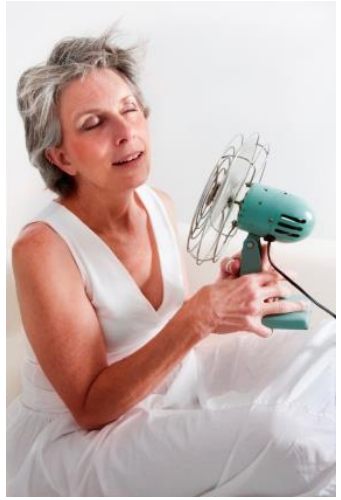
Menopause Hormones, no hormones and anti-hormones?

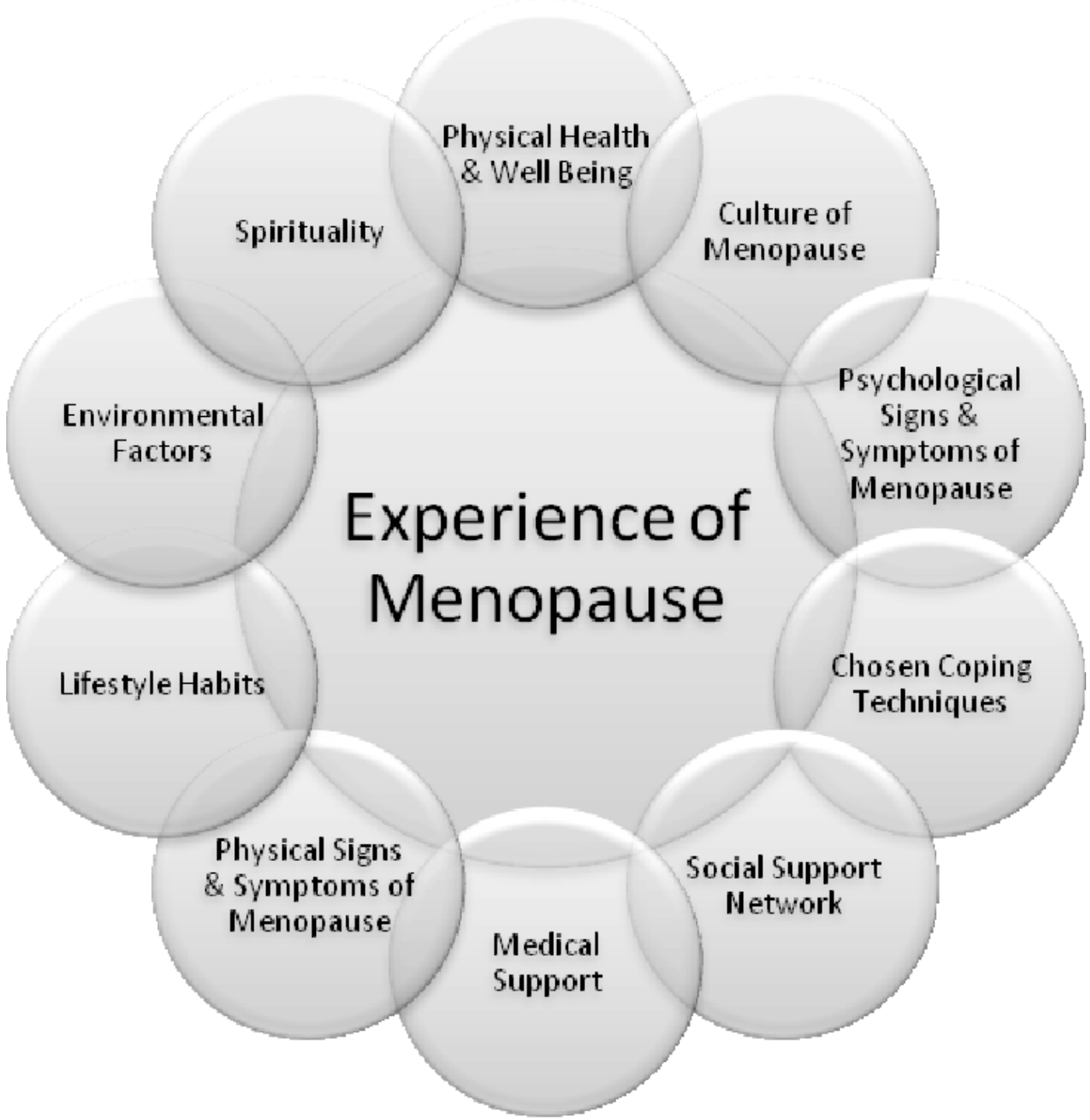


When hormones can not be used …

A Pintiaux MD, PhD

Conflict of interest & Disclosure

- Conflict of interest : None
- Disclosure : Speakers bureau &/or Advisory Boards : Gedeon Richter, Theramex/ Teva


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
Experience of Menopause

Hot Flushes

- Hot flashes are reported by up to 85% of menopausal women
- Hot flashes are present in as many as 55% of women even before the onset of the menstrual irregularity that defines entry into the menopausal transition and their incidence and severity increases as women traverse the menopause, peaking in the late transition and tapering off within the next several years
- Approximately 25% of women continue to have hot flashes up to 5 or more years after menopause.

Nanette Santoro Endocrinol Metab Clin North Am. 2015 September ; 44(3): 497–515. doi:10.1016/j.ecl.2015.05.001

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.

Hot flushes impact the daily activities of most postmenopausal women, especially those with more frequent/severe symptoms.

- affected work (46.0%)
- social activities (44.4%)
- leisure activities (47.6%)
- sleep (82.0%)
- mood (68.6%)
- concentration(69.0%),
- sexual activity (40.9%)
- total energy level (63.3)
- overall quality of life (69.3%)

Williams RE, Levine KB, Kalilani L, et al. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. Maturitas 2009;62:153–9

- frequency and severity of hot flushes had an approximately linear relationship with sleep parameters and menopause-specific quality of life (MSQoL),and that improvements in hot flushes are associated with improvements in sleep and in MSQoL

- 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.

What can we do ?

- To avoid iatrogenic flushes : thyroxin overdose, GnRHA or antagonist, aromatase inhibitors choice/ tamoxifene
- To maintain optimal blood pressure : the American Heart Association and American College of Cardiology (AHA/ ACC) 2017 guidelines for the management of high BP now recommend BP levels below 130/80 mmHg for all individuals, including older adults
- To avoid overweight/obesity, diabetes
- Smoking cessation program
- Diagnosis rare conditions as acromegaly, carcinoid tumors, phaeochromocytoma/ paraganglioma

Clinical case

- 62-year-old woman who had postmenopausal breast cancer. The patient was experiencing severe vasomotor symptoms from her cancer therapy and wanted to discontinue her treatment despite her risk of cancer returning.
- Symptoms hot flashes, hair loss, and lack of energy. The patient reported having to lay down every 10 min due to tiredness and low energy. She was very frustrated and wanted to quit taking the medication despite her breast cancer diagnosis.
- History :diagnosis of non-familial, postmenopausal ER+ breast cancer leading to a right mastectomy, hypertension, and mild chronic obstructive pulmonary disease. She had a 40-year history of smoking at least 5 cigarettes and wanted to quit.
- The patient's breast cancer was previously treated with anastrozole 1 mg following her mastectomy with the plan of treatment for a total of 5 years. Due to intolerable vasomotor symptoms, the patient's oncologist changed therapy to letrozole 2.5 mg once daily. The patient tolerated letrozole therapy for approximately one year when reoccurrence of severe vasomotor symptoms led to changing therapy again. The oncologist discontinued letrozole and initiated exemestane 25 mg once daily. Paroxetine 7.5 mg one capsule once daily was added two months later to assist with ongoing hot flash management.

Clinical case

- The patient expressed her irritation reporting she wanted to quit the breast cancer treatment to get back to “normal” quality of life, even if the risk of her cancer returning was elevated.
- When asked whether the paroxetine was helping with hot flash management, the patient reported that she didn’t believe it made any difference in the severity or frequency of hot flashes.
- Her questions included: 1) are there alternatives to the exemestane; 2) if she quits therapy, what does that mean for her risk of cancer returning

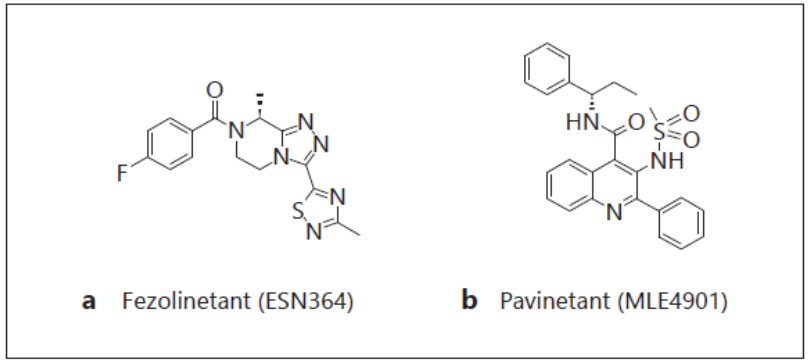
For patients who have a contraindication or intolerance to aromatase inhibitors, tamoxifen alone can be used for 5–10 years.
The most common side effects for tamoxifen include flushing, amenorrhea in premenopausal women, hot flashes, fluid retention, and nausea, but these side effects of lead to discontinuation of the medication less often than the aromatase inhibitors.

National Comprehensive Cancer Network. NCCN Guidelines for Patients; Invasive Breast Cancer. Accessed 17 August 2023 https://www.nccn.org/patientresources/patient-resources/guidelines-for-patients/guidelines-for-patients-details?patientGu idelineId=16; 2023.

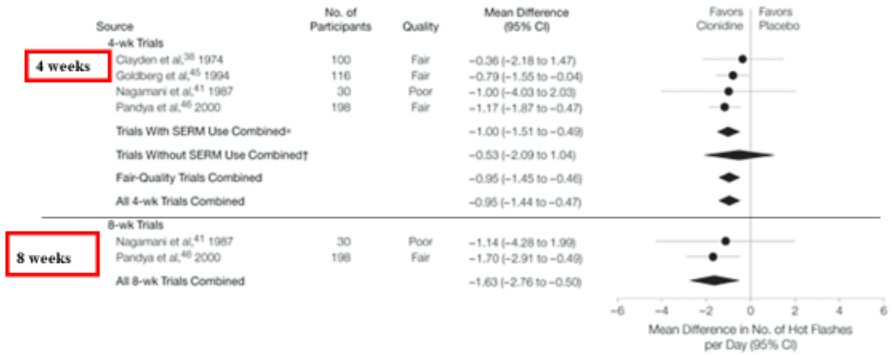
Neuroendocrine agents

- 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.



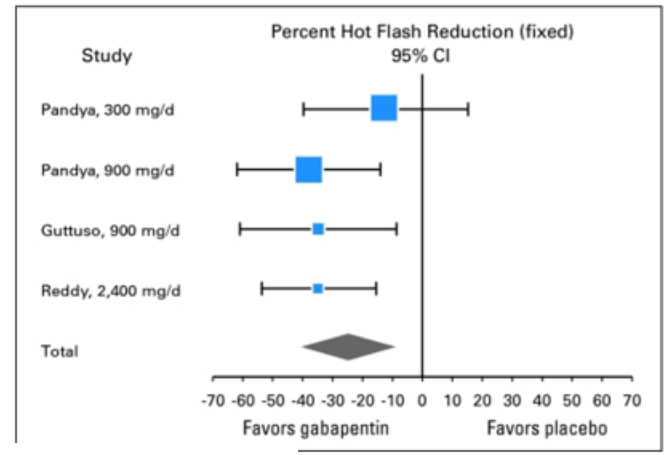
Metaanalysis of Clonidine



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

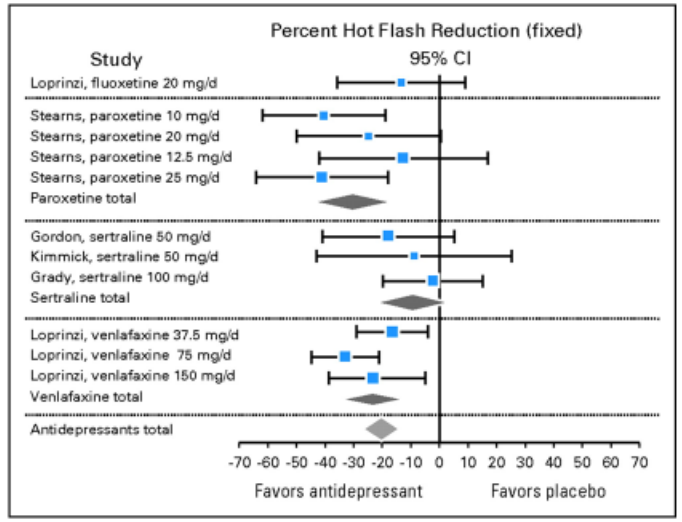
apply.

Metaanalysis of gabapentin



Loprinzi, 2009

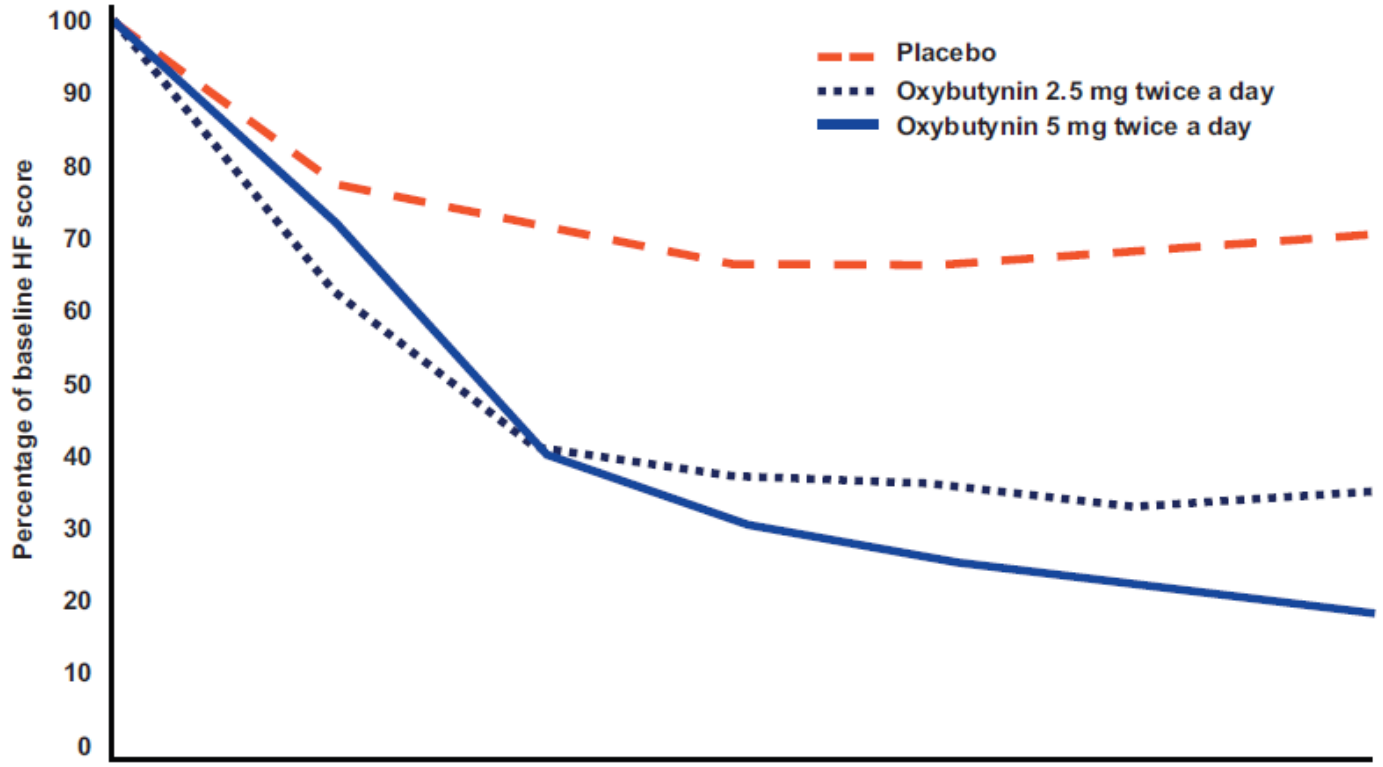
Forest plots of hot flash reduction in newer antidepressant studies.



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

JOURNAL OF CLINICAL ONCOLOGY

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

The selective serotonin 2C receptor agonist, lorcaserin, may have a beneficial effect on menopausal VMS in addition to its weight loss-inducing properties

- Lorcaserin is a selective serotonin 2C (5-HT2C) receptor agonist and is believed to promote satiety and decrease food intake by activating 5-HT2C receptors on anorexigenic pro-opiomelanocortin neurons in the arcuate nucleus of the hypothalamus
- Lorcaserin was approved by the FDA in 2012 for weight management in individuals with a body mass index (BMI) of ≥ 27 kg/m2 in the presence of at least one weight-related condition such as type 2 diabetes, hypertension or dyslipidemia or in those with obesity (BMI≥30 kg/m2).
- The potential role of the 5-HT (2C) receptor in VMS should be considered in future research investigating non hormonal strategies for management of VMS.

Ekta Kapoor , Menopause. 2020 November ; 27(11): 1228–1235

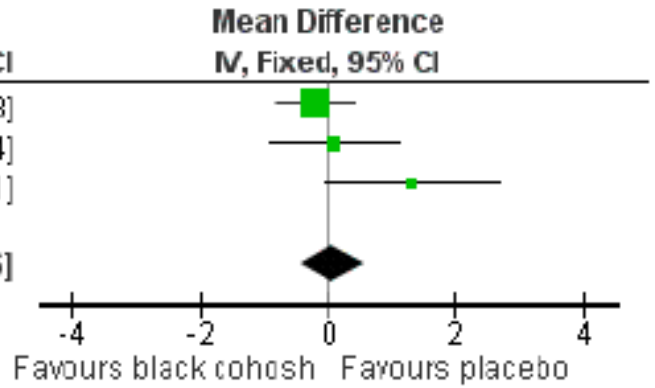
Black Cohosh

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

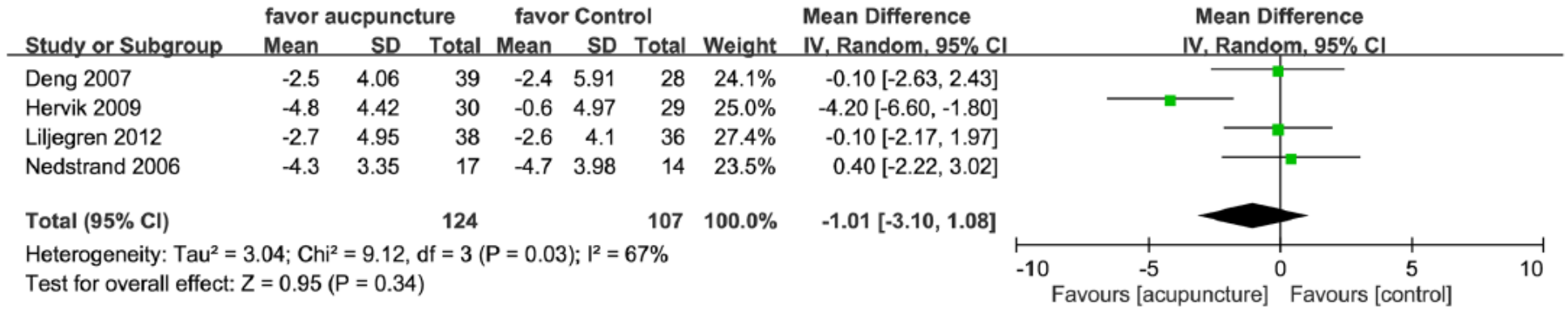


Fig 2. Forest plot of the effect of acupuncture on the frequency of hot flush. (times/day).

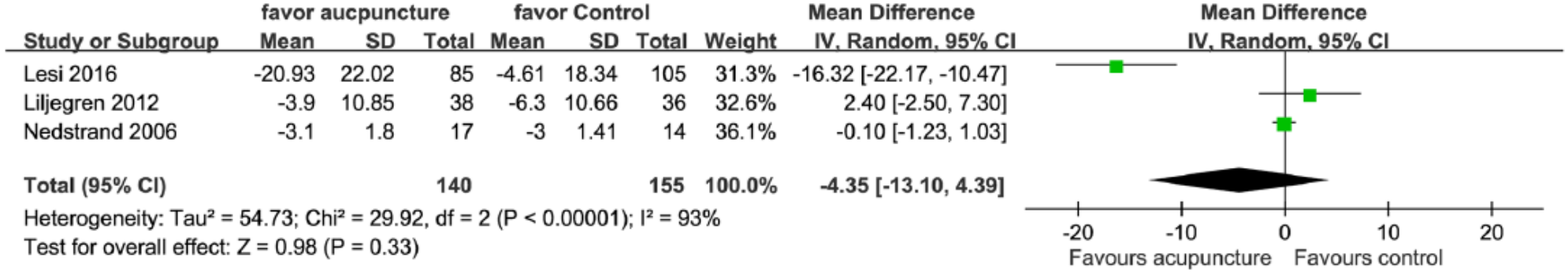


Fig 3. Forest plot of the effect of acupuncture on the severity of hot flush. (visual analog scale).

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

Natural products and proposed pathways of activity

Serotoninergic

- Black cohosh- *Actaea/ Cimicifuga racemosa*
- Valerian- *Valeriana officinalis*

Undefined

Vitamin E
Omega-3 fatty acid
Milk thistle *Chardon Marie*

Megan R. Undeberg Exploratory Research in Clinical and Social Pharmacy 11 (2023) 100324

Estrogenic

- Soy Isoflavones *Glycine* max
- Red clover *Trifolium pratense* Trèfle
- Rhubarb *Rheum rhaponticum*
- Kudzu *Pueraria lobata*
- Guinea-bissau *Eriosema laurentii*
- Hops *Humulus lupulus Houblon*
- Licorice *Glycyrrhiza* sp. Réglisse
- Chasteberry *Vitex agnus-castus*
- Flaxseed *Linum usitatissimum*
- Horny goat weed *Epimedium* sp. Fleur des Elfes
- Maca *Lepidium meyenii* Ginseng andin, péruvien et pavot péruvien
- Evening primrose *Oenothera biennis*
- Alfalfa *Medicago sativa* Luzerne
- Wild yam (topical) *Dioscorea villosa*
- Dong quai *Angelica sinensis*

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		+	+

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
Estetrol ** ‡	Reduction of weekly hot flashes: 66% at 4 weeks; 82% at 12 weeks	Further study needed	Further study needed to establish effective dose and safety

Non-hormonal alternatives for the management of menopausal hot flushes. Postmenopausal women management : CNGOF and GEMVi clinical practice guidelines

- Some selective serotonin reuptake inhibitors (paroxetine, citalopram and escitalopram), serotonin and norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine) gabapentin, pregabalin and clonidine have a statistically effect as compared with placebo in reducing, the frequency and/or severity of HF.
- Some phytoestrogens, such as genistein, may also reduce the frequency of HF.
- Non-pharmacological interventions, hypnosis, acupuncture or yoga have been analyzed with significant beneficial results, even if their evaluation is difficult by the absence of a good placebo group in most trials.
- Other approaches, both pharmacological or non-pharmacological, appear to be ineffective in the management of HT. These include homeopathy, vitamin E, alanine, omega 3, numerous phytoestrogens ,black cohosh, primrose oil, physical activity.
- In women suffering from breast cancer : all phytoestrogens are contraindicated and on the other hand, in patients using tamoxifen, the molecules, that interact with CYP2D6, are to be formally avoided because of potential interaction with this anti-estrogen treatment

B. Raccah-Tebeka, 2021

Non Hormonal Vaginal Approach

- Moisturisers
- Lubricants
- Sexual therapy

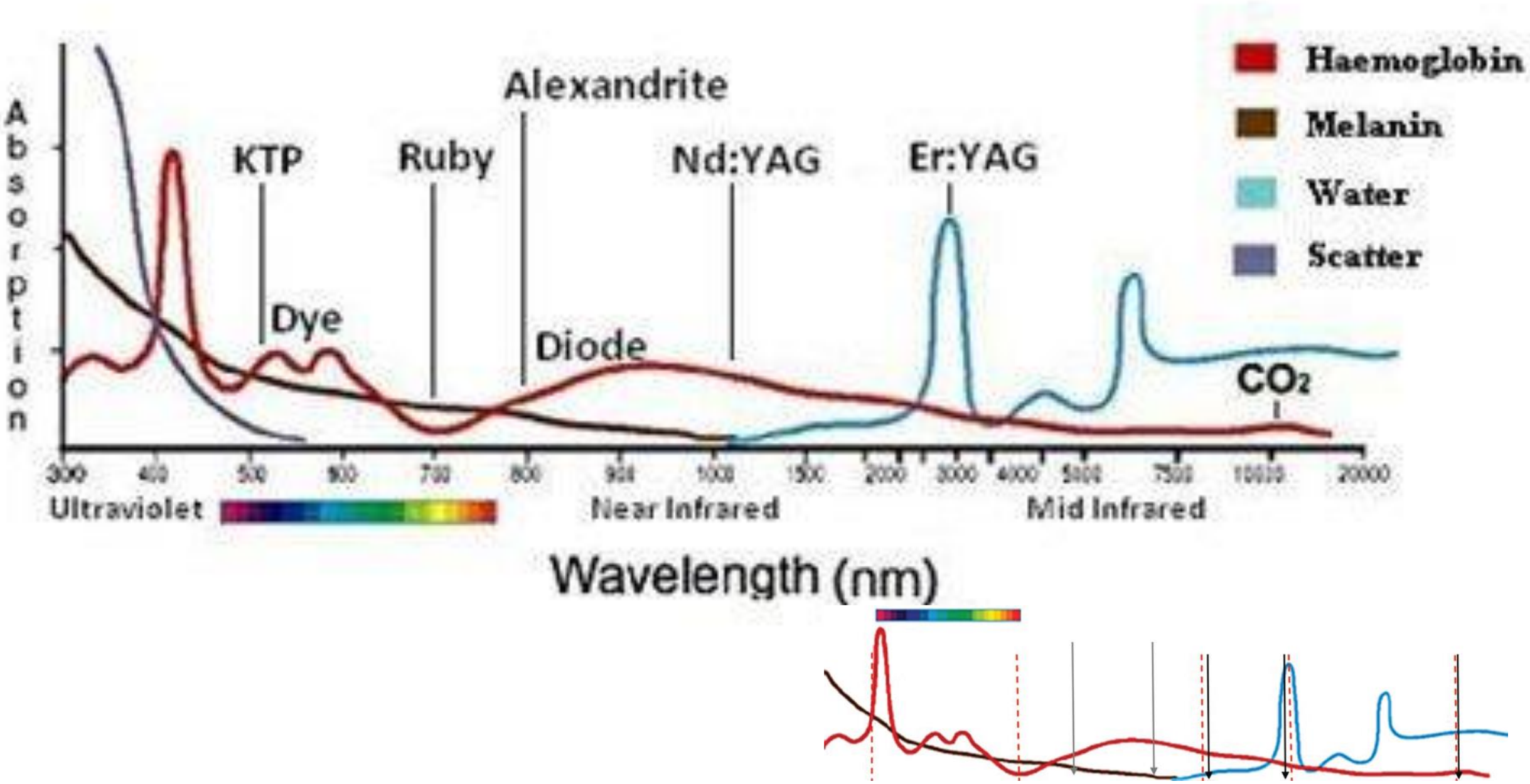
avoid parabens, silicone, perfums , coloring agents, oily preparation

Vaginal laser therapy for gynecologicconditions: re-examining the controversyand where do we go from here

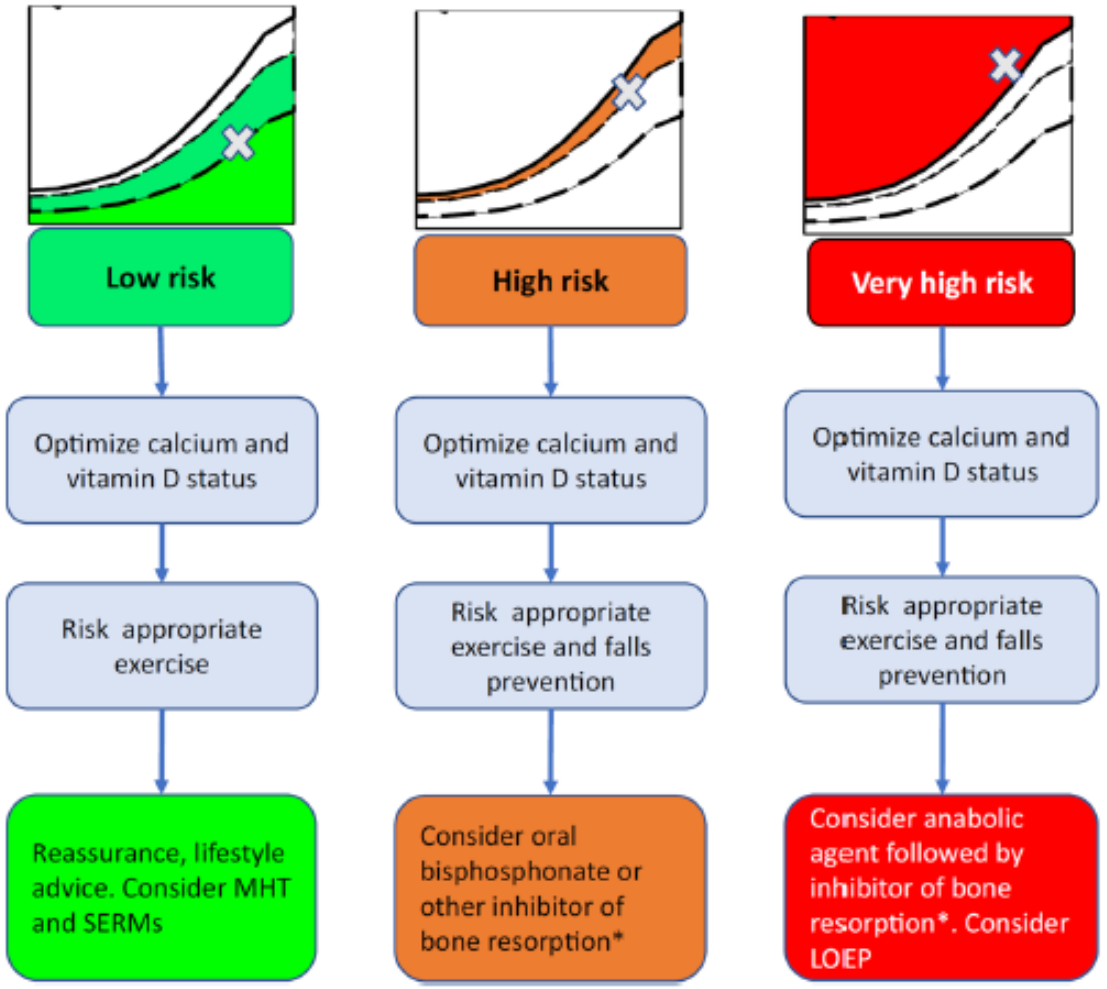
Vaginal laser (light amplification by stimulated emission of radiation) therapy for gynecologic conditions: re-examining the controversy and where do we go from here

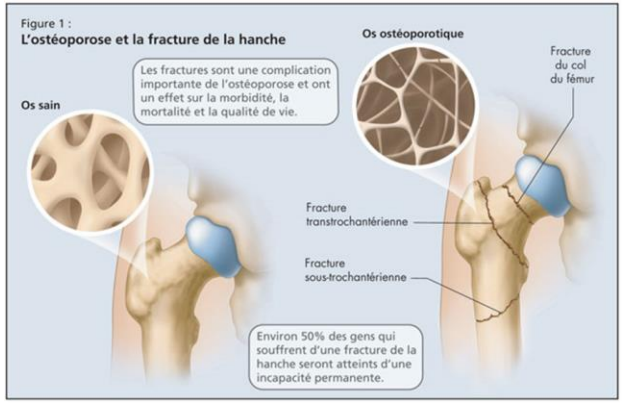
- When considering expert opinions, the peer-reviewed literature and specialty society guidance, one must thoughtfully consider the fact that **not all lasers are the same** and that **their efficacy is not proven in most vaginal conditions**.
- Vaginal lasers are used for treatment of various vaginal 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


Haemoglobin
Melanin
Water
Scatter
Alexandrite
KTP
Ruby
Nd:YAG
Er:YAG
Dye
Diode
CO_2
Absorption
Ultraviolet
Near Infrared
Mid Infrared
Wavelength (nm)

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)

Conclusions

- Tailored approach
- Regular evaluation and treatment adaptation
- Aim : health, comfort et non nocere (avoid drug interactions, automedication)- risk/ benefit balance

Menopause

breaking taboos


Abbott
Marc
L'Hermite
(Belgium)
Mieke
Hendrickx
(Belgium)