Il management diagnostico e terapeutico della donna in menopausa nella pratica clinica

Verona, Sabato 21 Maggio 2016

Le terapie alternative

Barbara Pirali

Humanitas Mater Domini
Castellanza (VARESE)

Preferisco resistere!

Ho paura degli ormoni!

Medical News & Perspectives *JAMA* January, 2016

Can Nonhormonal Treatments Dial Down the Heat During Menopause?

Julie A. Jacob, MA

Obstetrician-gynecologist Ruth Haskins, MD, president-elect of the California Medical Association.

Meno del 10% delle pazienti in cura con TOS

Le donne frequntemente chiedono come ridurre i sintomi menopausali ma non vogliono assumere terapia ormonale

Posadzki P, Lee MS, Moon TW, Choi TY, Park TY, Ernst E. Prevalence of complementary and alternative medicine (CAM) use by menopausal women: a systematic review of surveys.

Maturitas. 2013 May;75(1):34-43

Una revisione di **26 studi epidemiologici** sull'uso delle CAM in menopausa pubblicati dal 2000 al 2012, con dati riguardanti **32.465 donne** di Australia, Canada, Danimarca, Norvegia, Italia, Spagna, Corea del Sud e Stati Uniti ha mostrato che:

> 50% delle donne in menopausa

ha utilizzato specificamente CAM per i disturbi menopausali

La conclusione degli autori è che l'uso delle CAM in menopausa è elevato

Le ragioni che spingono le donne a rivolgersi alla CAM in menopausa sono varie ma soprattutto il timore degli effetti collaterali della TOS.

Problema: la maggiorparte delle donne non effettua un consulto medico, i rimedi più popolari sono quelli a base di erbe e fitoestrogeni

Alternative alla TOS…

Farmaci

- Antidepressivi
- Antiepilettici
- Agonisti Alfa-adrenergici

Altro

- Fitoestrogeni
- Erbe
- Agopuntura
- Ipnosi
- Esercizio fisico
- Tecniche cognitivo comportamentali
- Omega-3,Vitamina E
- Blocco del ganglio stellato

Menopause. 2013 :1027-35.
Low-dose Paroxetine (SSRI) 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials.
Simon JA, Portman DJ, Kaunitz AM, Mekonnen H, Kazempour K, Bhaskar S, Lippman J.

591 trattati con paroxetina 7.5 mg
593 con placebo

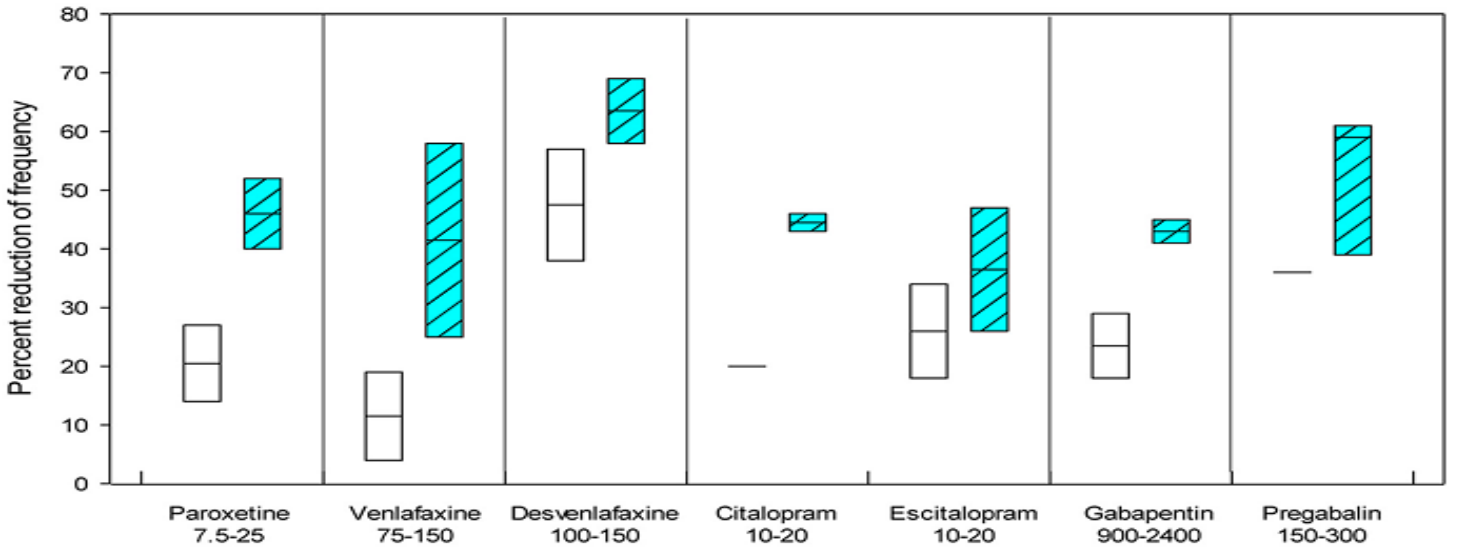
CONCLUSIONI: Paroxetina 7.5 mg è efficace nel ridurre sia la frequenza che la severità dei sintomi vasomotori della menopausa

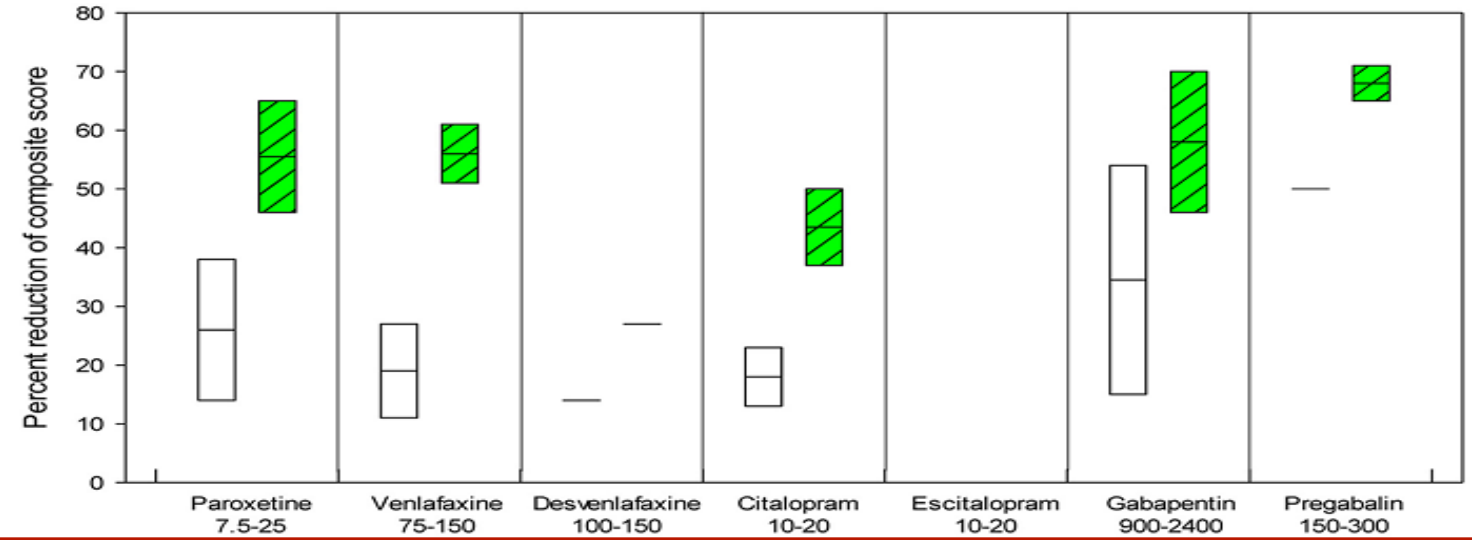
Efficace in tutta la durata del follow-up: 24 settimane

Nel 2013 la FDA ha approvato il primo trattamento non-ormonale (Paroxetina) per trattare i sintomi vasomotori in menopausa

Antidepressant (SSRI and SNRI) and Antiepilectics drugs

Hot flash frequency and composite score for relief of VMS





Hot Flash frequencies

< 25-69%

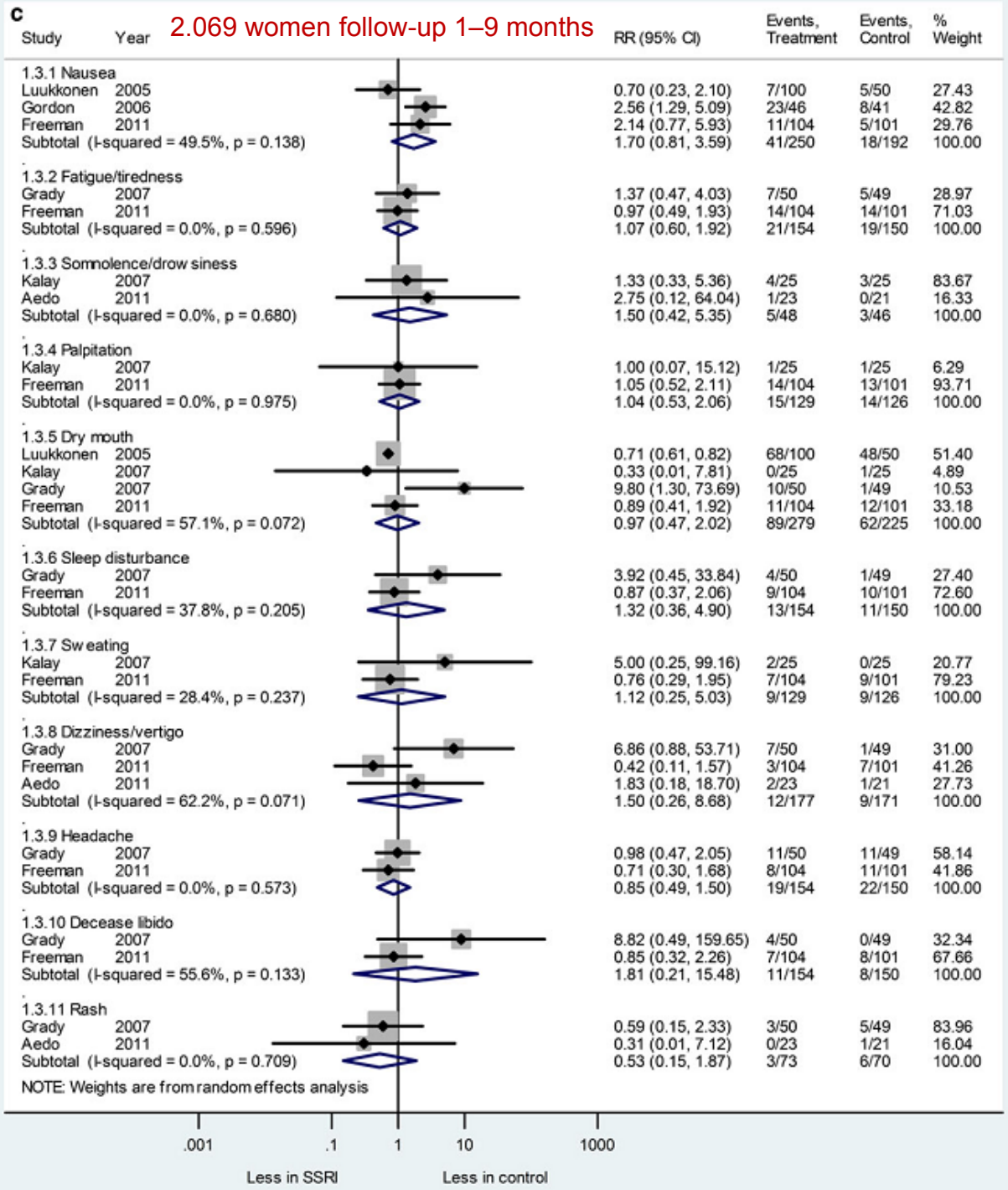
Hot Flash score

< 27-61%

Stuenkel et al Guideline on Menopause J Clin Endocrinol Metab 2015

SSRI-SNRI	mg/die in menopausa	Nome commerciale
Paroxetina Antidepressivo SSRI	**7.5-25**	Sereupin, Seroxat, Eutimil, Daparox
Venlafaxina Antidepressivo SNRI	**75-150**	Efexor,Faxine,Venlafax
Citalopram Antidepressivo SSRI	**10-20**	Seropram, Elopram,
Escitalopram Antidepressivo SSRI	**10-20**	Entact, Cipralex
Gabapentina Anti epilettico	**300-1200**	Neurontin
Pregabalina Anti epilettico	**150-300**	Lyrica

Off-label



SSRI
Eventi avversi

Nausea
(RR 1.7; CI 0.81 to 3.59),

Astenia
(RR 1.07; CI 0.60 to 1.92),

Sonnolenza
(RR 1.50; CI 0.42 to 5.35),

Palpitazioni
(RR 1.04;CI 0.53 to 2.06),

Secchezza delle fauci
(RR 1.29; CI 0.69 to 2.40),

Disturbi del sonno
(RR 1.32; CI 0.36 to 4.90),

Sudorazione
(RR 1.12; CI 0.25 to 5.03),

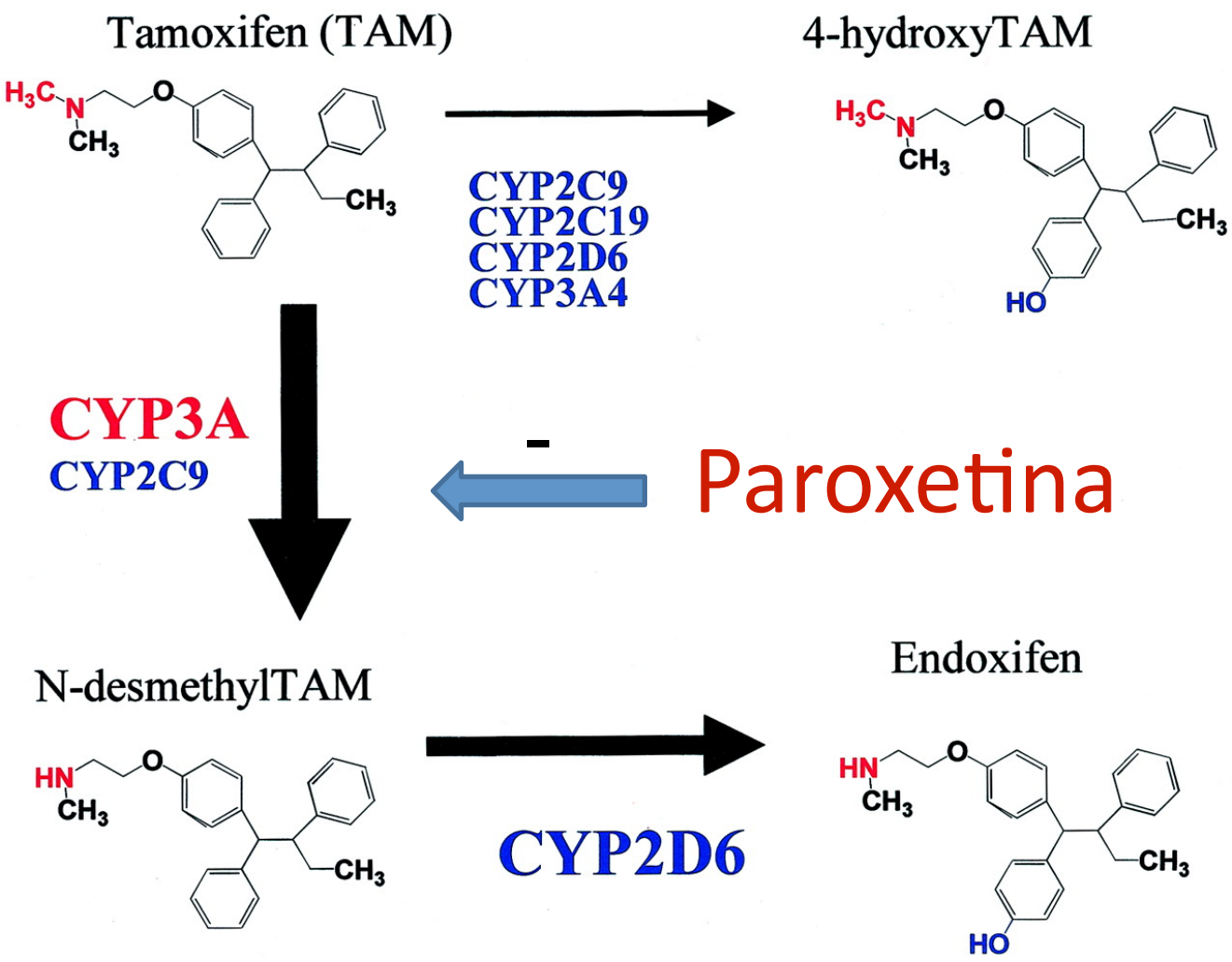
Vertigini
(RR 1.5; CI 0.26 to 8.68),

Cefalea
(RR 0.85; CI 0.49 to 1.5),

Riduzione libido
RR 1.81; CI 0.21 to 15.48)

Rash
(RR0.53; CI 0.15 to 1.87).

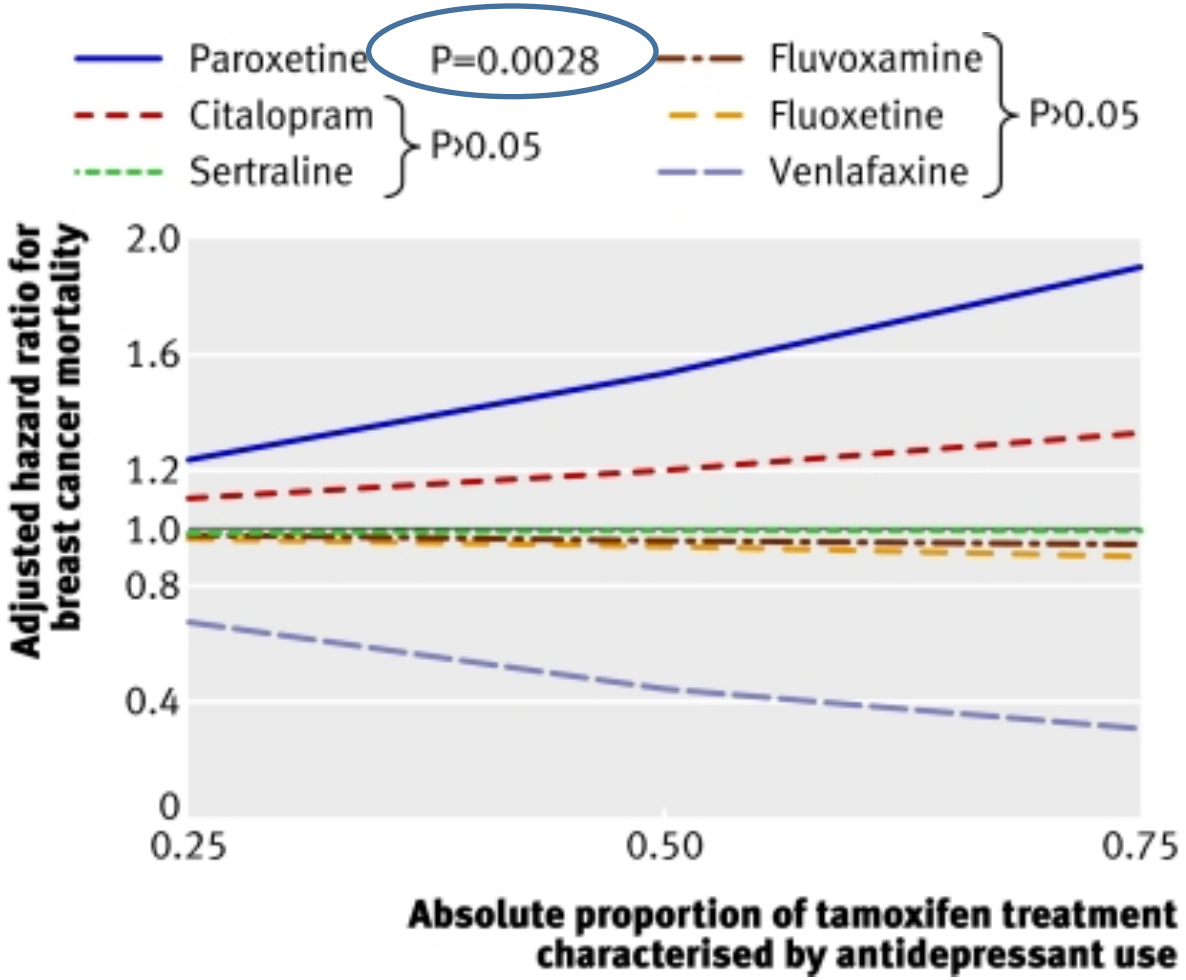
Shams et al.: SSRIs for Hot Flashes 2013
J Gen Intern Med 29(1):204–13



Paroxetine reduce tamoxifen's effectiveness by inhibiting its bioactivation by cytochrome P450 2D6 (CYP2D6)

Vered Stearns et al. JNCI J Natl Cancer Inst 2003;95:1758-1764

Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study



Donne trattate con tamoxifene + antidepressivi

Aumento della mortalità per k mammella in donne in terapia con paroxetina

Kelly CM et al *BMJ* 2010;340:c693

Clonidina

α-2 adrenergic-agonist

Dosi orali (0.1 mg/die) o transdermiche (1 mg/settimana) riducono in modo significativo (< 30-50%) gli episodi vasomotori.

Gli effetti collaterali
(xerostomia, insonnia, depressione)
ne limitano l'impiego

Da considerare in donne affette da ipertensione arteriosa

Pandya KJ et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. Ann Intern Med 2000,132:788-93.

Goldberg RM et al. Transdermal clonidine for ameliorating tamoxifen induced hot flashes. J Clin Oncol 1994;12:155– 158.

Nelson HD et al. Non hormonal therapies for menopausal hot flashes: Systematic review and meta-analysis. JAMA 2006; 295:2057–2071.

Rada G, Capurro D, Pantoja T, et al. Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev. 2010;9:CD004923.

Clinical Practice Guideline

Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline

2015

Cynthia A. Stuenkel, Susan R. Davis, Anne Gompel, Mary Ann Lumsden, M. Hassan Murad, JoAnn V. Pinkerton, and Richard J. Santen

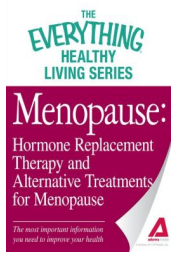
Nonhormonal prescription therapies for VMS

For women seeking pharmacological management for moderate to severe VMS for whom MHT is contraindicated, or who choose not to take MHT, we recommend

selective serotonin reuptake inhibitors (SSRIs)/serotonin or epinephrine reuptake inhibitors (SNRIs) or gabapentin or pregabalin (if there are no contraindications). (1⊗⊗⊗◯)

For those women seeking relief of moderate to severe VMS who are not responding to or tolerating the nonhormonal prescription therapies, SSRIs/SNRIs or gabapentin or pregabalin, we suggest a trial of **clonidine** (if there are no contraindications). (2⊗⊗◯◯)

Terapie Alternative



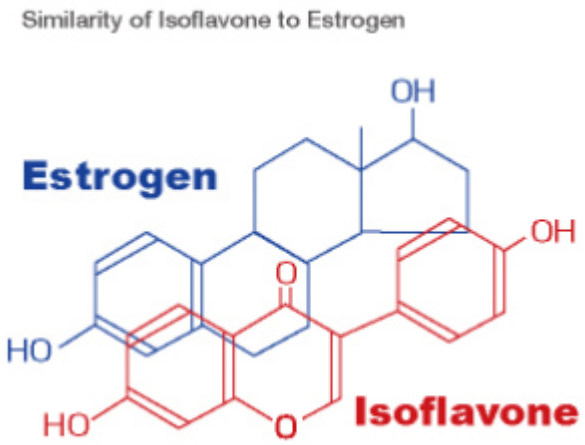
STUDY PROTOCOL Open Access

Hypnosis for hot flashes among postmenopausal women study: A study protocol of an ongoing randomized clinical trial

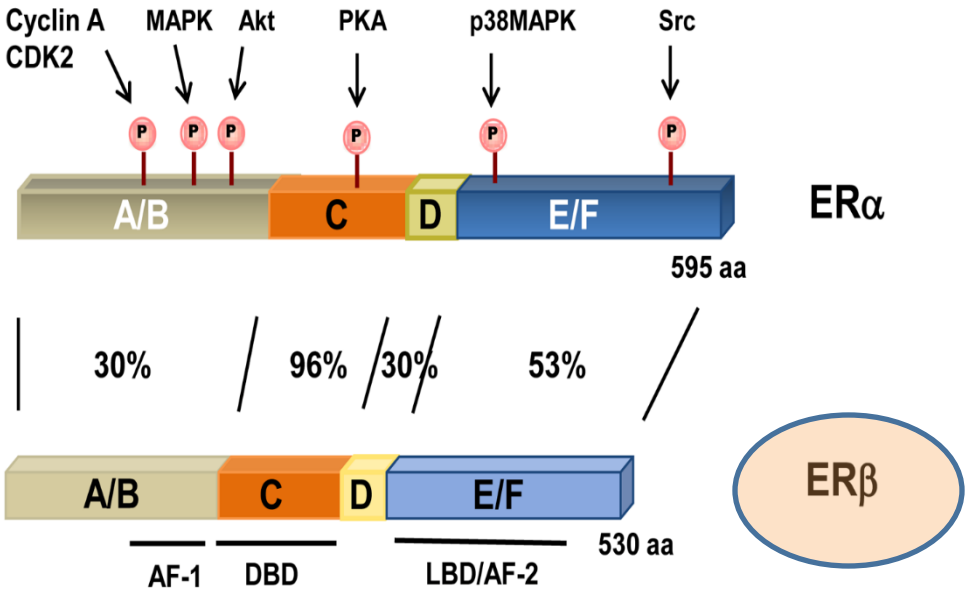
Gary R Elkins*, William I Fisher and Aimee K Johnson

OMEGA 3

Fitoestrogeni:



1. **Altà affinità per recettore beta**
2. **Possiedono attività sia estrogeniche che anti estrogeniche**
3. **Assorbiti dopo essere stati idrolizzati dai batteri intestinali**



Fitoestrogeni:

Isoflavoni →
- Genisteina
- Daidzeina
- Glycetina
- Formomonetina
- Biochanina A

→
- Soia
- Trifoglio rosso (Red clover)

Lignani →
- Enterodiolo
- Enterolactone
- Secoisolariciresinol(SECO)
- Matairesinolo (MAT)

→
- Semi di lino
- Grani
- Bacche

Cumestrani →
- Coumestrolo

→
- Germogli di soia

Menopause: The Journal of The North American Menopause Society
Vol. 18, No. 7, pp. 732-753
DOI: 10.1097/gme.0b013e31821fc8e0

NAMS 2011 Isoflavones Report

The role of soy isoflavones in menopausal health: report of The North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010)

Combined statistics of the 14 trials:

- Total number of women in the trials was 1,422 (761 in the isoflavone arms and 661 in the placebo arms).
- Dose of isoflavones ranged from 40 to 160 mg/day.
- Mean age was 53.
- Duration of trials ranged from 12 to 96 weeks.
- Majority of women were Caucasian and within 5 years of their final menstrual period.
- Daily prevalence of hot flashes at baseline ranged from 3 to 11 episodes.

Dosaggi di 50-60 mg/die
Riducono i sintomi
Nel 24%- 60% dei casi

Combined results of the 14 trials:

- A total of 11 showed significant improvement of vasomotor symptoms in the isoflavone arms compared to placebo, while three trials failed to show any benefit.
- The percentage of decrease in daily frequency of hot flashes ranged from 24% to 60%.
- The dose of 50 to 60 mg/day was sufficient for significant symptom improvement over placebo in many of the studies.
- Although some studies using higher doses of soy isoflavones also reported significant benefit, no linear dose-response relationship was observed.
- It appeared that women who benefitted from isoflavones experienced at least four episodes per day at baseline, which generally agrees with previously published data.[96]
- Women experiencing more than the four daily hot flashes did not necessarily show greater improvement over placebo.
- Trial duration of 12 weeks was sufficient to see a benefit in the isoflavone group over placebo; trials of longer duration did not necessarily result in a greater improvement in symptoms.

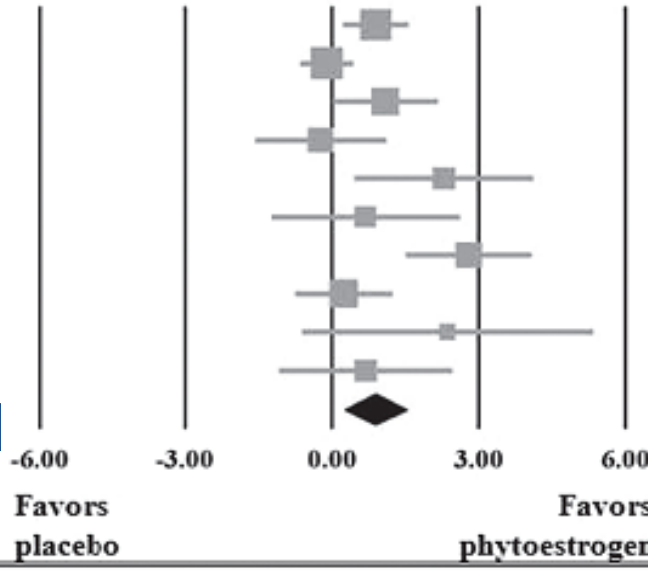
CLIMACTERIC 2015;18:260–269

Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review

(a)

M-N. Chen, C-C. Lin* and C-F. Liu†

Study name	Sample size	Mean difference (95%CI)	P-value	Forest plot for mean difference (95% CI)	Relative weight
Aso T (2012)	60 vs. 66	0.90 (0.24, 1.56)	0.008		14.88
Atkinson C (2004)	103 vs. 102	-0.10 (-0.64, 0.44)	0.714		15.79
Ferrari A (2009)	94 vs. 82	1.10 (0.03, 2.17)	0.044		11.77
Lewis JE (2006)	33 vs. 33	-0.22 (-1.55, 1.11)	0.746		9.92
Nahas EA (2007)	38 vs. 38	2.30 (0.47, 4.13)	0.014		7.14
Penotti M (2003)	34 vs. 28	0.70 (-1.22, 2.62)	0.474		6.72
Petri Nahas E (2004)	25 vs. 26	2.80 (1.53, 4.07)	0.000		10.34
Tice JA (2003)	85 vs. 167	0.25 (-0.74, 1.24)	0.620		12.39
van de Weijer PH (2002)	14 vs. 16	2.37 (-0.60, 5.34)	0.118		3.59
Van Patten CL (2002)	64 vs. 59	0.70 (-1.06, 2.46)	0.435		7.46
Pooled mean difference in random model		0.89 (0.26, 1.52)	<0.005		



Metanalisi di 10 studi

Conclusioni: Fitoestrogeni sembrano ridurre la frequenza di sintomi vasomotori nelle donne in menopausa

Maturitas 78 (2014) 79–81

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Editorial

Phytoestrogens for menopausal vasomotor symptoms: A Cochrane review summary

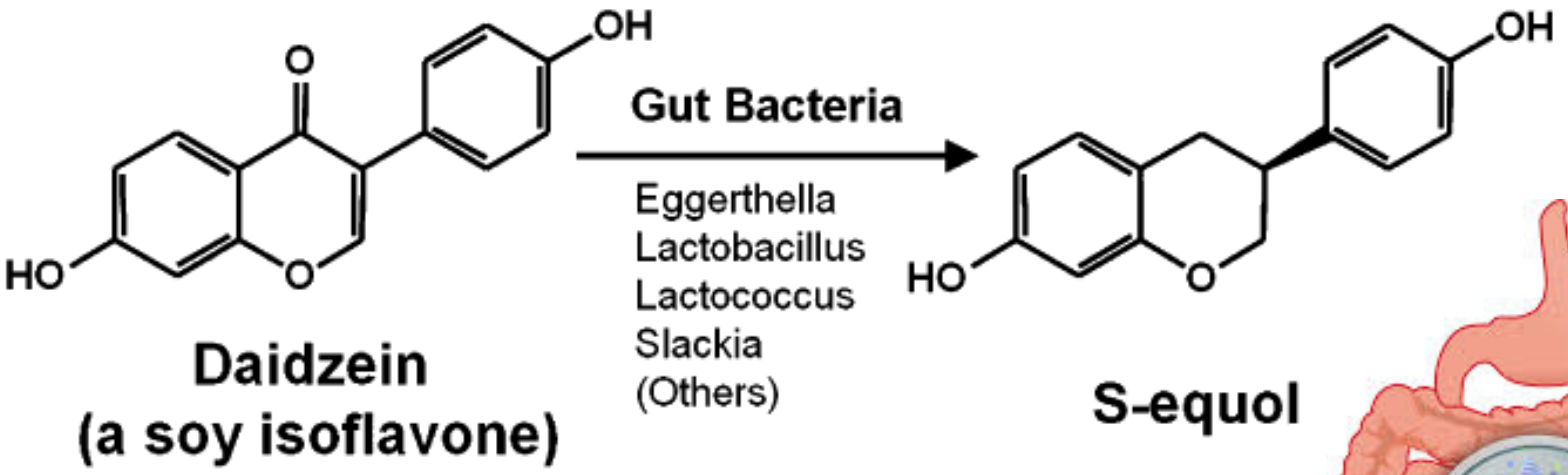
43 randomised controlled trials (4.364 partecipants)

Non è stato evidenziato un sicuro beneficio nei sintomi vasomotori della menopausa

Eccezione: prodotti che contenevano almeno 30 mg di Genisteina (< 30%-50% vs placebo, valutati per 2 anni in 4 studi)

LIMITI: composizione dei prodotti non controllata ed estremamente varia nei componenti, popolazioni studiate non ben definite.

Daidzeina metabolizzata a Equolo



Capacità di produrre Equolo

28.2% in Europa

27.6% in USA

31.3% in Australia

50% - 60% in Asia

Occorrono ulteriori studi!

Erbe

Box 2
Botanicals recommended for menopause: supposed mechanism of action

Hormone mediators/modulators

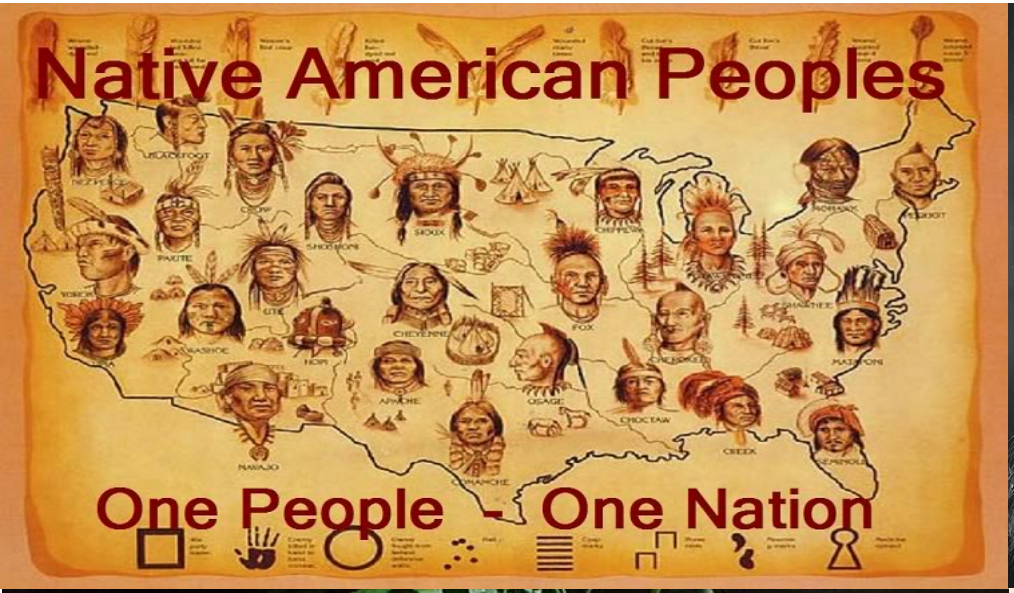
- Alfalfa (*Medicago sativa*)
- Black cohosh (*Actaea racemosa*)
- Chaste berry (*Vitex agnus-castus*)
- Aniseed, dill, fennel, fenugreek (all members of the dill family)
- Dong quai (*Angelica sinensis*)
- Evening primrose oil (*Oenothera biennis*)
- Flaxseed (*Linum usitatissimum*)
- Gotu kola (*Centella asiatica*)
- Green tea (Camellia sinensis)
- Hops (*Humulus lupulus*)
- Kudzu (*Pueraria lobata*)
- Licorice (*Glycyrrhiza glabra*) (also mineralocorticoid activity)
- Maca (*lepidium peruvianum*)
- Milk thistle (*Silybum marianum*)
- Red clover (*Trifolium pratense*)
- Rhubarb (*Rheum rhaponticum*)
- Sarsaparilla (*Smilax regelii*)
- Sage (*Salvia officinalis*)
- Soy (*Glycine max*) and its derivatives daidzein, genistein, S-equol, and other isoflavones
- Wild yam (*Dioscorea villosa*)

Central/neurotransmitter mediators

- Ginkgo (*Ginkgo biloba*)
- Kava kava (*Piper methysticum*)
- *Panax ginseng* (also said to be estrogenic)
- St. John's wort (*Hypericum perforatum*)
- Valerian (*Valeriana officinalis*)

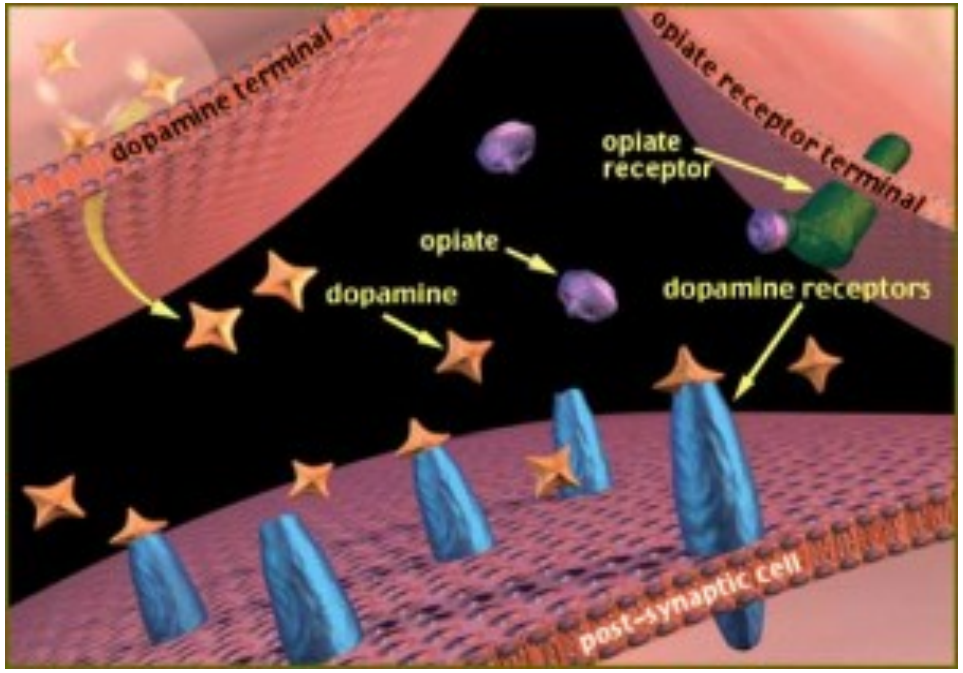
Black Cohosh (Actaea racemosa)

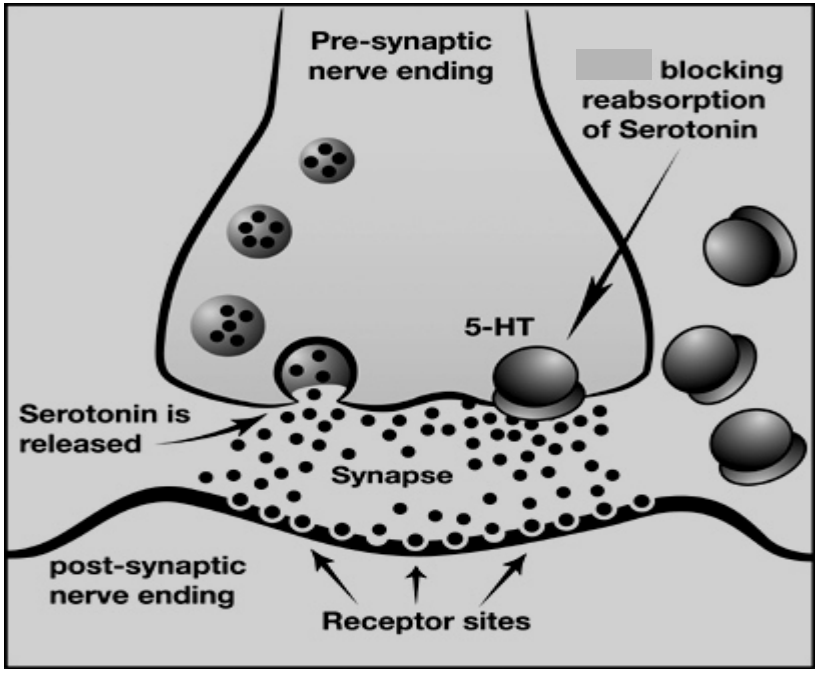
(ex Cimicifuga racemosa)



Black Cohosh (Actaea racemosa)

(ex Cimicifuga racemosa)





Azione mediata da
recettori della serotonina e dopamina

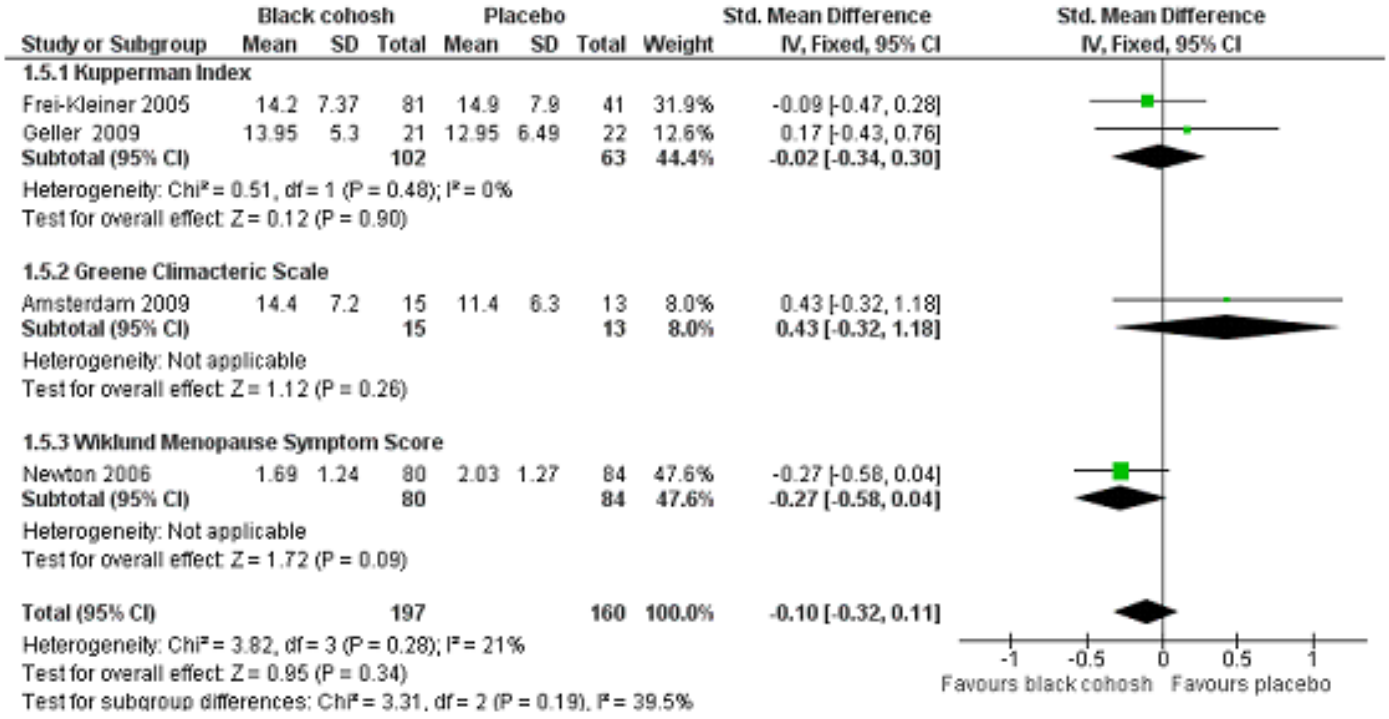
Black cohosh (*Cimicifuga* spp.) for menopausal symp (Review)

Leach MJ, Moore V

2012

THE COCHRANE COLLABORATION®

Figure 5. Forest plot of comparison: 1 Black cohosh versus placebo, outcome: 1.5 Menopausal Symptom Score.



16 trials randomizzati, 2027 donne in menopausa

Preparato orale di black cohosh ad un dosaggio medio di 40 mg
Follow up: 24 settimane

Al momento evidenze di efficacia non sufficienti, necessità di condurre altri studi

Agopuntura

Acupuncture for vasomotor menopausal symptoms: a systematic review

SH Cho and WW Whang. Review published: **2009**.

A systematic review, including 11 randomised controlled trials with a total of 764 patients

Authors' conclusions

None found a significant difference between groups.

There was no consistent evidence that acupuncture was effective for treating menopausal vasomotor symptoms compared to sham acupuncture or hormone therapy; further research was required.

Acupuncture for menopausal hot flushes

Dodin S. et. al. Cochrane Database Syst Rev. **2013**

Sixteen studies, with 1155 women, were eligible for inclusion.

Authors' conclusions

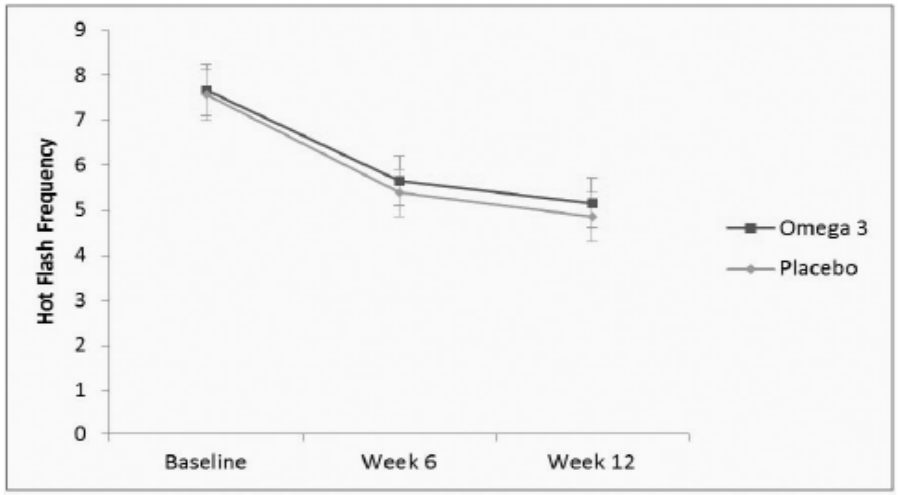
No significant difference was found between the groups for hot flush frequency but flushes were significantly less severe in the acupuncture group.

Omega-3

Published in final edited form as:
Menopause. 2014 April ; 21(4): 347–354. doi:10.1097/GME.0b013e31829e40b8.

Efficacy of Omega-3 Treatment for Vasomotor Symptoms: A Randomized Controlled Trial:

Omega-3 treatment for vasomotor symptoms



Each capsule contained:
ethyleicosapentaenoic acid (EPA 425 mg) docosahexaenoic acid (DHA 100 mg) and other Omega-3s (90mg).

Figure 2.
Hot flash frequency over time by omega-3 assignment [1]
1. Mean difference in number of hot flashes/day from baseline to week 12; Baseline = 0.1 (−0.7,0.9); Week 6-baseline = 0.2 (−0.5, 0.9); Week 12-baseline =0.3 (−0.5, 1.0)

Exercise for menopausal Symptoms

Cochrane Library

Trusted evidence.
Informed decisions.
Better health.

Cochrane Database Syst Rev. 2014 Nov
Exercise for vasomotor menopausal symptoms.
Daley A et al. University of Birmingham, England, UK.

5 RCTs (733 donne)

Published in final edited form as:
Menopause. 2014 April ; 21(4): 330–338. doi:10.1097/GME.0b013e31829e4089.

Efficacy of Exercise for Menopausal Symptoms: A Randomized Controlled Trial

Barbara Sternfeld, PhD[1], Katherine A. Guthrie, PhD[2], Kristine E. Ensrud, MD, MPH[3], Andrea Z. LaCroix, PhD[2], Joseph C. Larson, MS[2], Andrea L. Dunn, PhD[4], Garnet L. Anderson, PhD[2], Rebecca A. Seguin, PhD[5], Janet S. Carpenter, PhD, RN, FAAN[6], Katherine M. Newton, PhD[7], Susan D. Reed, MD, MPH[8], Ellen W. Freeman, PhD[9], Lee S. Cohen, MD[10], Hadine Joffe, MD, MSc[10], Melanie Roberts, MS[11], and Bette J. Caan, DrPH[1]

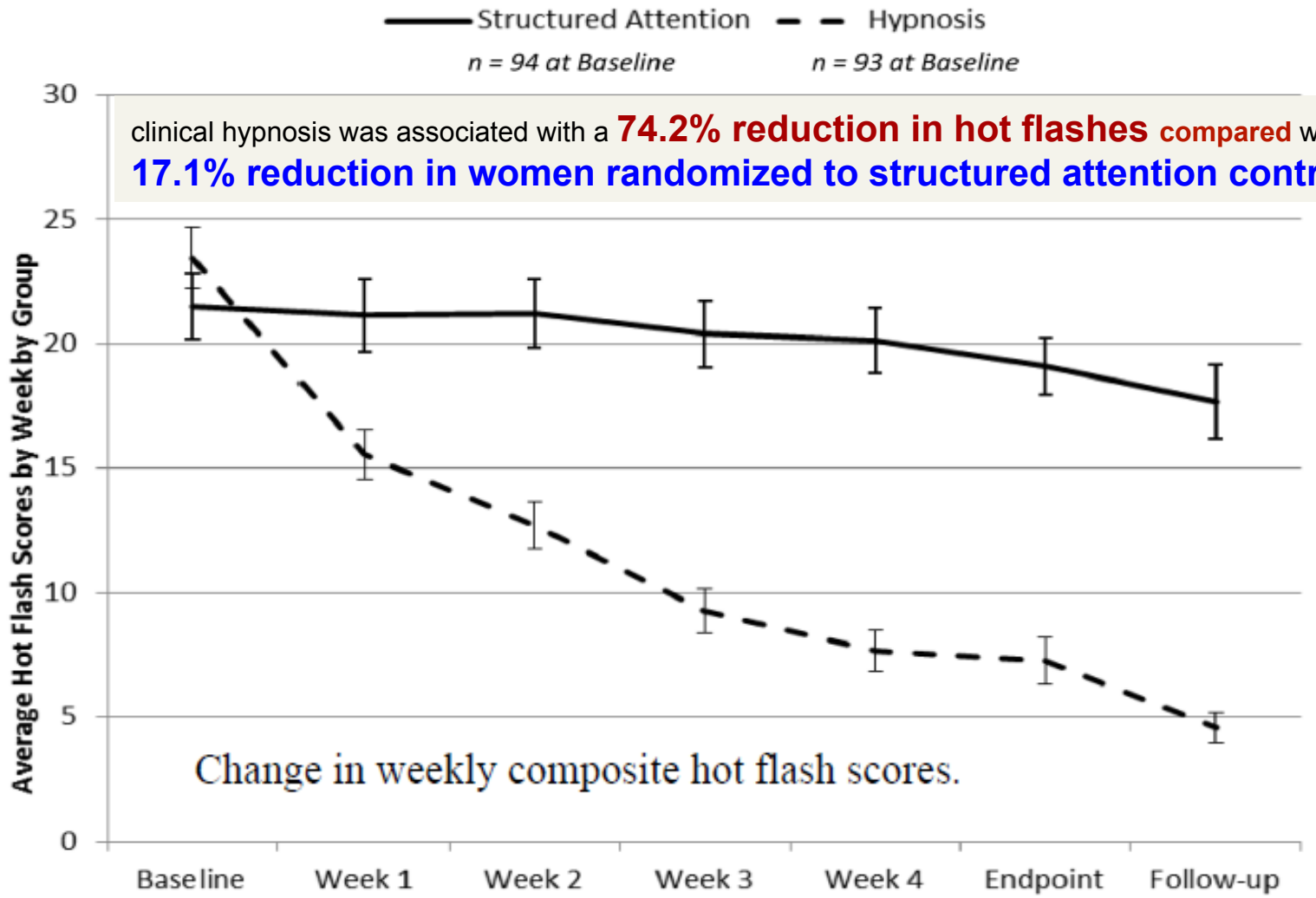
METHODS—Late-peri and post-menopausal, sedentary women with frequent vasomotor symptoms (VMS) participated in a randomized controlled trial conducted at three sites: 106 to exercise and 142 to usual activity. The exercise intervention consisted of individual, facility-based aerobic exercise training 3 times/week for 12 weeks. VMS frequency and bother were recorded on daily diaries at baseline and weeks 6 and 12. Intent to treat analyses compared between group differences in changes in VMS frequency and bother, sleep symptoms (Insomnia Severity Index, Pittsburgh Sleep Quality Index) and mood (Patient Health Questionnaire-8 and Generalized Anxiety Disorder-7 questionnaire).

RESULTS—At the end of week 12, changes in VMS frequency in the exercise group (mean change of −2.4/day, 95% CI −3.0, −1.7) and VMS bother (mean change of −0.5 on a 4 point scale, 95% CI −0.6, −0.4) were not significantly different from those in the control group (−2.6 VMS/day, 95% CI −3.2, −2.0, p=0.43; −0.5 points, 95% CI −0.6, −0.4, p=0.75). The exercise group reported greater improvement in insomnia symptoms (p=0.03), subjective sleep quality (p=0.01), and depressive symptoms (p=0.04), but differences were small and not statistically significant when p values were adjusted for multiple comparisons. Results were similar when considering treatment-adherent women only.

CONCLUSION—These findings provide strong evidence that 12-weeks of moderate-intensity aerobic exercise does not alleviate VMS but may result in small improvements in sleep quality, insomnia and depression in midlife, sedentary women.

Clinical Hypnosis in the Treatment of Post-Menopausal Hot Flashes: A Randomized Controlled Trial

187 donne con almeno 7 episodi al giorno



Elkins et al.
Texas

Menopause. 2013 March ; 20(3):

Terapia cognitivo comportamentale

Alcuni trials clinici randomizzati e in doppio cieco hanno dimostrato che i trattamenti cognitivo-comportamentali, che associno **tecniche di rilassamento, igiene del sonno e l'imparare ad assumere un atteggiamento positivo e salutare nei confronti dei disturbi della menopausa**, **sono molto efficaci nel ridurre la percezione negativa delle donne nei confronti delle vampate**, anche se non il loro numero.

Cognitive behavioral therapy (CBT) is an effective treatment for bothersome VMS for both breast cancer survivors and menopausal women.

POSITION STATEMENT

Non hormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society

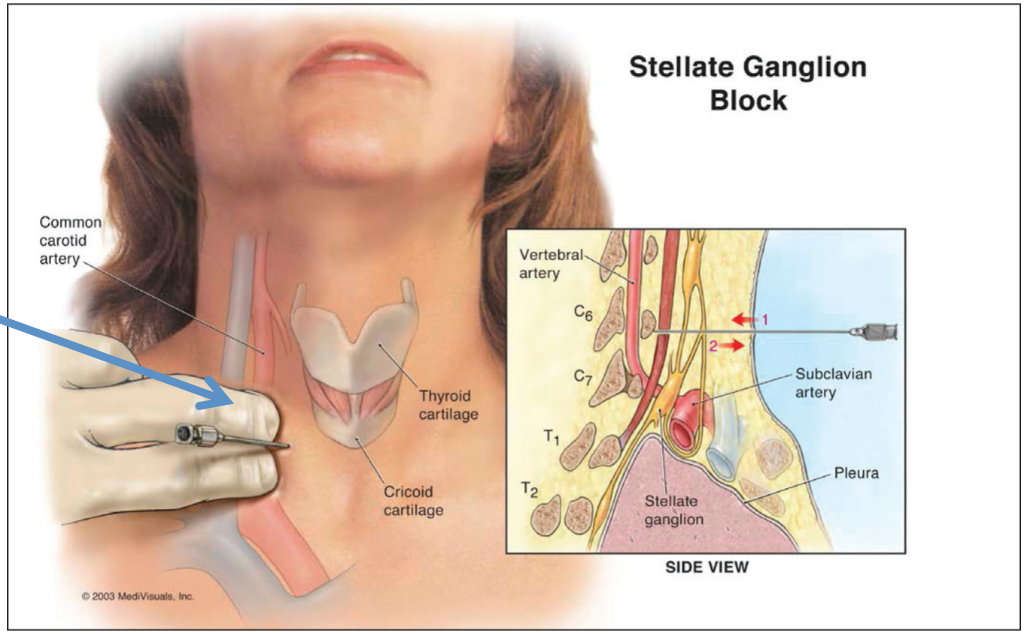
Level I evidence

Blocco del ganglio stellato

Procedura utilizzata in terapia del dolore
Numerose evidenze ma servono ulteriori trial clinici

Iniezione di anestetico locale

Ganglio nervoso del Sistema simpatico
Sito all'altezza della settima vertebra cervicale



van Gastel P,Kallewaard JW, van der Zanden M, de Boer H. Stellateganglion block as a treatment for severe postmenopausal flushing.Climacteric 2013;16:41-47.
Walega DR, Rubin LH, Banuvar S, Shulman LP, Maki PM. Effects of stellate ganglion block on VMS: findings from a randomized controlled clinical trial in postmenopausal women. Menopause 2014;21: 807-814
Haest K, Kumar A, Van Calster B, et al. Stellate ganglion block for the management of hot flashes and sleep disturbances in breast cancer survivors: an uncontrolled experimental study with 24 weeks of follow-up. Ann Oncol2012;23:1449-1454.

Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline

2015

Cynthia A. Stuenkel, Susan R. Davis, Anne Gompel, Mary Ann Lumsden, M. Hassan Murad, JoAnn V. Pinkerton, and Richard J. Santen

Alternative Therapies for Treatment of VMS

Agents	Comments
Agents with inconsistent reports of benefit	
Genistein	Purified isoflavone ±Estrogenically active Breast safety not established
Daidzein	Purified isoflavone ±Estrogenically active Breast safety not established
S-equol	Metabolite of daidzein
Nonpurified isoflavones	Breast safety not established
Flaxseed	
Red clover	Breast safety not established
High-dose extracted or synthesized phytoestrogen	
Dietary soy	Agreement about breast safety
Vitamin E	10% benefit in some studies
Reports with predominantly no benefit	
Black cohosh	Some short-term trials report benefit, most report no benefit Breast safety not established Reports of liver toxicity
Omega-3 fatty acids	No benefit in MSFLASH trial
Acupuncture	Not effective when compared to "sham acupuncture" controls
Exercise	Exercise with sweating may increase hot flashes
Other complementary approaches	Ginseng, dong quai, wild yam, progesterone creams, traditional Chinese herbs, reflexology, magnetic devices
Agents requiring further study	
Stellate ganglion block	Need further RCTs to establish lack of complications
Guided relaxation	Stress management, deep breathing, paced respiration, guided imagery, mindfulness training
Hypnosis	Recent studies suggest efficacy
Cognitive behavior modification	Recent studies suggest efficacy with trained practitioners

Agenti che producono modesti benefici

Agenti che non producono benefici nella maggior parte dei casi

Agenti che necessitano di ulteriori studi

Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society.

Menopause 2015 Nov;22(11):1155-72

Raccomandati:

-Terapia cognitivo-comportamentale e ipnosi

-Paroxetina (unica terapia approvata da FDA), ma anche gli altri inibitori selettivi del reuptake di serotonina / norepinefrina, gabapentin e clonidina hanno evidenze di chiara efficacia.

Raccomandati con cautela:

Terapie che possono alleviare la sintomatologia sono:

Calo ponderale, riduzione dello stress mediante tecniche di mindfulness, isoflavoni (S-equolo) e blocco del ganglio stellato.

MA servono ulteriori studi su queste terapie

AL MOMENTO NON RACCOMANDATI

Esercizio fisico, yoga, omeopatia, agopuntura, interventi chiropratici

Grazie