Associazione Medici Endocrinologi
AME 2003 - 3° Congresso Nazionale
Palermo, 7-9 novembre 2003

Workshop Clinici Interattivi

1. Trattamento della Menopausa

Discussant
Angela Maria Becorpi (Firenze)
Domenico Gullo (Palermo)

Scenario Clinico

• La signora Chiara è una dirigente aziendale di 49 anni (170 cm x 61 kg) con tre gravidanze a termine, che ha assunto, in maniera discontinua (cicli di 18-24 mesi), contraccettivi orali di II generazione, fino all'età di 45 aa.

• Negli ultimi sei mesi cicli oligomenorroici con ipermenorrea e/o franca menometrorragia.

Scenario Clinico

• Storia familiare di:
- infarto del miocardio (zia paterna)
- osteoporosi (zia paterna)
- carcinoma mammario (zia materna)

• Menarca regolare, eumenorrea (fino a 6 mesi fa), attività fisica scarsa, alimentazione irregolare (fast food a pranzo)

• Non fuma; consumo saltuario e moderato di alcolici

Scenario Clinico

• Valutazione ginecologica nei limiti di norma

• PAP-test regolare con predominanza di cellule superficiali

• Esami ematochimici nella norma eccetto il colesterolo totale lievemente aumentato (215 mg%).

• Ecografia transvaginale: spessore endometriale 14.5 mm in prima fase avanzata.

Scenario Clinico

• Viene prescritta terapia progestinica per prevenire l'iperplasia endometriale e la conseguente insorgenza di sanguinamento uterino anomalo.

• Medrossi-Progesterone Acetato (MAP) 5 mg, 1 cpr, dal XVI gg del ciclo, per 14 gg/ciclo.

• Si consiglia alla paziente rivalutazione clinico-ecografica al IV ciclo per eventuali aggiustamenti terapeutici.

Scenario Clinico

• Al controllo (IV ciclo) la sig.ra Chiara è eumenorroica e lo spessore endometriale si è ridotto 8.7 mm (fase follicolare).

• Il trattamento con MAP viene confermato per ulteriori sei cicli, quindi sospeso

• La paziente rimane eumenorroica per sei mesi, quindi si ripresenta per oligomenorrea con ipermenorrea e/o menometrorragia.

• Si ri-prescrive MAP 5 mg, 1 cpr, dal XVI gg del ciclo, per 14 gg/ciclo, per sei mesi

Scenario Clinico

• Al quarto ciclo di MAP la paziente (51 anni) va in amenorrea, lamentando una sintomatologia vasomotoria di entità lieve-moderata.

• Preoccupata dall'aumento di rischio di cancro mammario, particolarmente enfatizzato da amiche e mass-media, vuole essere informata sui rischi e benefici di un'eventuale terapia ormonale sostitutiva (TOS).

CLINICAL QUESTIONS

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1. Se l'obiettivo del trattamento è la riduzione della sintomatologia vasomotoria, quale trattamento ritieni più appropriato nella signora Chiara?

1. Estrogeni
2. Progestinici ad alte dosi
3. TOS
4. Tibolone
5. Altri farmaci

Decisione clinica (1)

• Si prescrivono:
- TOS a basse dosi, con schema sequenziale continuo: 1 mg/die di estradiolo per 28 gg + 10 mg di diidrogesterone (associato alle ultime 14 cpr).
- calcio e vitamina D

CLINICAL QUESTIONS

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2. Una volta stabilizzato l'effetto terapeutico sulla sintomatologia vasomotoria, dopo quanto tempo ritieni necessario rivalutare, nella signora Chiara, il trattamento con TOS?

1. Un mese
2. Sei mesi
3. Un anno
4. Tre anni
5. Cinque anni

Scenario Clinico

• La TOS, rapidamente efficace sulla sintomatologia vasomotoria, viene confermata nei mesi successivi.

• Nel frattempo, il colesterolo totale è rientrato nei limiti di norma (186 mg%).

CLINICAL QUESTIONS

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3. Nella prevenzione primaria di patologie croniche (malattia coronarica, osteoporosi, neoplasie) ritieni che la TOS sia:

1. Utile
2. Probabilmente utile
3. Da valutare caso per caso
4. Di utilità non determinata
5. Di utilità discutibile
6. Inutile o dannosa

Scenario Clinico

• Dopo 3 anni di TOS a basso dosaggio, la paziente accusa saltuaria mastodinia.

• La mammografia mostra una densità ghiandolare elevata.

• Una densitometria ossea documenta una lieve osteopenia (T score -1.2 DS su colonna, -1.5 DS sul collo femorale sn).

CLINICAL QUESTIONS

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4. Considerata la durata del trattamento (3 anni), la storia familiare (ca mammario, malattie cardiovascolari), e la modesta osteopenia cosa consiglieresti alla signora Chiara?

1. Continuare la TOS
2. Sospendere la TOS
3. Modificare il regime della TOS

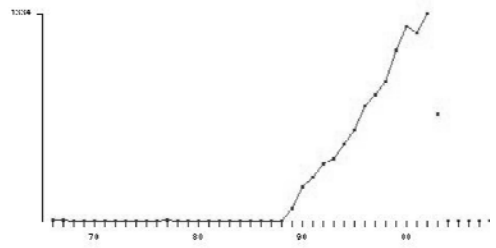
Decisione clinica (2)

• In accordo con la paziente, la TOS viene sospesa.

BMJ, 2003

MEDLINE

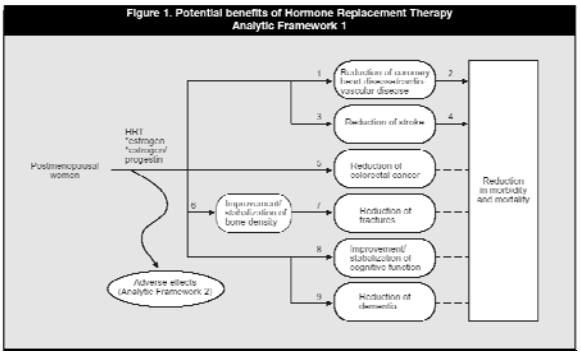
"Hormone Replacement Therapy" [mh]: 10.433 articoli



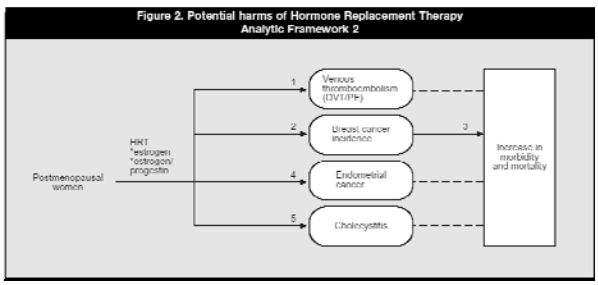
U.S. Preventive Services Task Force.

Hormone Replacement Therapy for Primary Prevention of Chronic Conditions

October 2002
Agency for Healthcare Research and Quality
Rockville, MD



Agency for Healthcare Research and Quality (AHRQ), October 2002



Agency for Healthcare Research and Quality (AHRQ), October 2002

Figure 3. Key Questions

Potential benefits

Does HRT reduce risks for:

1. Coronary heart disease and cardiovascular disease incidence?
2. Coronary heart disease and cardiovascular disease mortality?
3. Stroke incidence?
4. Stroke mortality?
5. Colorectal cancer?
6. Low bone density?
7. Fractures?
8. Decline in cognitive function?
9. Dementia?

Potential harms

Does HRT increase risks for:

1. Venous thromboembolism (deep vein thrombosis and pulmonary embolism)?
2. Breast cancer incidence?
3. Breast cancer mortality?
4. Endometrial cancer?
5. Cholecystitis?

Agency for Healthcare Research and Quality (AHRQ), October 2002

Beral V, Banks E, Reeves G.

Evidence from randomised trials on the long-term effects of hormone replacement therapy

Lancet 2002;360:942-4

- Nell'ultimo decennio,nei paesi occidentali,è aumentato l'uso della terapia ormonale sostitutiva (TOS) nelle donne in età postmenopausale
- Sono stati condotti diversi studi clinici per valutarne gli effetti a lungo termine su end point rilevati (malattia coronarica, neoplasie)
- In particolare quattro studi WHI,HERS, EVTET, WEST hanno incluso più di 20.000 donne in post-menopausa, per un periodo medio di 4,9 anni.

Beral V, et al. Lancet 2002

Studi clinici	*Donne reclutate*	*Numero / Follow up (anni)*	*Trattamento attivo (per os / die)*	*Commenti*
Women's Health Initiative (WHI)	Donne sane con utero intatto	16.608 / 5,2	0,625 mg estrogeno equino e 2,5 mg MPA	Multicentrico USA; terminato precocemente; principali risultati pubblicati
	Donne sane senza utero	10.739 / 8 (pianificati)	0,625 mg estrogeno equino	Multicentrico USA; conclusione prevista 2005; ancora nessun risultato
Heart and Estrogen/ progestin Replacement Study (HERS)	Donne con precedenti patologie cardiovascolari	2.763 / 4,1	0,625 mg estrogeno equino e 2,5 mg MPA	Multicentrico USA; principali risultati pubblicati
Thromboembolism Trial (EVTET)	Donne con precedente VTE	140 / 1,3	2 mg estradiolo e 1 mg noretisterone acetato	Norvegia, terminato precocemente; risultati pubblicati
Women's Estrogen for Stroke Trial (WEST)	Donne con precedenti di stroke	664 / 2,8	1 mg 17 ß-estradiolo	Multicentrico USA; principali risultati pubblicati

Beral V, et al. Lancet 2002

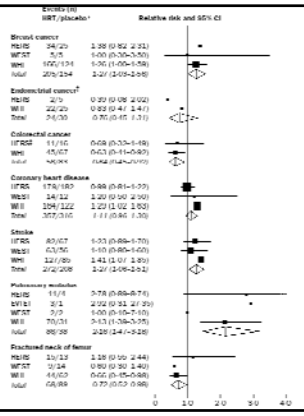
Panel 1: Randomised trials of HRT versus placebo (n> 100) set up to study cancer and cardiovascular disease as endpoints

Study	Women recruited	Number*/ follow-up (yrs)	Active treatment (orally per day)	Comments
Heart and Estrogen/progestin Replacement Study (HERS)[4]	With previous heart disease	2 763 4·1	0·625 mg equine oestrogen and 2·5 mg MPA	Multicentre USA; main results published[4,5]
Estrogen in Venous Thromboembolism Trial (EVTET)[6]	With previous VTE	140 1·3	2 mg estradiol and 1 mg norethisterone acetate	Norway; terminated early, after reports that HRT increased VTE risk; VTE results published.[6]
Women's Estrogen for Stroke Trial (WEST)[7]	With previous stroke	664 2·8	1 mg 17β-oestradiol	Multicentre USA; main results published[7]
Women's Health Initiative (WHI)[8]	(a) Healthy women with intact uterus	16 608 5·2	0·625 mg equine oestrogen and 2·5 mg MPA	Multicentre USA; terminated early; main results published.[8]
	(b) Healthy women without uterus	10 739 8 (planned)	0·625 mg equine oestrogen	Multicentre US/c due to end 2005; no results yet.
Oestrogen in the Prevention of Re-Infarction Trial (ESPRIT)[9]	With first myocardial infarction	1017 2 (planned)	2 mg oestradiol valerate	UK; due to end in 2002; no results yet
Women's International Study of Long Duration Oestrogen after the Menopause (WISDOM)[10]	Healthy women	~27 000 10 (planned)	As for WHI, except 0·625 mg equine oestrogen and 2·5 mg MPA also used in hysterectomised women	UK, Australia, New Zealand; due to end 2012; no results yet

*Approximately equal numbers randomised to placebo and active treatment in each trial. MPA=medroxyprogesterone acetate. VTE=venous thromboembolism.

Beral V, et al. Lancet 2002

Quali risultati su end-point rilevanti a lungo termine della TSO, rispetto al placebo?



Beral V, et al Lancet 2002

AUMENTANO
- cancro mammario
- stroke
- embolia polmonare

SI RIDUCONO
- cancro colon-retto
- frattura della testa del femore

NESSUNA DIFFERENZA
- cancro dell'endometrio
- malattia coronarica

Beral V, et al. Lancet 2002

Quali "vere novità" dai nuovi trials?

• La sintesi dei risultati di tali RCTs concorda con gli studi osservazionali per gli effetti della TSO su:
- carcinoma mammario
- carcinoma del colon retto
- embolia polmonare
- fratture della testa del femore

• I risultati sono invece discordanti, riguardo la prevenzione (sia primaria che secondaria) della malattia coronarica,dove i RCTs hanno smentito i risultati degli studi osservazionali.

Beral V, et al. Lancet 2002

Grodstein F, Clarkson TB, Manson JE.

Understanding the divergent data on postmenopausal hormone therapy

N Engl J Med 2003;348:645-50

Table 1. **Potential Explanations for Discordant Findings from Randomized Trials and Observational Studies Regarding Postmenopausal Hormone Therapy and Coronary Heart Disease.**

Methodologic differences
- Confounding ("healthy user") bias
- Compliance bias
- Incomplete capture of early clinical events

Biologic differences
- Hormone regimen (formulation and dose)
- Characteristics of study population (endogenous estrogen level, time since menopause, and stage of atherosclerosis)

Grodstein F, et al. N Engl J Med 2003

Panel 2: **Estimated change in incidence of major, potentially fatal, conditions in 1000 healthy postmenopausal women from western countries using HRT over 5-year period, based on results from randomised trials (see appendix for methods)**

	Women aged ~50–59 years	Women aged ~60–69 years
Excess incidence per 1000 HRT users, over 5-year period, for:		
Breast cancer	3·2	4·0
Stroke	1·2	4·0
Pulmonary embolism	1·6	4·0
*Total excess**	*~6 per 1000, ~1 in 170 users*	*~12 per 1000, ~1 in 80 users*
Reduction in incidence per 1000 HRT users, over 5-year period, for:		
Colorectal cancer	1·2	3·0
Fracture of neck of femur	0·5	2·5
*Total deficit**	*~1·7 per 1000, ~1 in 600 users*	*~5·5 per 1000, ~1 in 180 users*
Overall balance*	**Net excess:** *~4·3 per 1000, ~1 in 230 users*	**Net excess:** *~6·5 per 1000, ~1 in 150 users*

*Giving equal weight to each type of event.

Beral V, et al. Lancet 2002

Absolute Differences in the Rates of Major Disease End Points among Postmenopausal Women Receiving Estrogen–Progestin Therapy as Compared with Those Receiving Placebo.*

End Point	First 2 Yr	5.2-Yr Period
	no. of events per 1000 women followed	
Coronary heart disease	3 more	4 more
Stroke	1 more →	4 more
Venous thromboembolism	6 more →	9 more
Invasive breast cancer	No more† →	4 more
Hip fracture	1 fewer	2 fewer
Colorectal cancer	No difference	3 fewer
Death	No difference	No difference

* Data are from Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
† The rate was lower in the hormone-therapy group.

Solomon CG, et al
N Engl J Med 2003

Alla luce di queste evidenze, subito dopo la pubblicazione del WHI, tutte le principali società scientifiche hanno immediatamente rivisto le proprie raccomandazioni sulla TOS nel trattamento della menopausa o hanno pubblicato dei position statement ad hoc

2002

- U.S. Preventive Services Task Force
- American Association of Clinical Endocrinologists (PS)
- North American Menopause Society
- American College of Obstetricians and Gynecologists
- Prodigy
- Society of Obstetricians and Gynaecologists of Canada
- New Zealand Guidelines Group
- American College of Cardiology, American Heart Association

Progetto per le Linee-guida
LINEE GUIDA PER LA MENOPAUSA

- Stato: il Gruppo di lavoro ha concluso la stesura degli elaborati e sta procedendo ad un lavoro di editing ed ad un aggiornamento su alcuni argomenti
- Data prevista ultimazione lavori: 26 aprile 2003
- Il Congresso nazionale della SIGO che si è tenuto a Catania nel mese di ottobre 2003 ha dedicato un'apposita sessione alla discussione di queste linee-guida

The North American Menopause Society

Amended report from the NAMS Advisory Panel on Postmenopausal Hormone Therapy

Menopause 2003;10:6-12

Unresolved issues

What are current acceptable definitions of short-term and long-term hormone therapy?

• Short-term hormone: 3 to 5 years and long-term > 5 years.

• Current data provide no assistance in determining at what time point risks would outweigh benefits for an individual woman.

• Clinicians should **re-evaluate the benefit-risk profile of an individual woman and the indication(s) for HTR therapy at each visit**.

NAMS, 2003

Unresolved issues

How long should hormone therapy be prescribed for symptom relief?

• Although no definitive recommendations were made, the panelists agreed that guiding principal should be **the lowest effective dose for the shortest time**

NAMS, 2003

Rymer J, et al. BMJ 2003

Rymer J, et al BMJ 2003

American Association of Clinical Endocrinologists
The Voice of Clinical Endocrinology

AACE Position Statement
Women's Health Initiative
2002

AACE Position

Policy: AACE believes that menopausal hormone therapy considerations must be individualized taking into consideration the benefits, risks and alternatives. It is essential for a woman contemplating menopausal hormone therapy to discuss these issues with her physician.

Limitations: AACE recognizes the limitations of the WHI study with respect to the particular preparation used (CEE/MPA) as well as the study population, which is older, more likely to have cardiovascular disease, and less symptomatic from estrogen deficiency than the typical woman being considered for menopausal hormone therapy.

Indications: In the absence of contraindications, menopausal hormone therapy is appropriate for women with moderate to severe vasomotor symptoms associated with estrogen deficiency, quality of life symptoms resulting from estrogen deficiency, and significant symptoms related to vaginal atrophy.

Although menopausal hormone therapy is also approved for the prevention of postmenopausal osteoporosis and has demonstrated fracture efficacy in the WHI CEE/MPA study, AACE strongly recommends consideration of alternative pharmacologic therapy options for prevention and treatment of osteoporosis in patients not electing to take menopausal hormone therapy. The use of periodic bone density assessments is recommended to determine if and when pharmacologic intervention is needed (*2*).

AACE supports the position that menopausal hormone therapy is <u>not</u> indicated solely for primary or secondary prevention of cardiovascular disease.

Use: The use of menopausal hormone therapy should be at the minimum dose that improves symptoms and used for only so long as symptoms remain significant when assessed intermittently off of therapy. Appropriate counseling regarding the risks and benefits is needed in all patients. The type of menopausal hormone therapy, route of administration and dose should be individualized based on the clinical assessment.

Grady D

Postmenopausal hormones
Therapy for symptoms only

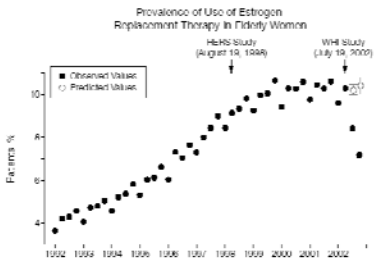
N Engl J Med 2003;348:1835-7

Il Women's Health Initiative ha modificato la prescrizione/assunzione di estroprogestinici?

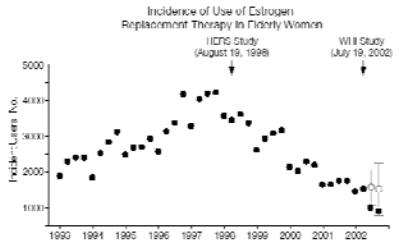
Austin PC, Mamdani MM, Tu K, Jaakkimainen L.

Prescriptions for estrogen replacement therapy in Ontario before and after publication of the Women's Health Initiative Study

JAMA 2003;289:3241-2



Austin PC,et al. JAMA 2003



Austin PC,et al. JAMA 2003

Lawton B, Rose S, McLeod D, Dowell A.

Changes in use of hormone replacement therapy after the report from the Women's Health Initiative

BMJ 2003;327:845-6

- Of the 734 respondents, 423 (58%) stopped taking HRT.
  - 132 (18%) had restarted at the time of our survey
  - 291 (40%) had not
- 610 respondents (83%) reported that they had discussed HRT with a health professional
- Of the 132 women who restarted:
  - 100 did so because of the return of symptoms
  - 16 because they “felt better” on HRT
  - 15 for other reasons.

• In Italy:
  - estrogens: decrease in prescriptions (-18%) and in expenditure (-27%)
  - progestins: 7% decrease in DDDs and a 7% increase in expenditure.

• **Tibolone prescription increased, approximately by 38%** and its expenditure has reached the second place.

• We question the shift towards tibolone which lacks data from RCTs showing its effectiveness (or harms) based on clinical end-points (fractures, myocardial infarction, breast cancer or other events) and not surrogated ones.

Marata AM. BMJ 2003
Dati OSMED

Morris E, Rymer J

Menopausal symptoms

*Clinical Evidence, October 2003**

**Updated November 2002*

Tibolone: Utile

• No systematic review

• RCTs have found that tibolone improves vasomotor symptoms and sexual function compared with placebo.

• Two RCTs found that tibolone improved sexual function compared with hormone replacement therapy.

• We found insufficient evidence from RCTs about effects of tibolone on vasomotor symptoms and vaginal dryness compared with oestrogen.

Clinical Evidence, October 2003

Modelska K, Cummings S.

Tibolone for postmenopausal women: systematic review of randomized trials

J Clin Endocrinol Metab 2002;87:16-23

• Computerized search without language restrictions: MEDLINE, Gallen II, EMBASE, Cochrane library.

• 21 unique RCTs that assessed the clinical effects of tibolone (2.5 mg/d) in postmenopausal women.

• No meta-analysis:
  - substantial methodological differences
  - evidence in the investigated areas did not permit formal analysis.
  - most areas we reviewed had too few placebo-controlled trials to combine in a meta-analysis

Modelska K, et al. J Clin Endocrinol Metab 2002

• Tibolone significantly reduces hot flushes and sweating and increases BMD in postmenopausal women.

• Other effects of tibolone in postmenopausal women, such as its influence on lipid metabolism, hemostasis, and sexual function, are less certain.

• In addition,the long-term effects of tibolone, particularly in reducing fractures, breast cancer, and cardiovascular disease are still unknown.

Modelska K, et al. J Clin Endocrinol Metab, 2002

Scenario Clinico

• Dopo 8 settimane dalla sospensione della TOS, la sig.ra Chiara manifesta una sindrome da estrogeno-deficienza di grado lieve-moderato: turbe dell'umore, saltuarie caldane, secchezza vaginale, riduzione della libido, tachicardia e lieve incremento della pressione sistolica.

Scenario Clinico

• La signora, preferisce non riprendere la TOS e vuole conoscere il profilo rischio/beneficio dei fitoestrogeni, perché in una nota trasmissione televisiva, ha appreso che "la loro assunzione è associata a riduzione dei disturbi vasomotori, del rischio cardiovascolare e di carcinoma mammario e riduce la perdita minerale ossea".

CLINICAL QUESTIONS

?

5. Le evidenze che supportano l'efficacia dei fitoestrogeni riguardano:

1. La ↓ della sintomatologia vasomotoria
2. La ↓ degli eventi cardiovascolari
3. La ↓ del rischio di ca mammario
4. La ↓ della demineralizzazione ossea
5. Tutte le precedenti
6. Nessuna delle precedenti

Morris E, Rymer J

Menopausal symptoms

*Clinical Evidence, October 2003**

**Updated November 2002*

Fitoestrogeni: Probabilmente efficaci

• **Sintomatologia vasomotoria**
  • 7 RCTs (550 pz)
    • Notevole eterogeneità, metodologia discutibile
    • Risultati contrastanti
    • I 3 studi positivi riducono la severità, ma non la frequenza dei sintomi vasomotori

• **Altri sintomi** (psicologici, muscolo-scheletrici, genito-urinari)
  • 1 RCTs negativo

• **Qualità di vita**
  • No RCTs

Clinical Evidence, October 2003

Kronenberg F, Fugh-Berman A.

Complementary and alternative medicine for menopausal symptoms. A review of randomized, controlled trials.

Ann Intern Med 2002;137:805-13

DATA SOURCES

• Searches of MEDLINE for articles published from January 1966 through March 2002, of the Alternative and Complementary Database (AMED) of the British Library for articles published from 1985 through 2000, and of the authors' own extensive files.

STUDY SELECTION

• 29 RCTs of complementary and alternative medicine (CAM) for hot flashes and other menopausal symptoms
  • 12 dealt with soy or soy extracts
  • 10 with herbs
  • 7 with other CAM therapies

Kronenberg F,et al. Ann Intern Med 2002

DATA SYNTHESIS

• **Soy** seems to have modest benefit for hot flashes, but studies are not conclusive.

• **Isoflavone** preparations seem to be less effective than soy foods.

• **Black cohosh** may be effective for menopausal symptoms, but the lack of adequate long-term safety data precludes recommending long-term use.

• Single clinical trials have found that don quai, evening primrose oil, a Chinese herb mixture, vitamin E, and acupuncture do not affect hot flashes

• Two trials have shown that red clover has no benefit for treating hot flashes.

Kronenberg F,et al. Ann Intern Med 2002

CONCLUSIONS

• Black cohosh and foods that contain phytoestrogens show promise for the treatment of menopausal symptoms.

• Clinical trials do not support the use of other herbs or complementary therapies.

• Long-term safety data on individual isoflavones or isoflavone concentrates are not available.

Kronenberg F,et al. Ann Intern Med 2002

ACP JOURNAL CLUB

Evidence-Based Medicine for Better Patient Care

• Sorveglianza *core* di riviste (40-50)

• Selezione articoli in base a
  - Rilevanza clinica
  - Adeguatezza metodologica

• Abstract strutturato e commentato

• 1 articolo = 1 pagina

ACP JOURNAL CLUB

Evidence-Based Medicine for Better Patient Care

• Most herbal therapies do not have efficacy or safety data supporting their use, are expensive and have no guarantee that they contain the supposed active ingredient or that contaminants do not exist.

• Soy and soy extracts are promising but require further studies.

• As health care providers and researchers, we should advocate for more **standardization and regulation of CAM therapies and more vigorous research into their long-term efficacy and safety.**

Cheung AM, Walji R. ACP J Club. Jul-Aug 2003

Brewer D, Nashelsky J.

What non-hormonal therapies are effective for postmenopausal vasomotor symptoms?

J Fam Pract 2003;52:324-5

TABLE

Nonhormonal therapies for postmenopausal vasomotor symptoms

Agent	Effective	SOR[a]	Comments
Soyisoflavones	Maybe	D	Multiple RCTs with conflicting results, no formal meta-analysis. Does have a positive effect on lipid profile
Clonidine (Catapres)	Yes	A	Multiple small RCTs
Venlafaxine* (Effexor)	Yes	B	Single RCT
Fluoxetine* (Prozac)	Yes	B	Single RCT
Gabapentin (Neurontin)	Yes	A	Single RCT
Megestrol* (Megace)	Yes	B	Single RCT
Exercise	Maybe	C	Single observational study
Black cohosh	Maybe	C	German E commission recommendation positive in 1989, but only 1 of 7 trials cited had placebo control. Recent RCT showed no benefit
Other: Bellergal, methyldopa, evening primrose oil, ginseng, wild yam extract, mai quan, flaxseed	No	C	All have been advocated but no positive trials for any evidence of effect

*Trials conducted only with patients with breast cancer and interventional menopause, most of whom were on anti-estrogen therapy.
See page 290 for a description of strength of recommendation.
SOR: strength of recommendation; RCT: randomized controlled trial

Brewer D, Nashelsky J.
J Fam Pract 2003

Tice JA, Ettinger B, Ensrud K, et al

Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study. A randomized controlled trial.

JAMA 2003;290:207-14

DESIGN, SETTING, AND PARTICIPANTS

• Randomized, double-blind, placebo controlled trial of menopausal women (45-60 years), who were experiencing at least 35 hot flashes per week.

• The study included women who were recently postmenopausal, experiencing 8.1 hot flashes per day.

• Women were exluded if they were vegetarians, consumed soy products more than once per week, or took medications affecting isoflavone absorption.

Tice JA, et al. JAMA 2003

INTERVENTION

252 participants were randomly assigned to
• Promensil (82 mg of total isoflavones per day)
• Rimostil (57 mg of total isoflavones per day)
• Identical placebo

The follow-up was 12 weeks

MAIN OUTCOME MEASURE

• The change in frequency of hot flashes measured by participant daily diaries.
• Changes in quality of life and adverse events.

Tice JA, et al. JAMA 2003

RESULTS

• The reductions in mean daily hot flash count at 12 weeks were similar for the Promensil (5.1), Rimostil (5.4), and placebo (5.0) groups.

• In comparison with the placebo group, participants in the Promensil group (41%; 95% confidence interval [CI], 29%-51%; P=.03), but not in the Rimostil group reduced hot flashes more rapidly.

• Quality-of-life improvements and adverse events were comparable in the 3 groups.

Tice JA, et al. JAMA 2003

CONCLUSIONS

Although the study provides some evidence for a biological effect of Promensil, neither supplement had a clinically important effect on hot flashes or other symptoms of menopause.

Tice JA, et al. JAMA 2003

Mishra SI, Dickerson V, Najm W.

Phytoestrogens and breast cancer prevention. What is the evidence?

Am J Obstet Gynecol 2003;188(5 Suppl):S66-70.

• Research in humans has been limited to observational (case-control) epidemiologic studies and is far from conclusive.

• A critical evaluation through controlled trials of phytoestrogens' breast cancer-protective role needs to be performed before they are adopted as chemopreventive agents

Mishra SI, et al. Am J Obstet Gynecol 2003

Valtuena S, Cashman K, Robins SP, et al

Investigating the role of natural phyto-oestrogens on bone health in postmenopausal women

Br J Nutr 2003;89(Suppl 1):S87-99

• Research on the bone effects of natural phyto-oestrogens after menopause is at a relatively early stage.

• Published studies are few, difficult to compare and often inconclusive, due in part to design weaknesses.

• The questions can only be addressed by conducting well-planned, randomised clinical trials

Valtuena S, et al. Br J Nutr 2003

Phytoestrogens: cardiovascular diseases and osteoporosis

Evidence is inconclusive to determine whether phytoestrogens (isoflavones such as iproflavone, which are found in soy milk, soy flour, tofu, and other soy products) are effective for reducing the risk for osteoporosis or cardiovascular disease.

U.S. Preventive Service Task Force, 2002