentin	900-2400 mg/day in three divided doses.	Commence with 100-300 mg nighttime dose.
Fezolinetant	45 mg/day[1]	Single dose, no titration needed
Oxybutynin	2.5-5 mg twice daily	Commence with lowest dose then titrate upwards
Clonidine[2]	50-150 µg/day in twice daily dosing[1]	Commence with 25 µg twice daily and titrate upwards.
This does not represent the entire list as published in (North American Menopause Society., 2023).		
Non-Pharmacological		
Cognitive behavioural therapy		
Hypnosis		

[1]Government approved in some countries for use for vasomotor symptoms

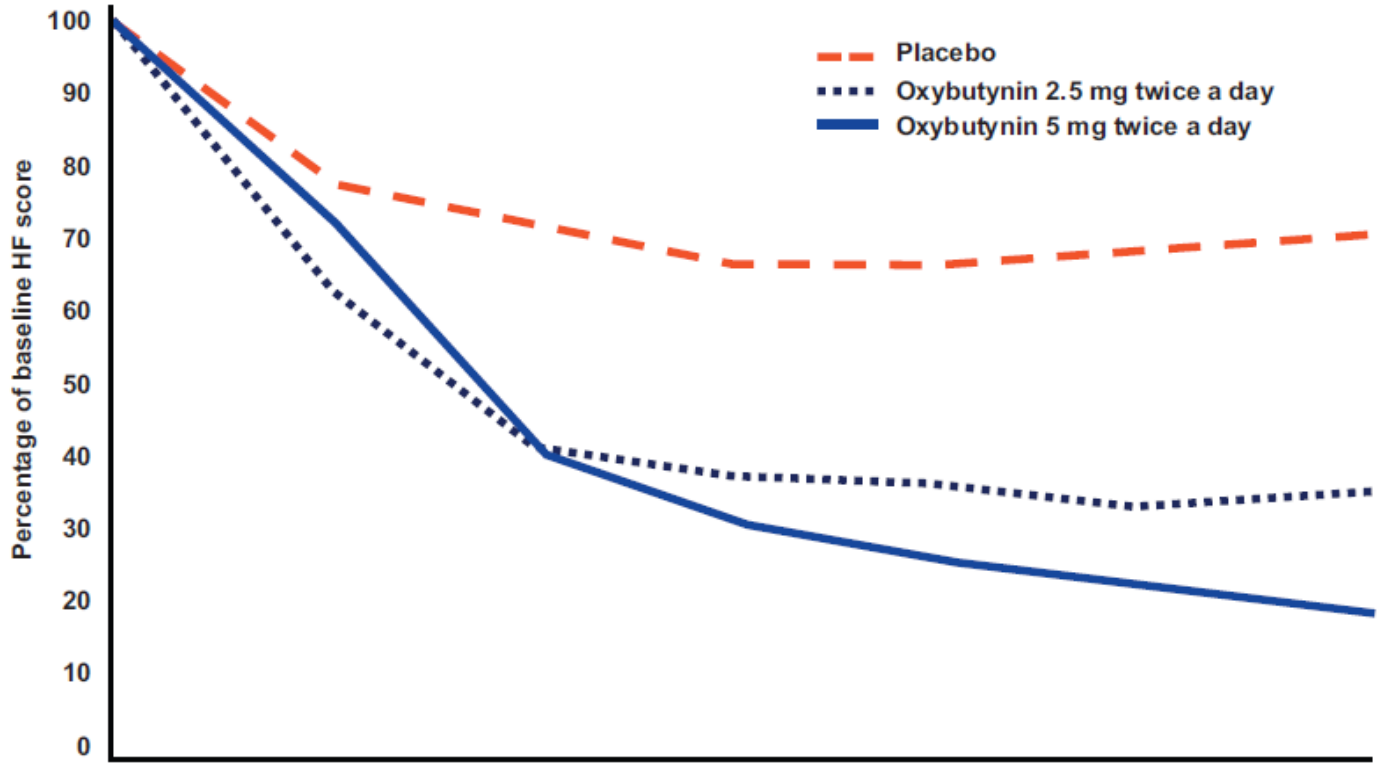
[2] Clonidine was not included in the original NAMS publication

Non-Hormonal Options for Vasomotor Symptoms

Abbreviations: SSRI = Selective Reuptake Inhibitor; SNRI = Selective Norepinephrine Reuptake Inhibitor; NK3R = Neurokinin 3 Receptor
Notes: *FDA approved for the treatment of VMS. **Off label. ‡Further study needed to establish dose

Medication Name and Dose	Vasomotor Symptom Effect	Common Side Effects (%)	Additional concerns
SSRI Paroxetine mesylate 7.5 mg/d* Paroxetine HCl 10-25 mg/d** Citalopram 10-20 mg/d** Escitalopram 10-20 mg/d** *SNRI* Desvenlafaxine100-150 mg/d** Venlafaxine 37.5-150 mg/d**	Hot flash reduction from 25 – 69% Composite hot flash frequency and severity improved from 27 – 61%	Nausea or dizziness, which usually improves after 1 to 2 weeks	Avoid potent CYP2D6 inhibitors in Tamoxifen users Patients with bipolar disease, uncontrolled seizures, liver or kidney insufficiency, uncontrolled hyponatremia or poorly controlled hypertension, concurrent use of other SSRIs or SNRIs Black box warnings: uncommon suicidal thoughts within first few months
Gabapentinoids Gabapentin 900-2,400 mg/d** Pregabalin 150-300 mg/d**	31 – 89.5% reductions in VMS	Dizziness, unsteadiness, and drowsiness which usually improves by week 4	Lower doses often effective. Start with 100-300 mg at night and up titrate until effective dose Since drowsiness is a common adverse side effect of gabapentin, it may be a good choice for women with disruptive sleep from VMS
Oxybutynin 5-15 mg/d**	50-77% reduction in hot flash frequency	Dry mouth, urinary issues, constipation	Anticholinergic side effects best tolerated at lower doses

Oxybutynin vs Placebo for Hot Flashes in Women With or Without Breast Cancer: A Randomized, Double-Blind Clinical Trial (ACCRU SC-1603)



Weeks	Baseline	1	2	3	4	5	6
Placebo	38	38	38	37	35	35	35
Oxybutynin 2.5 mg twice a day	40	40	38	36	35	35	34
Oxybutynin 5 mg twice a day	35	35	34	32	32	31	31

R. A. Leon-Ferre et al., JNCI Cancer Spectrum (2020) 4(1): pkz088

Oxybutynin vs Placebo for Hot Flashes in Women With or Without Breast Cancer: A Randomized, Double-Blind Clinical Trial

- Mean (SD) age was 57 (8.2) years.
- Oxybutynin (2.5mg twice a day or 5mg twice a day) or placebo for 6 weeks.
- 65% were taking tamoxifen or an aromatase inhibitor.
- Patients on both oxybutynin doses reported greater reductions in the weekly HF score (5mg twice a day: 16.9 [SD 15.6], 2.5mg twice a day: 10.6 [SD 7.7]), placebo 5.7 (SD 10.2); P<.005 for both oxybutynin doses vs placebo [SD 4.3];
- Patients on both oxybutynin arms reported more side effects than patients on placebo, particularly dry mouth, difficulty urinating, and abdominal pain. Most side effects were grade 1 or 2. There were no differences in study discontinuation because of adverse effects.

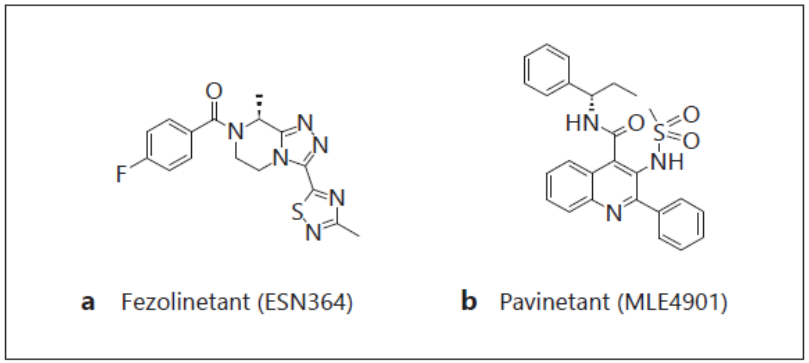
Roberto A. Leon-Ferre, JNCI Cancer Spectrum, 2020, Vol. 4, No. 1

Agent Study	Class Type of study	Cognitive impairment	Strengths and weaknesses of the study
Oxybutynin	C		
Callegari et al. [55]	Animal study	Yes	BBB permeability based on physicochemical properties: significant/*In vivo*: moderate/*in vitro*: high
Maruyama et al. [56]	Animal study	Yes	*In vivo* autoradiography/DDR: yes
Yoshida et al. [57]	Animal study	Yes	*In vivo* PET study/potential adverse effects on the CNS: yes
Yamamoto et al. [44]	Animal study	Yes	*In vivo* PET study/occupied central mAChR/cognitive impairment: yes
Katz et al. [48]	Clinical trial	Yes	RCT/n = 12/healthy volunteer/daily doses: 5 mg, 10 mg/cognitive impairment: yes
Esin et al. [65]	Clinical trial	No	Prospective study/n = 43/patients with OAB ≥ 65 years of age/no data about the DDR
Wagg et al. [50]	Clinical trial	Yes	RCT/n = 26/study subjects: ≥ 75 years of age MCI/daily dose: 10 mg
Pietzko et al. [49]	Clinical trial	Yes	Phase I study/n = 12/mean age: 26 years of age/daily dose: 20 mg/change of EEG alpha range: yes

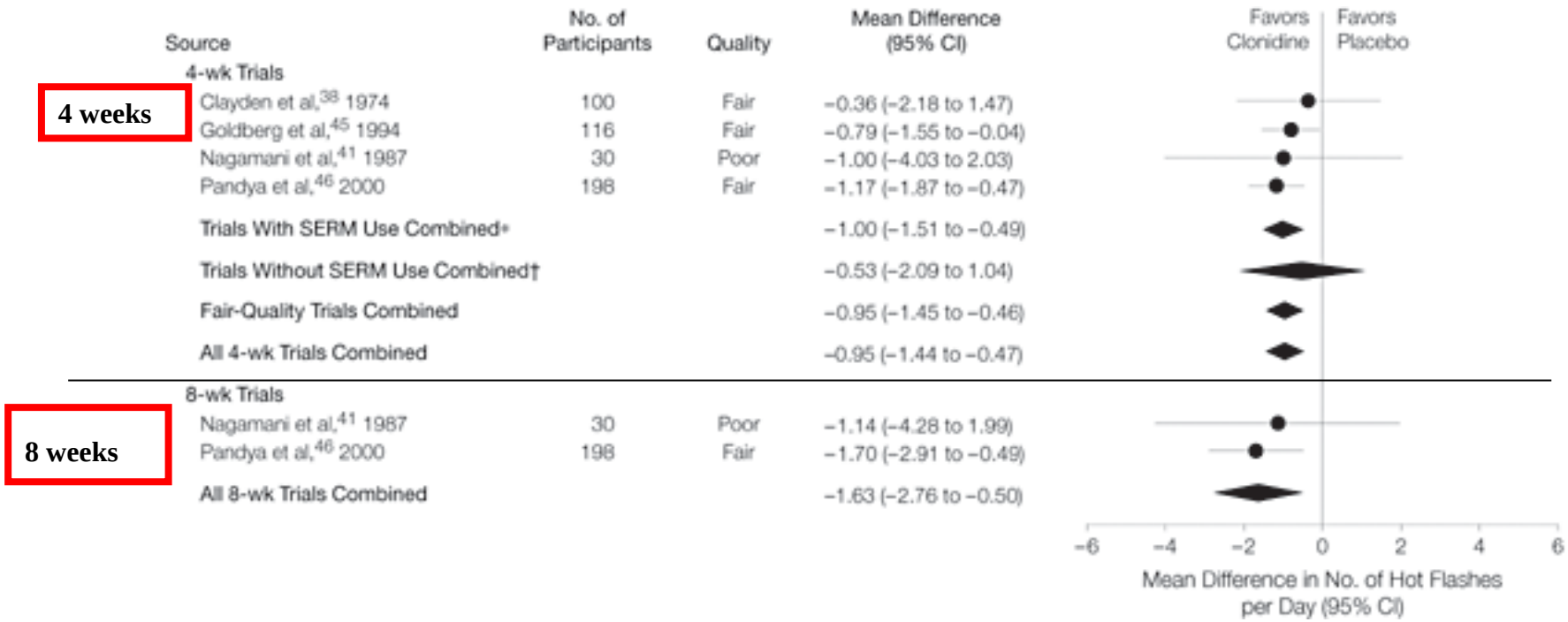
Neuroendocrine agents

- Recognition of a neuroendocrine role in hot flashes
  - Antidopaminergic (methyldopa and veralipride)
  - α-adrenergic-receptor agonists (clonidine)

- In *The Lancet*, Julia Prague and colleagues[8] report the findings from their phase 2, randomised, double blind, placebo-controlled trial investigating the oral neurokinin 3 receptor (NK3R) antagonist MLE4901 as a new therapy for menopausal hot flushes (2017)
  - have not been tested in clinical trials in patients with breast cancer.



Metaanalysis of Clonidine



4 weeks

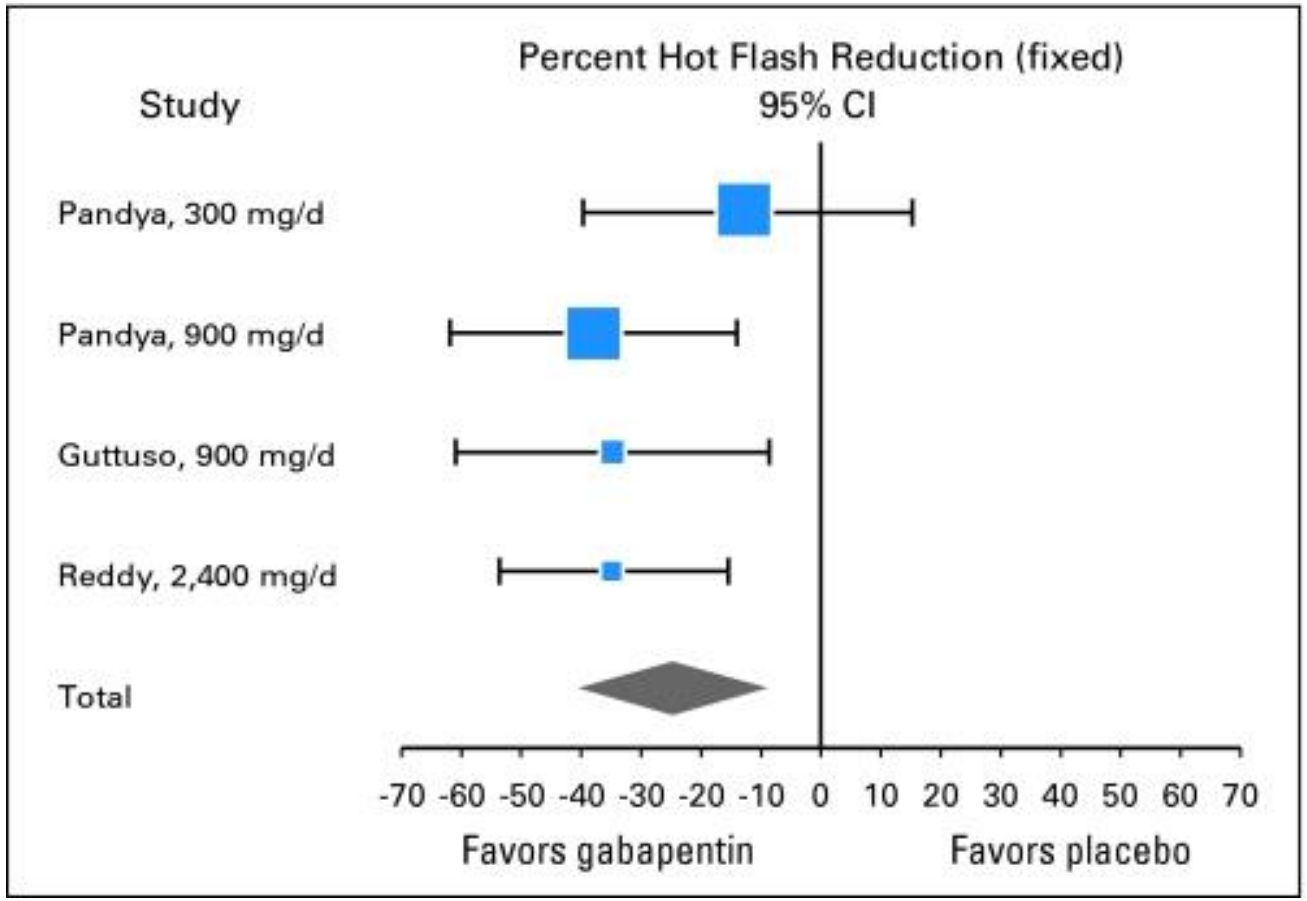
8 weeks

Nelson, H. D. et al. JAMA 2006;295:2057-2071.

apply.

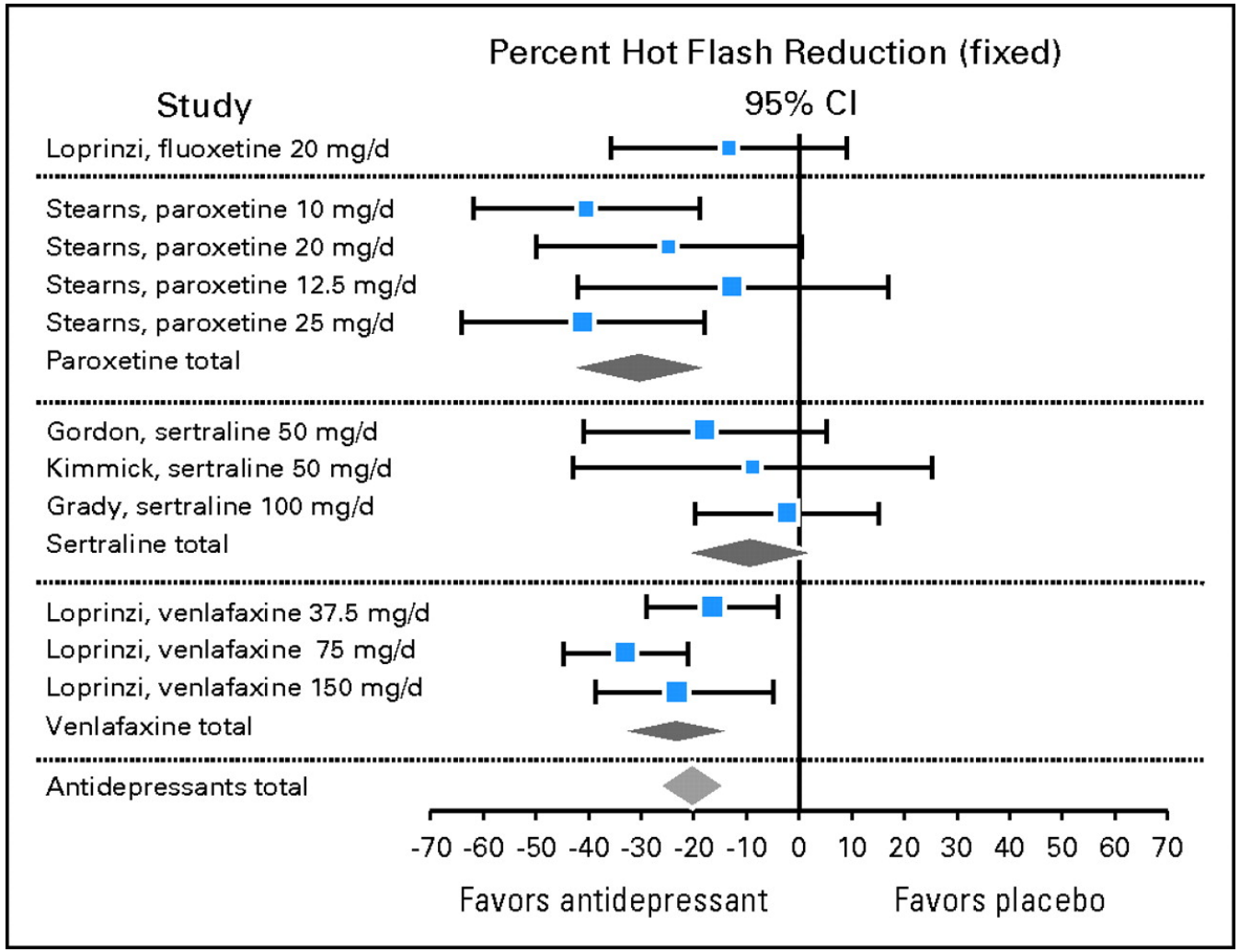
JAMA

Metaanalysis of gabapentin



Loprinzi, 2009

Forest plots of hot flash reduction in newer antidepressant studies.



Loprinzi C L et al. JCO 2009;27:2831-2837

Is MHT superior to SSRIs for the improvement of QoL?

In women suffering from climacteric symptoms, MHT is superior to selective serotonin reuptake inhibitors (SSRIs) for the improvement of QoL

Caan B, LaCroix AZ, Joffe H, et al. Effects of estrogen and venlafaxine on menopause-related quality of life in healthy postmenopausal women with hot flashes. Menopause 2015;22:607–15

Source : lamenopc

Table 1 SSRI/SNRI and CYP2D6 Activity

Potent Inhibitors	Moderate Inhibitors	Weak Inhibitors	No Activity CYP2D6
Fluoxetine	Sertraline	Citalopram	Venlafaxine
Paroxetine	Duloxetine	Escitalopram	Desvenlafaxine
Bupropion	Fluvoxetine		Mirtazapine

Generic	Dose	CYP2D6 concern	Safe with tamoxifene	Safe with AI
Paroxetine	7.5 mg to 20 mg daily at bedtime	inhibitor	no	+
Fluoxetine	20 to 60 mg/d	inhibitor	no	+
Sertraline	25 to 100 mg/d	inhibitor (lesser)	?	+
Citalopram Escitalopram	10 to 20 mg/d		+	+
Duloxetine	60 to 120 mg/d	inhibitor	no	+
Venlafaxine	37,5 to 150 mg/d	no	+	+
Desvenlafaxine	100 mg/j	no	+	+
Oxybutinine	5 mg 2x/d	no	+	+

Generic	Dose	CYP2D6 concern	Safe with tamoxifene	Safe with AI
Gabapentin	Initiate at 100 mg at bedtime, may increase in 100 mg increments up to 900 mg at bedtime. May trial daytime doses; titrated regimen up to 600 mg three times daily. Success has also been determined with a regimen of 600 mg every morning and 1200 mg daily at bedtime	no	+	+
Fezolinetant	45 mg/d		+	+

Black Cohosh

- unable to draw any conclusions about the effect of orally administered monopreparations of black cohosh (*C. racemosa;* at doses ranging from 8 to 160 mg daily, for periods varying between four and 52 weeks) on the frequency and intensity of vasomotor symptoms, or global changes in menopausal symptom scores.
- The effect of black cohosh on vulvovaginal atrophic symptoms, HRQoL, sexuality and bone health is inconclusive also.
- No evidence was found that black cohosh was associated with more risk of harm than placebo, but there was insufficient good evidence to reach a firm conclusion on safety.

Leach MJ, Moore V. Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database of Systematic Reviews 2012

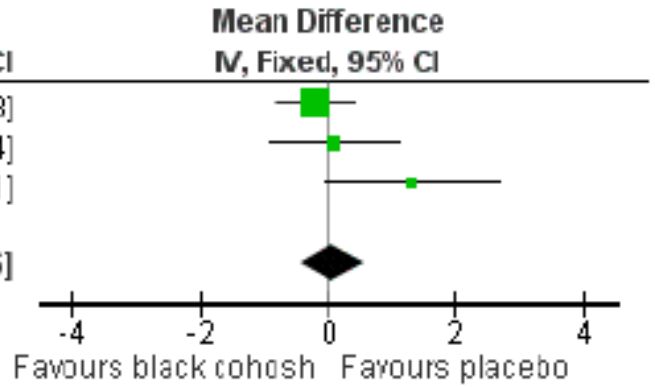
Black Cohosh

Figure 4. Forest plot of comparison: 1 Black cohosh versus placebo, outcome: 1.1 Vasomotor symptoms: daily hot flush frequency.

Study or Subgroup	Black cohosh Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Frei-Kleiner 2005	1.66	1.69	81	1.85	1.62	41	64.4%	-0.19 [-0.81, 0.43]
Newton 2006	3.31	3.36	80	3.21	3.41	84	22.9%	0.10 [-0.94, 1.14]
Pockaj 2006	5.86	3.97	53	4.54	3.32	54	12.7%	1.32 [-0.07, 2.71]
Total (95% CI)			**214**			**179**	**100.0%**	**0.07 [-0.43, 0.56]**

Heterogeneity: Chi² = 3.80, df = 2 (P = 0.15); I² = 47%

Test for overall effect: Z = 0.27 (P = 0.79)



Leach MJ, Moore V. Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database of Systematic Reviews 2012

Black Cohosh

- Current evidence : no association between black cohosh and increased risk of breast cancer.
- lack of evidence supporting the efficacy of black cohosh for reduction of hot flashes in breast cancer patients

Black Cohosh and Breast Cancer: A Systematic Review, Heidi Fritz, Integrative Cancer Therapies 2014, Vol. 13(1) 12–29

Phytoestrogens in healthy peri and postmenopausal women

- The meta-analysis of included studies assessing the effect of red clover isoflavone extract on menopausal symptoms showed a statistically moderate relationship with the reduction in the daily frequency of hot flushes.

Study	RCE			Control			WMD (random)		WMD (random) 95% CI	Weight
	DM	SD	N	DM	SD	N	95% CI	*p*	*Favours RCE* — *Favours control*	%
Atkinson, 2004	−0.8	2.1	45	−1.1	1.8	54	0.20 (−0.58, 0.98)	0.6149		13,29
Baber. 1999	−1.37	17.66	25	−2.47	14.57	26	1.10 (−7.80, 10.00)	0.8087		2.49
Jeri, 2002	−3.4	1.83	15	−0.6	1.53	15	−2.80 (−4.01, −1.59)	0.0000		12.69
Knight, 1999 (160)	−3.1	5.39	13	−2.8	4.98	12	−0.30 (−4.36, 3.76)	0.8850		7.08
Knight, 1999 (40)	−2.0	4.4	12	−2.8	4.90	12	0.80 (−2.96, 4.56)	0.6767		7.61
Lambert, 2017	−2.97	4.74	30	0.04	6.55	29	−3.01 (−5.94, −0.05)	0.0438		9.24
Lipovac, 2012	−8.6	4.64	50	−0.9	7.47	50	−7.70 (−9.66, −5.74)	0.0000		11.27
Tice, 2003 (80)	−3.4	4.99	84	−2.8	3.32	85	−0.60 (−1.88, 0.68)	0.3567		12.58
Tice, 2003 (57)	−2.7	3.92	83	−2.8	3.42	85	0.10 (−1.00, 1.20)	0.8585		12.86
van de Weijer, 2002	−2.08	3.09	15	0.29	3.71	11	−2.37 (−6.12, 1.38)	0.0306		10.89
Total (95% CI)			**372**			**379**	**−1.73 (−3.28, −0.18)**	**0.0292**		100.00

Hetrogeneity: Q = 71.1148; df = 9 (p = 0.0000); Tau^2 = 4.5675; I^2 = 87.34%

−10 −8 −6 −4 −2 −9 −7 −5 −3 −1 0 1 2 3 4 5 6 7 8 9 10

Figure 4. Effects of isoflavones with red clover (*Trifolium pratense*) vs. placebo on the daily frequency of hot flushes in peri- and post-menopausal women. Number in brackets following author's name refers to dose of isoflavones in the study with more than one active group [33–38,41,44]. Abbreviations: RCIE, red clover isoflavone extract; WMD, weighted mean difference.

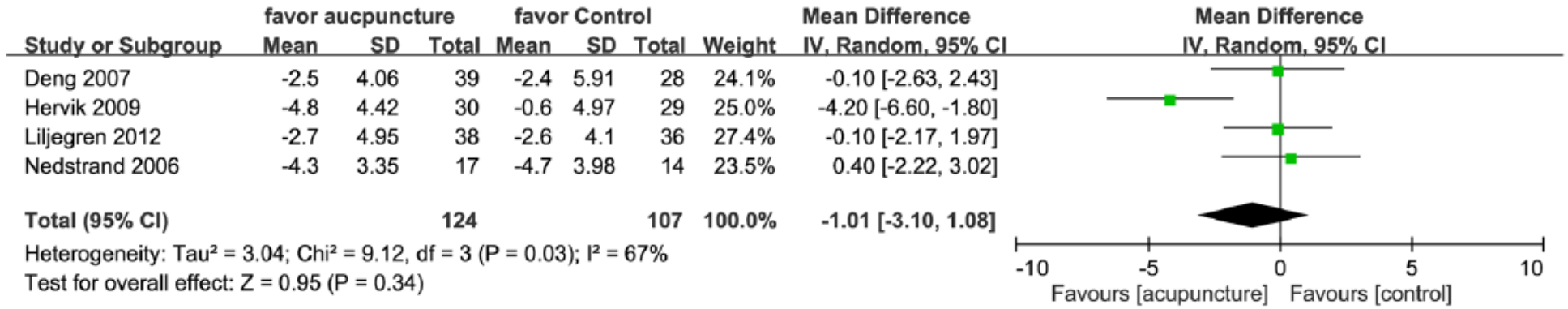
Wiesław Kanadys, Nutrients 2021, 13, 1258

Soy, Red Clover, and Isoflavones and Breast Cancer: A Systematic Review

- lack of evidence showing clear effects of soy consumption or supplementation on reduction of hot flashes in breast cancer patients.

Fritz H, Seely D, Flower G, Skidmore B, Fernandes R, et al. (2013) Soy, Red Clover, and Isoflavones and Breast Cancer: A Systematic Review. PLoS ONE 8(11): e81968. doi:10.1371/journal.pone.0081968

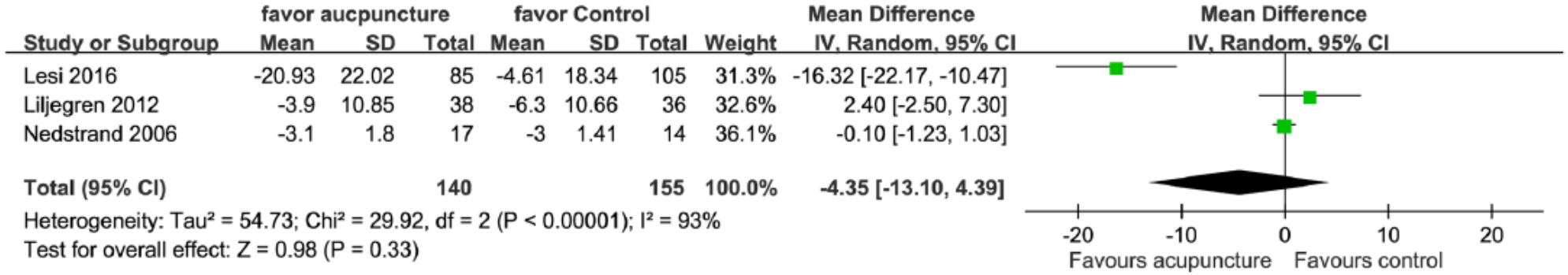
Effect of acupuncture on hot flush and menopause symptoms in breast cancer- A systematic review and meta-analysis



Study or Subgroup	favor aucpuncture Mean	SD	Total	favor Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Deng 2007	-2.5	4.06	39	-2.4	5.91	28	24.1%	-0.10 [-2.63, 2.43]
Hervik 2009	-4.8	4.42	30	-0.6	4.97	29	25.0%	-4.20 [-6.60, -1.80]
Liljegren 2012	-2.7	4.95	38	-2.6	4.1	36	27.4%	-0.10 [-2.17, 1.97]
Nedstrand 2006	-4.3	3.35	17	-4.7	3.98	14	23.5%	0.40 [-2.22, 3.02]
Total (95% CI)			**124**			**107**	**100.0%**	**-1.01 [-3.10, 1.08]**

Heterogeneity: Tau² = 3.04; Chi² = 9.12, df = 3 (P = 0.03); I² = 67%
Test for overall effect: Z = 0.95 (P = 0.34)

Fig 2. Forest plot of the effect of acupuncture on the frequency of hot flush. (times/day).



Study or Subgroup	favor aucpuncture Mean	SD	Total	favor Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lesi 2016	-20.93	22.02	85	-4.61	18.34	105	31.3%	-16.32 [-22.17, -10.47]
Liljegren 2012	-3.9	10.85	38	-6.3	10.66	36	32.6%	2.40 [-2.50, 7.30]
Nedstrand 2006	-3.1	1.8	17	-3	1.41	14	36.1%	-0.10 [-1.23, 1.03]
Total (95% CI)			**140**			**155**	**100.0%**	**-4.35 [-13.10, 4.39]**

Heterogeneity: Tau² = 54.73; Chi² = 29.92, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 0.98 (P = 0.33)

Fig 3. Forest plot of the effect of acupuncture on the severity of hot flush. (visual analog scale).

Chien T-J, Hsu C-H, Liu C-Y, Fang C-J (2017). PLoS ONE12(8): e0180918.

How to assess insomnia in midlife women?

- Sleep history[163]: current and past sleep patterns
  - Frequency of sleep difficulties (number of nights/week)
  - Duration of sleep difficulties
  - Impact on daytime function
  - Timing of sleep difficulties in relation to menopausal symptoms
- Medical and psychiatric history and recent stressful life events
- Menopausal factors (changes in bleeding patterns, menopausal symptoms like HFs)
- Sleep diary[164]: include question about frequency/bother from HFs/night sweats
- Screen for sleep breathing and movement disorders (eg, Stop-bang questionnaire[165])*

*women may present with atypical symptoms.[127]

When should hormone therapy be considered?

Hormone therapy improves sleep quality in women with concomitant HFs. Independent effects of estrogen vs progesterone/progestin compounds need further evaluation[147]

- Hot flash-related sleep disruption
- No contraindications
- Follow guidelines, ie, when the balance of potential benefits and risks is favorable for the individual.[167]

Note: Abrupt discontinuation of HT is associated with hot flash relapse, which could lead to insomnia.[54]

What are the non-hormonal pharmacological options?

Non hormanal options for treating HFs are available. A small number of trials have investigated their efficacy for insomnia symptoms[146]

- Low-dose selective serotonin/serotonin norepinephrine reuptake inhibitors reduce HFs and modestly reduce insomnia symptoms in women with HFs.* (eg, 168–170)
- Gabapentin improve sleep quality in perimenopausal women with HFs and insomnia.[171]
- Sedative hypnotics should be used with caution in the short term.[146]

*Insomnia is a common adverse event of higher dose/SNRis in patients with depression; however, it was not common in a trial in healthy women with HFs.[168]

Note: Discontinuation of SSRIs is associated with HF relapse, which could lead to insomnia.[172]

Comorbidities and differential diagnoses

Insomnia symptoms can coexist with, or be better accounted for, by mental/physical health conditions and medication use.

- Mood and anxiety disorders*
- Sleep disordered breathing#
- Periodic limb movement disorder
- Disorders associated with chronic pain
- Substance-use disorder*

#There is a high prevalence of comorbid insomnia/sleep disordered breathing in midlife women, with bidirectional causal pathways.[166]

*Adjunctive treatment of sleep difficulties in these cases should be considered.

Are there effective non-pharmacological options?

CBT-I is the first-line treatment for insomnia. Some other non-pharmacological options have modest benefits.[146]

- Cognitive behavioral therapy for insomnia
- High-intensity exercise
- Yoga
- Soy isoflavones

Note: While poor sleep hygiene can exacerbate insomnia, limited data indicate that insomnia in midlife women is not associated with negative sleep hygiene behaviors.[166]

Fiona C Baker, Nature and Science of Sleep 2018:10 73–95

MHT and perimenopause : Mood and depressive symptoms

- Some data support a potential beneficial effect of MHT on mood
- MHT should **not be proposed to non-depressed, asymptomatic** peri-menopausal women to prevent or alleviate mood symptoms.
- Estrogen seems to have a potential role among specific **sub-populations** at risk of depressive symptoms during menopausal transition.
- Estrogens can be considered in menopausal women with other concurrent conditions such as vasomotor symptoms as they may **increase the response to anti-depressants.**
- Only a small proportion of women experience depressed mood in relation to menopause, it is mandatory to accurately investigate the **origin of depressive** symptoms in order to detect those women who had history of depression before the menopause transition and those who had the onset during the menopausal transition.
- **Antidepressants remain the first-line treatment of depression for patients with previous history of depression**

Giulia Gava, Medicina 2019, 55, 668, Maki, P.M.; Kornstein, S.G.; Joe, H.; Bromberger, J.T.; Freeman, E.W.; Athappilly, G.; Bobo,W.V.; Rubin, L.H.;Koleva, H.K.; Cohen, L.S.; et al. Guidelines for the evaluation and treatment of perimenopausal depression:Summary and recommendations. Menopause 2018, 25, 1069–1085

Midlife body changes

- The steady weight gain, of about 0.5 kg per year, seen in women at midlife is associated with age and environmental factors, not menopause.
- Variables associated with a greater likelihood of obesity in women at midlife include

1. urbanization
2. lower level of education,
3. inactivity,
4. higher parity,
5. family history of obesity
6. marriage at earlier age
7. disruption of the circadian rhythm by shift work and sleep deprivation

Jacoby E, Goldstein J, Lopez A, Nunez E, Lopez T. Social class, family, and life-style factors associated with overweight and obesity among adults in Peruvian cities. Prevent Med 2003;37:396–405
5. Hajian-Tilaki KO, Heidari B. Prevalence of obesity, central obesity and the associated factors in urban population aged 20-70 years, in the north of Iran: a population-based study and regression approach. Obes Rev 2007;8:3–10

Midlife body changes

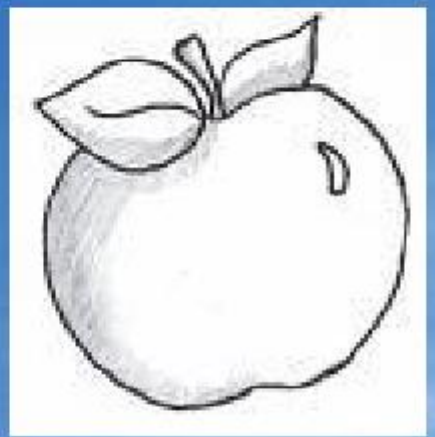
- The change in the hormonal milieu at menopause is associated with significant increases in **waist circumference and central abdominal fat**. Increased waist circumference occurs in relation to final menstrual period and significant increases in central abdominal fat have been seen in longitudinal studies of Caucasian and Asian women(gynoid to an android pattern).
- Total mass, **percentage fat mass**, truncal fat mass and **visceral fat** also increase in non obese women across the menopausal transition.

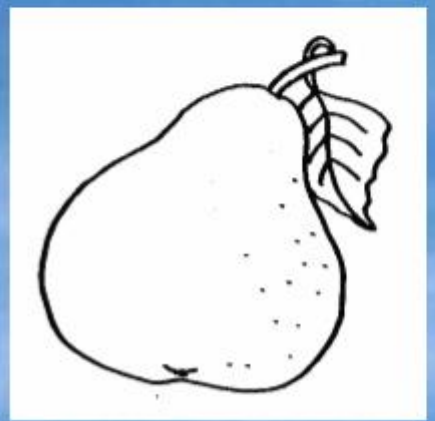
Ho SC, Wu S, Chan SG, Sham A. Menopausal transition and changes of body composition: a prospective study in Chinese perimenopausal women. Int J Obes (Lond) 2010;34:1265–74

Abdulnour J, Doucet E, Brochu M, et al. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging
Team group study. Menopause 2012;19:760–7

BODY SHAPES AND OVERWEIGHT

APPLE OR PEAR





MORPHOTYPE	UPPER BODY OVERWEIGHT	LOWER BODY OVERWEIGHT
ADIPOSE TISSUE	ABDOMINAL AND VISCERAL	FEMORAL
METABOLIC RISK	++++	-
CARDIOVASCULAR	+++	±
CANCER	++	+

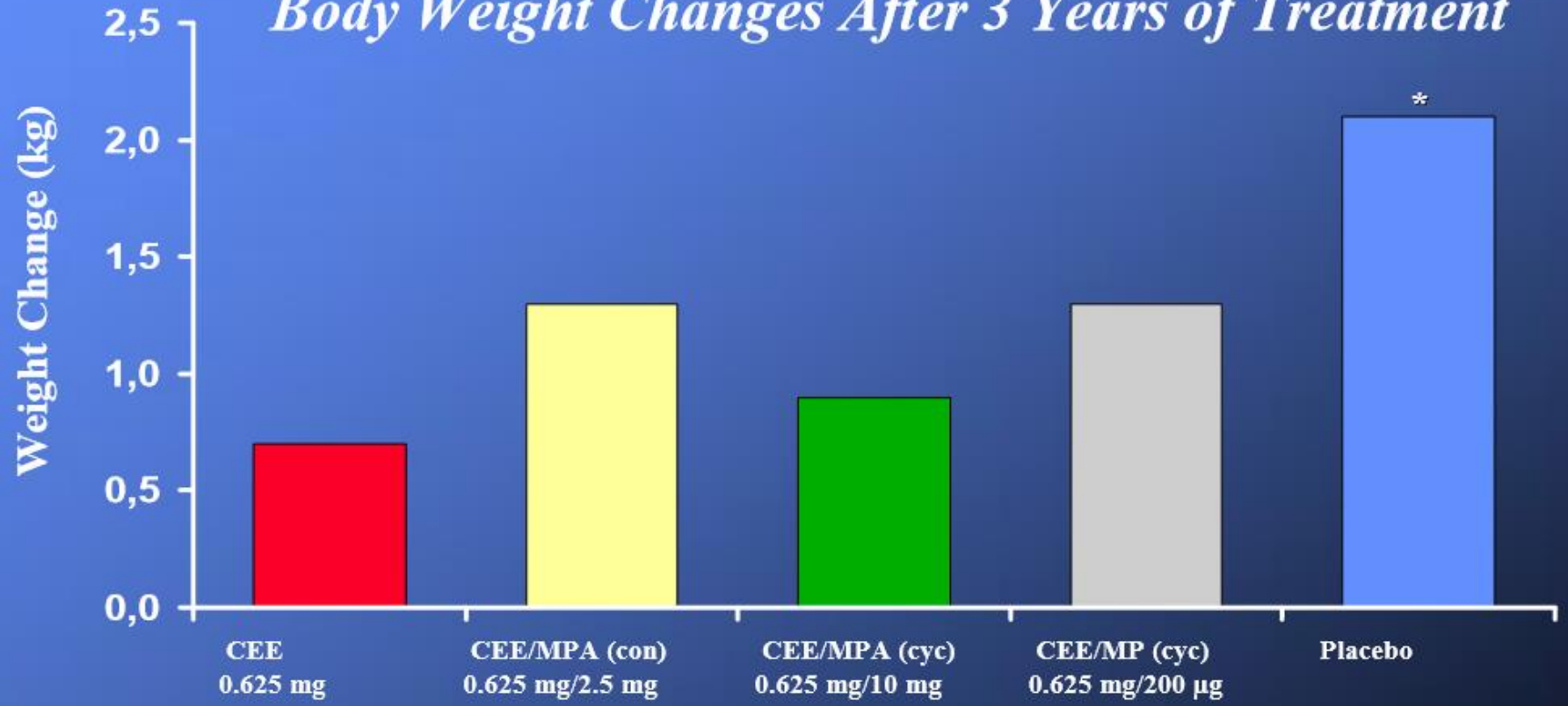
Primary approach to weight management-

- encouragement of a healthy diet and physical activity.
- contrary to widespread belief, menopausal hormone therapy is not associated with weight gain and may ameliorate perimenopausal accumulation of abdominal fat.
- if depression requires pharmacotherapy, medications associated with weight gain commonly used such as clozapine, imipramine, and amitriptyline should be avoided if possible.

Raeder MB, Ferno J, Vik-Mo AO, Steen VM. SREBP activation by antipsychotic- and antidepressant-drugs in cultured human liver cells: relevance for metabolic side effects? Mol Cell Biochem 2006;289:167–73

Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial

Body Weight Changes After 3 Years of Treatment



****P* = .006 vs all active therapy groups; no differences were observed between E-only and E+P groups.**
Con = continuous regimen; cyc = cyclic regimen (progestin first 12 days of each cycle).
Espeland MA, et al. *J Clin Endocrinol Metab.* 1997;82:1549-56.

Key messages

- The hormonal changes that accompany menopause are associated with increases abdominal fat, even in lean women.
- Maintenance of a healthy diet and avoidance of caloric excess combined with physical activity are important components of weight management.
- **Menopausal abdominal fat accumulation is ameliorated by estrogen therapy**, with a reduction in overall fat mass, improved insulin sensitivity and a lower rate of development of type 2 diabetes.

Vaginal approach

- Moisturisers
- Lubricants
- Sexual therapy

Avoid parabens, silicon, perfumes , colourings

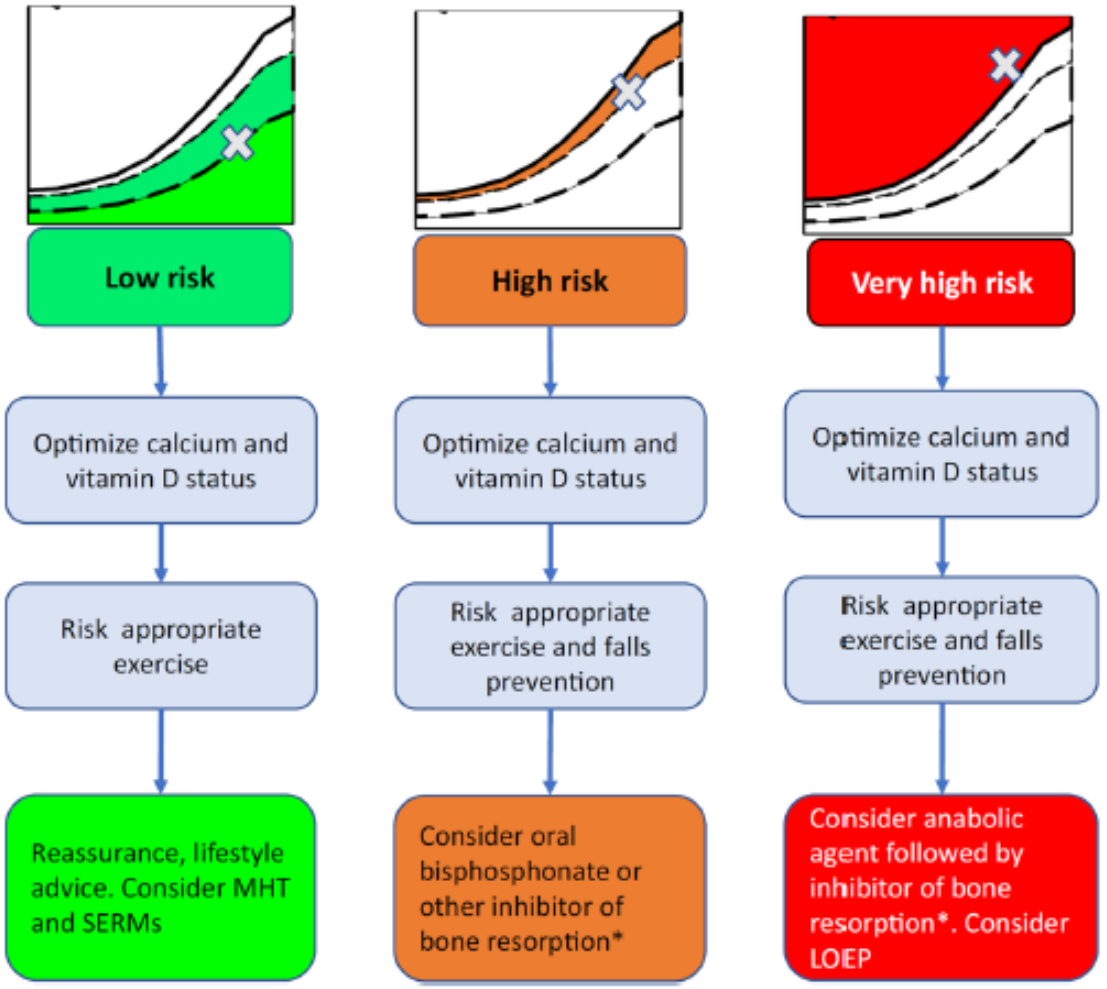
Aqueous: dries reapply
Aqueous + organic alcohol (glycerol, propylene glycol...) slippery texture and retains moisture.
Silicone polymer (Dimethicone, Dimethiconol and Cyclomethicone): non-drying and slippery texture but vaginal residue, (+environmental pollution)
Oily: the oil degrades the latex, making it porous and promoting condom breakage.

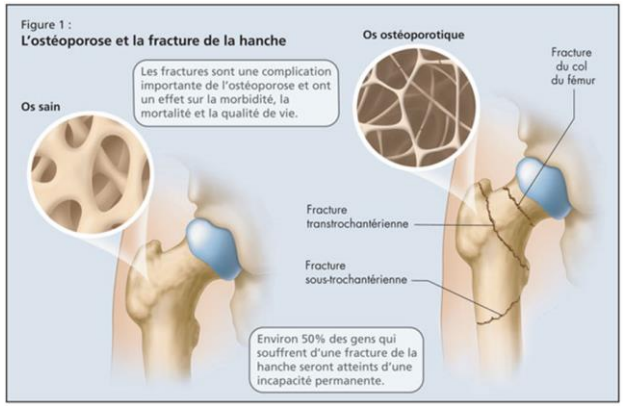
Vaginal laser (light amplification by stimulated emission of radiation) therapy for gynecologic conditions: re-examining the controversy and where do we go from here

- When considering expert opinions, the peer-reviewed literature and specialty society guidance, one must thoughtfully consider the fact that **not all lasers are the same** and that **their efficacy is not proven in most vaginal conditions**.
- Vaginal lasers are used for treatment of various vaginal conditions that negatively impact women, including vaginal atrophy, dryness, prolapse, incontinence and dyspareunia.
- • Ablative vaginal lasers are proposed for symptoms of atrophy, dryness and pain associated with genitourinary syndrome of menopause : **the duration of effect and long-term efficacy are unknown..**
- • Evidence is lacking to guide treatment protocols; therefore, vaginal ablative lasers should only be used with caution and following extensive patient counseling regarding **limited evidence on efficacy and safety**.
- • Clinicians should understand the difference between ablative and non-ablative lasers (photobiomodulation);non-ablative lasers may have a lower risk of injury and can target deeper vaginal and pelvic tissues.
- • Early research suggests transvaginal photobiomodulation may improve pain originating from deeper vaginal and pelvic tissues; however, more research is needed.

Ralph Zipper,J. Comp. Eff. Res. (2022) 11(11), 841–849

ALGORITHM FOR THE MANAGEMENT OF PATIENTS AT LOW, HIGH AND VERY HIGH RISK OF OSTEOPOROTIC FRACTURES





Kanis JA, Harvey NC,McCloskey E et al Osteoporos Int (2019) - S. Rozenberg, Osteoporosis International (2020)

Conclusion

- Personalized approach based on complaints
- Evaluate and adapt regularly
- Objective: health, comfort and do no harm (drug interactions, self-medication, alternative medicine) - risk/benefit balance