

Alternatives to HRT for the Management of Menopausal Symptoms

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Introduction

- In every day, the same conversation takes place in hundreds of doctors' offices between women going through menopause and their doctors.
- Hot flashes - 75% of postmenopausal women (one of the **most distressing symptoms**)
- Treatment - a common **clinical challenge**.
- estrogen pills or patches replace the hormones
- cure hot flashes and slow bone loss.





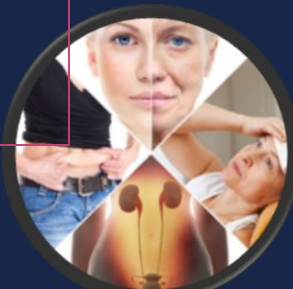
- patient asks **if the pills cause cancer.**
- there is an **increased risk of uterine and breast cancer**
- but argues that the benefits are worth taking the chance
- **Other risks**, such as heart disease, strokes, and blood clots
- **looking for something safe**, something that doesn't cause more problems than it solves.





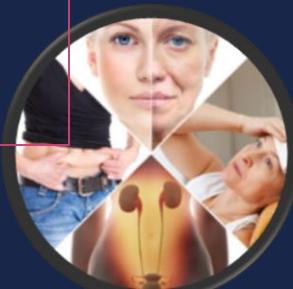
- Given the **potentially negative health consequences** of HRT on cardiovascular health and breast cancer.
- **40% - 50%** of women in Western countries choose to use complementary therapies, including plant-based therapies.

(Vashisht A et al 2001 and Hsu CC et al 2011)



Why

- many patients may be unable or unwilling to undergo hormonal treatment
- Publication of the **results WHI (2002) and MWS** → considerable uncertainties about the role of HRT among health professionals and women.
- HRT for VMS - **limited to the shortest duration.**
- **HRT effectively** reduces vasomotor symptoms by 80-90%,





Premarin

- Premarin is a commonly prescribed estrogen preparation from Wyeth Pharmaceuticals.
- Although it is as “natural” for women, it is actually a **horse estrogen**.
- On farms in the US and Canada, mares are impregnated and then confined from the 4-11 months pregnancy.
- so their urine can be gathered in a collection harness called a “pee bag.”





- After they give birth, the mares are reimpregnated.
- Their urine **estrogens are packed into pills.**
- The trade name “Premarin” (pregnant mares’ urine”) - hardly a natural substance for human beings to swallow.
- While Premarin contains estradiol and estrone, two types of estrogen that are made in humans,
- it also contains an enormous amount of equilin, a horse estrogen that never occurs at all in humans





Studies regarding HRT and long term health risks

- In 2002, WHI → observed an increased risk of breast cancer, potentially deadly blood clots, strokes and heart disease in women taking hormones (compared with those in the placebo group who remained drug free)

(Rossouw JE et al. 2002)

- In 2002, Heart and Estrogen/ Progestin Replacement Study (HERS) – hormones did not reduce the risk of heart problem in postmenopausal women with heart disease.

(Grady D et al. 2002)





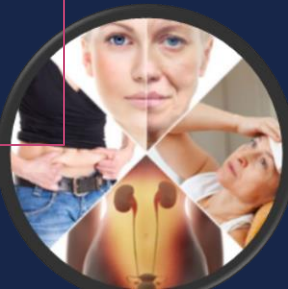
- All of these concerns have generated interest in **non-hormonal treatment** of hot flashes.
- **However, non-hormonal** treatment, readily available for the menopausal patient could become a **therapeutic nightmare** - especially when taken without physician supervision





Alternatives to traditional HRT for menopausal symptoms

- a) Life-style measures
- b) Non-pharmacological alternative for vaginal dryness
- c) Pharmacological alternatives for postmenopausal symptoms
- d) Complementary therapy
- e) Diet and supplement
- f) Homeopathy
- g) Stellate ganglion blockade





LIFE-STYLE MEASURES





- 1. **Environmental manipulation** – to keep core temp as cool as possible

2. **Behavioral changes**- aerobic exercise, avoiding hot flashes triggers, paced respiration, lowering BMI and smoking cessation





- several RCTs found that **aerobic exercise** can result in **significant improvements** in several common menopause-related symptoms relative to non-exercise comparison groups.
- Low intensity exercise (**yoga**) - beneficial in reducing VMS and improving psychological wellbeing in menopausal women.





- **Infrequent** high-impact exercise can actually make symptoms **worse**.
- **best activity** - regular sustained aerobic exercise such as swimming or running.

(Lindh-Astrand et al, 2004).

- Avoidance or reduction of spicy foods, hot drinks, alcohol and caffeine intake can reduce the severity and frequency of VMS

(Greendale GA and Gold EB 2005).



vaginal
dryness?



**Non-pharmacological alternatives
for vaginal dryness**



- in the UK: ReplensMD™ (Anglian Pharma, Overton, Hants) and Sylk (SYLK Ltd, Hemel Hempstead, Herts).
- consist of a combination of protectants and thickening agents in a water-soluble base
- to relieve vaginal dryness during intercourse
- do not provide a long-term solution.
- contain a bioadhesive polycarbophil-based polymer that attaches to mucin and epithelial cells on the vaginal wall and retains water





Oscar et al, 2016

- A systematic review and meta-analysis →
- Analysis of intervention studies evaluating the association of plant based therapies with menopausal symptoms (VMS, Vg dryness and night sweat)
- 62 studies (6653 women) → composite and specific phytoestrogens supplementation was associated with a **modest reduction** in frequency of daily hot flushes and **vaginal dryness** but no significant reduction in night sweat

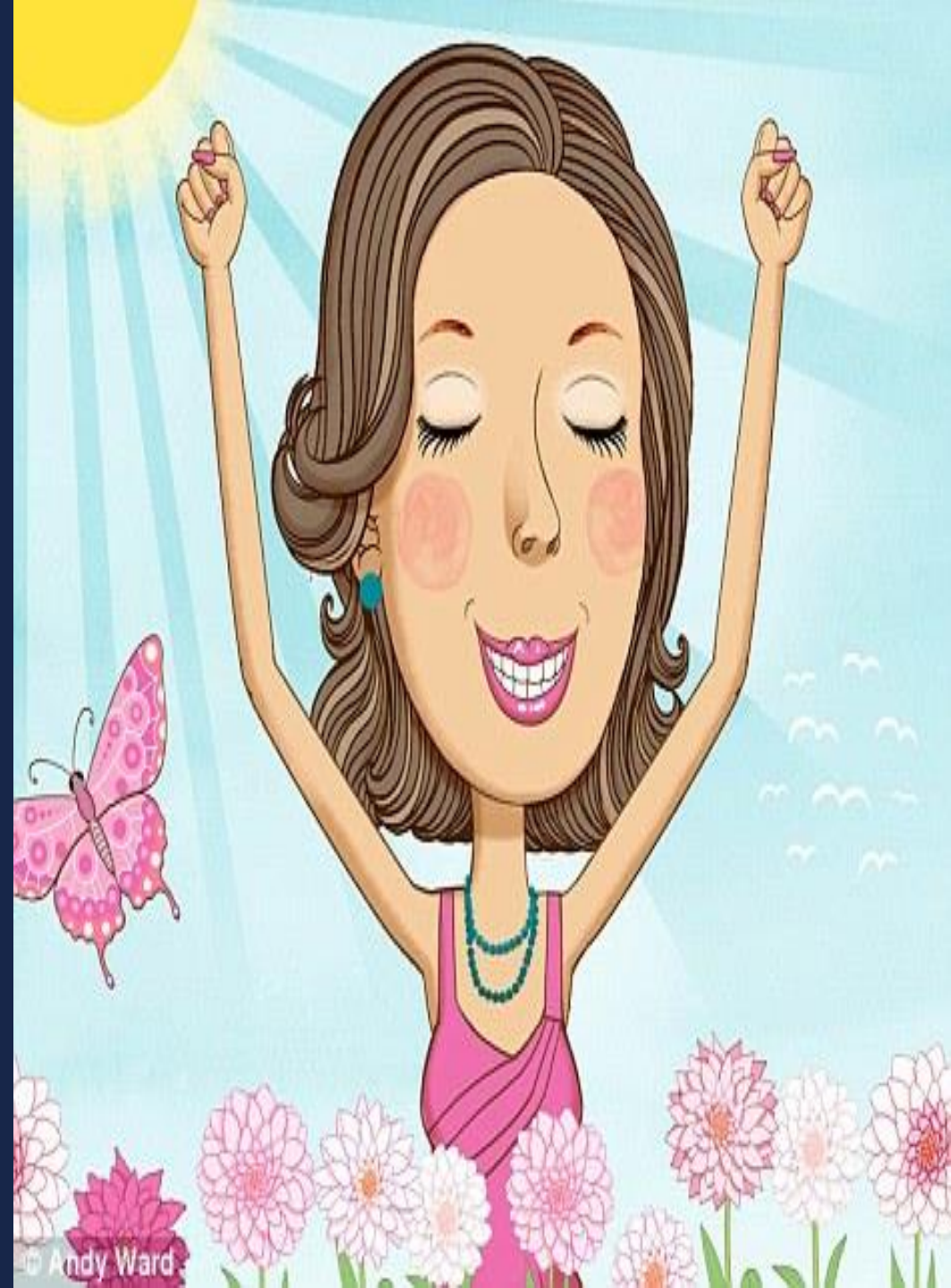




Pharmacological alternatives for postmenopausal symptoms



- a. Progestogens
- b. Alpha-2 agonists
- c. Selective serotonin and noradrenaline reuptake inhibitors
- d. Gabapentin
- e. Dehydroepiandrosterone
- f. Transdermal progesterone creams
- g. Beta-blockers

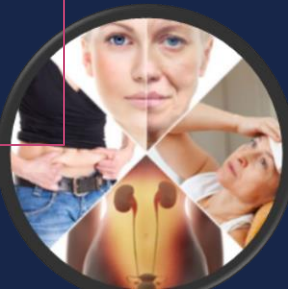




a. Progestogen

- a **popular** alternative to combined HRT in women with intractable VMS
- contraindications to estrogen, such as breast and uterine cancer or VTE
- RCTs shown a benefit for megestrol acetate over placebo for VMS

(Loprinzi et al 1994)





- WHI - **increase in risk of breast cancer** with HRT is due to the combination of estrogen and progestogen (rather than estrogen alone)
- inappropriate - women at risk of breast cancer with progestogens, particularly women with progesterone-receptor-positive tumours.
- Doses of progestogens that achieve VMS control can **increase the risk of VTE.**

(Vasilakis et al, 1999)





b. Alpha-2 agonists

- Clonidine- **most popular** alternative preparations for the treatment of vasomotor symptoms.
- Unfortunately, the trial **data are contradictory** and RCTs - **no evidence for hot flush reduction**

(Wren BG, Brown LB, **1986**)





Other trial using transdermal clonidine did demonstrate efficacy for hot flush reduction.

- It may be that avoiding first-pass metabolism will increase efficacy.

(Wren BG and Brown LB 1994)

- A systematic review and meta-analysis -confirmed a **marginally significant benefit** of clonidine over placebo
- Adverse effects may restrict the use of clonidine for many women.

(Nelson et al, 2006)





c. Selective serotonin and noradrenaline reuptake inhibitors

- One of the most commonly used - as an alternative to HRT.
- SSRIs (fluoxetine and paroxetine) and the SNRI (venlafaxine) at a dosage of 37.5 mg twice daily lasting few weeks- **data were convincing**

(Loprinzi, 2000)

- 9-month placebo-controlled study of citalopram and fluoxetine - no benefit.
- (SE- nausea, reduced libido, sex response)

(Suvanto-Luukkonen, 2005)

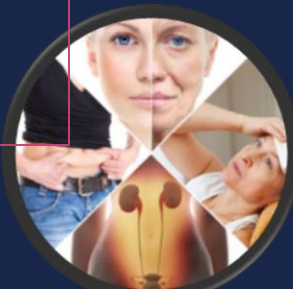




d. Gabapentin

- efficacy for hot flush reduction compared with placebo.
- dosage of 900 mg/day, a 45% reduction in hot flush frequency and a 54% reduction in symptom severity
- the **adverse effect** profile (drowsiness, dizziness, fatigue) **restrict use of Gabapentin**

(Guttuso et al, 2003)





e. Dehydroepiandrosterone (DHEA)

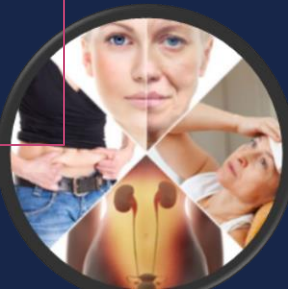
- In USA- supposed as food supplement in **antiaging effects** in postmenopausal women.
- Some studies have shown benefits on the skeleton, cognition, wellbeing, libido and the vagina
- An uncontrolled pilot study showed a **modest reduction** in hot flushes with DHEA
- However, placebo control is necessary to prove efficacy and **further studies are essential.**





f. Transdermal progesterone creams and Beta-blockers

- Transdermal progesterone creams - short-term treatment with topical **wild yam extract** appears to have **little effect** on menopausal symptoms but later study did not .
- Beta-blockers - possible option for treating VMS, but the small trials (**disappointing**).





Complementary therapies

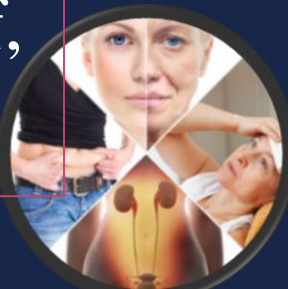




- be safer and more natural alternatives to traditional HRT.
- However, the efficacy and safety of a number of these preparations have not been properly evaluated.

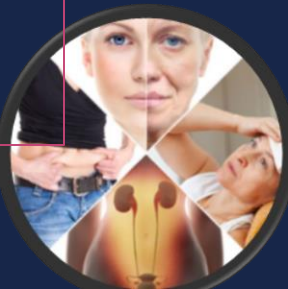
Botanicals

(Phytoestrogens: soy and red clover, Black cohosh, Evening primrose oil, Chinese herbs, Ginseng, St John's wort, Agnus Castus (chasteberry) and other herbs such as Ginkgo biloba, hops, sage leaf, liquorice and valerian root)





- **Other complementary therapies** -
- acupressure, acupuncture, Alexander technique,
- Ayurveda, osteopathy, hypnotherapy,
- reflexology, magnetism and Reiki



Botanicals



- Evidence of clinical trials about **variety of botanical product - limiting and conflicting**
- Studies may use **different products** that are not chemically consistent, making comparison difficult.
- Also, the stability of individual chemicals may vary. Botanicals may contain many chemical compounds whose individual and **combined effects are unknown.**





A major concern

- have pharmacological actions and thus can cause **unwanted effects** and have **potentially dangerous** interactions with other medicines (both herbal and conventional)
- Some are unlicensed
- resulted in cases of poor quality unlicensed herbal remedies on the market (e.g. in some Ayurvedic and Chinese herbal products)
- **substitution of herbs** with other alternatives, sometimes toxic ingredients, leading to contamination or adulteration with **undeclared prescription-**only pharmaceutical ingredients or heavy metals, and mislabelling,





Phytoestrogens: soy and red clover

- have **similar effects to estrogens**. These are **isoflavones** and **lignans**.
- major isoflavones (genistein and daidzein) and major lignans (enterolactone and enterodiol).
- Isoflavones - found in **soybeans, chickpeas** and **red clover**, and probably in other **legumes** (beans and peas).



- **Lignans** - flaxseed, cereal bran, whole cereals, vegetables, legumes and fruit.
- **populations** consuming a diet high in isoflavones, such as the **Japanese** → have lower rates of menopausal VMS, CVS disease, osteoporosis and breast, colon, endometrial and ovarian cancers





Somjen et al, 2005

- RCT- A soy-derived preparation, DT56a → an effect on hot flush reduction in a dose ranging study.
- Clinical and preclinical studies suggested that DT56a has (SERM)-like properties, with **agonistic activity** on the estrogen receptors in the **CNS and bone** and **antagonistic effects** on estrogen receptors in the **breast** and the **uterus**





A systematic review of 30 randomised trials (Lethaby et al, 2007)

- lasting at least **12 weeks** and involving a total of **2730 participants** → assessed efficacy, safety and acceptability of foods and supplements including high levels of phytoestrogens
- (i.e. red clover extracts, dietary soy, soy extracts, other types of phytoestrogens)
- for reducing hot flushes and night sweats in peri- or postmenopausal women





- found **no difference overall** in the frequency of hot flashes between red clover extract and placebo (weighted mean difference -0.57 , 95% CI -1.76 to 0.62).
- **two** with dietary soy, **five** with soy extracts ; and one with the isoflavone genistein **found a reduction** in hot flashes (versus placebo).
- **Other** trials \rightarrow **no difference** between phytoestrogen therapy and placebo or control intervention
- Unwanted effects were not increased with phytoestrogens.
- **Conclusion** \rightarrow there was no evidence that phytoestrogen treatments helped to relieve menopausal symptoms



Powles et al, 2008

- **concerns** about safety in hormone-sensitive tissues such as the breast and uterus
- drug interactions with SERM (tamoxifen) and aromatase inhibitors (letrozole).
- relatively **large study among red clover isoflavone** users → **no effect** was found on breast cancer risk in women with a significant family history





Black cohosh

(*Actaea racemosa*, formerly known as *Cimicifuga racemosa*)



- Herbaceous perennial plant native to North America **used widely** to alleviate menopausal symptoms.
- **no consensus** as to the **mechanism** by which it relieves hot flashes.
- Data only from in vitro or animal models, which cannot necessarily be extrapolated to humans.



- **concerns** about its use in women with hormone-sensitive conditions.
- **RCTs Results** from placebo-controlled trials or comparisons with other agents such as tibolone or estrogen, whether black cohosh is used alone or combined with other botanicals, **are conflicting**
- Little is known about the **long-term safety**
- **Liver toxicity** has been reported





Evening primrose oil

- Rich in gamma-linolenic and linolenic acid.
- Even though it is **widely used** by women, there is no evidence for its **efficacy in the menopause**.
- One small RCT → be **ineffective** for treating hot flushes.

(Chenoy et al 1994)



Chinese herbs (Haines et al, 2008)



- Dong quai (*Angelica sinensis*) - perennial plant native to southwest China
- **not superior to placebo** in a randomised trial, but may be effective when combined with other herbs.
- Interactions with warfarin and **increasing the risk of bleeding and photosensitisation**
- A recent trial has examined the efficacy of another Chinese herb, Danggui Buxue Tang, on a variety of VMS
- Benefit - **only for mild hot flushes.**

Ginseng (Hartley et al, 2004)



- used extensively in eastern Asia.
- Studies → on its effects on quality of life issues in menopausal women.
- **not superior** to placebo for VMS
- associated with **PMB and mastalgia**;
- **interactions** have been observed with warfarin (leading to a reduced INR), phenelzine and alcohol

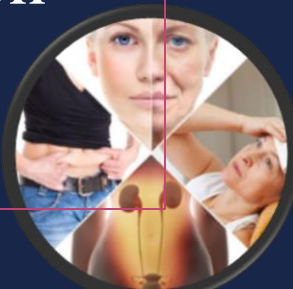


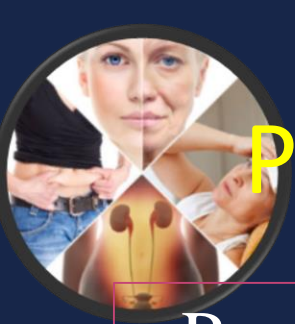


St John's wort (*Hypericum perforatum*)



- SSRI type effect - **efficacious in mild to moderate depression in both peri- and premenopausal women**
- reported improved menopause - specific quality of life and a non-significant improvement in hot flushes.
- **Interactions** with many other medications.
- E.g. it decreases the blood concentrations of cyclosporin, midazolam, tacrolimus, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline

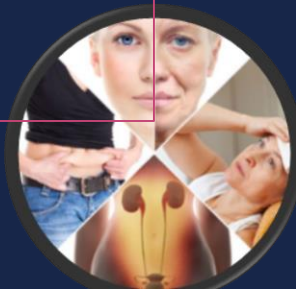




Postmenopausal Depression---



- Proven first line treatment- antidepressant and psychotherapy along with regular exercise for peri- and postmenopausal depression
- Even HRT is not approved for treatment of depression in postmenopausal women
- **Insufficient data** for recommending **any botanical or complementary / alternative approaches** for treating depression





Agnus Castus (chasteberry)



- Limited data
- A combination herbal product → reduced VMS in a randomised controlled trial.
- Further data are required for this preparation.





Other herbs Ginkgo biloba, hops, sage leaf, liquorice and valerian root are popular, but there is **no good evidence** that they have any **effect on menopausal symptoms**



Other complementary therapies

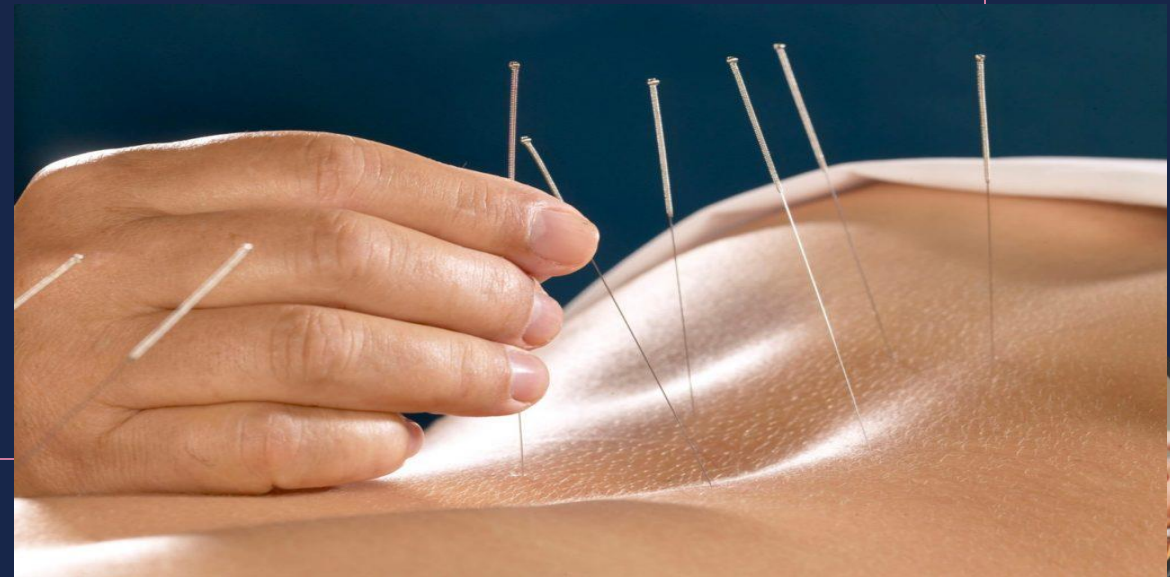
- include acupressure, acupuncture, Alexander technique, Ayurveda, osteopathy, hypnotherapy, reflexology, magnetism and Reiki





Acupuncture

- The evidence is **conflicting**.
- In a recent meta-analysis → **failed to show beneficial effects** of acupuncture over 'placebo' for control of menopausal hot flashes.





Reflexology

(Williamson et al, 2002)

- **aims to relieve stress** or treat health conditions through the application of pressure to specific points or areas of the feet, hands and ears.
- One randomised trial has been published (**67** women aged 45–60 years with VMS reflexology Vs nonspecific foot massage)
- a reduction in symptoms in both groups, but there was **no significant difference between the groups**.





Magnetism

- Magnets are marketed in various forms such as bracelets and insoles.
- **no known mechanism** of action for magnet therapies for the treatment of hot flushes.
- There is **no evidence** of benefit at present.





Diet and supplements

Choosing the Best Sources of Protein during Menopause

The image shows a woman with short blonde hair and a white t-shirt standing next to a wooden table. On the table are several food items: a plate of soy beans, a piece of chicken, a plate of eggs, a plate of beans, and a plate of vegetables (including a cucumber, tomato, and bell pepper). Lines connect the labels to the corresponding food items.

Soy beans

Chicken

Eggs

Veggies

Beans

A small logo in the bottom right corner of the image, featuring a green square with a white silhouette of a woman's profile.



Healthy Calcium

- Calcium –waster → animal protein, sodium, caffeine, tobacco and sedentary lifestyle
- WHO- 800mg per day for postmenopausal woman on a diet low in animal protein
- 30% of Calcium – absorbed, 70%- excreted in faeces
- Most healthy Calcium sources- greens and Bean
- E.g one cup of collard green has 226 mg of Calcium





- Vitamins, such as E and C, and minerals, such as selenium, are present in various supplements.
- **Limited evidence** of any benefit.

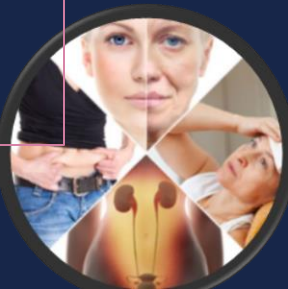




Vitamin E

(Biglia et al, 2009)

- **few trials** about the use of vitamin E
- A statistically significant reduction (but not clinically significant) in hot flush frequency with vitamin E 800 iu/day compared with placebo;





Homeopathy

- The **mechanisms** - unclear.
- Data from case histories, observational studies and a small number of randomised trials are **encouraging**.





Stellate ganglion blockade (Lipov et al, 2008)

- involves local anaesthetic injection into the stellate ganglion,
- as a new technique against hot flushes and sweating refractory to other treatments or where HRT is contraindicated, such as in women with breast cancer.
- Preliminary studies reported encouraging efficacy with minimal complications



Conclusion

- alternative preparations
- their efficacy continues to be **lower than with traditional HRT** (maximally **50–60% symptom reduction** compared with 80–90% with traditional HRT).
- Trials on alternatives → remain small and of short duration
- **Limited value** in determining efficacy and safety.





- Alternatives are **not without their own adverse effects and risks**,
- considerable **doubt and conflict** in the literature regarding the efficacy and safety of soy, red clover and black cohosh;
- more trials are required.
- There are **increasing data for SNRIs** and their metabolites.





- New techniques such as stellate ganglion blockade are showing some promise for refractory VM S.
- Ultimately, it is hoped that some of these products will have sufficiently robust data to be licensed by the Medicines
- providing health professionals and their patients with affordable alternatives to HRT that are safe, efficacious and licensed for the indication.





Caution

- **However, non-hormonal** treatment, readily available for the menopausal patient could become a **therapeutic nightmare** - especially when taken without physician supervision
- Their choice - still remains confusing*



References

- Lindh-Astrand L, Nedstrand E, Wyon Y, Hammar M. Vasomotor symptoms and quality of life in previously sedentary postmenopausal women randomised to physical activity or estrogen therapy. *Maturitas* 2004;48:97–105.
- Greendale GA, Gold EB. Lifestyle factors: are they related to vasomotor symptoms and do they modify the effectiveness or side effects of hormone therapy? *Am J Med* 2005;118 Suppl 12B:148–54.
- Powles TJ, Howell A, Evans DG, McCloskey EV, Ashley S, Greenhalgh R, et al. Red clover isoflavones are safe and well tolerated in women with a family history of breast cancer. *Menopause Int* 2008;14:6–12.
- Hartley DE, Elsabagh S, File SE. Gincosan (a combination of Ginkgo biloba and Panax ginseng): the effects on mood and cognition of 6 and 12 weeks' treatment in post-menopausal women. *Nutr Neurosci* 2004;7:325–33.
- Scientific Impact Paper No. 6 © Royal College of Obstetricians and Gynaecologists

- Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994;331:347–52.
- Vasilakis C, Jick H, del Mar Melero-Montes M. Risk of idiopathic venous thromboembolism in users of progestogens alone. *Lancet* 1999;354:1610–1.
- Lethaby AE, Brown J, Marjoribanks J, Kronenberg F, Roberts H, Eden J. Phytoestrogens for vasomotor menopausal symptoms. *Cochrane Database Syst Rev* 2007;(4):CD001395.
- Somjen D, Katzburg S, Livne E, Yoles I. DT56a (Femarelle) stimulates bone formation in female rats. *BJOG* 2005;112:981–5.
- Wren BG, Brown LB. A double blind trial with clonidine and a placebo to treat hot flushes. *Med J Aus* 1986;144:369–70.
- Chenoy R, Hussain S, Tayob Y, O'Brien PM, Moss MY, Morse PF. Effect of oral gamma-linolenic acid from evening primrose oil on menopausal flushing. *BMJ* 1994;308:501–3.

- Goldberg RM, Loprinzi CL, O'Fallon JR, Veeder MH, Miser MW, Mailliard JA, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol* 1994;12:155–8.
- Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006;295:2057–71.
- Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000;356:2059–63.
- Suvanto-Luukkonen E, Koivunen R, Sundström H, Bloigu R, Karjalainen E, Häivä-Mällinen L, et al. Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study. *Menopause* 2005;12:18–26.
- Guttuso T Jr, Kurlan R, McDermott MP, Kieburz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101:337–45.

- Haines CJ, Lam PM, Chung TK, Cheng KF, Leung PC. A randomized, double-blind, placebocontrolled study of the effect of a Chinese herbal medicine preparation (Dang Gui Buxue Tang) on menopausal symptoms in Hong Kong Chinese women. *Climacteric* 2008;11:244–51.
- Williamson J, White A, Hart A, Ernst E. Randomised controlled trial of reflexology for menopausal symptoms. *BJOG* 2002;109:1050–5.
- Biglia N, Sgandurra P, Peano E, Marengo D, Moggio G, Bounous V, et al. Non-hormonal treatment of hot flushes in breast cancer survivors: gabapentin vs. vitamin E. *Climacteric* 2009;12:310–8.
- Lipov EG, Joshi JR, Sanders S, Wilcox K, Lipov S, Xie H, et al. Effects of stellate-ganglion block on hot flashes and night awakenings in survivors of breast cancer: a pilot study. *Lancet Oncol* 2008;9:523–32.
- Oscar H, Rajiv Chowdhury, Jenna Troup, Trudy Voortman (2016). Use of plant-based Therapies and Menopausal Symptoms; A systematic Review and Meta-analysis, *JAMA*. 315(23):2554-2563



FOR

THANK YOU
YOUR ATTENTION

