Integrating complementary therapies (CAMS) with prescription medications – a conservative approach to vasomotor symptom management

RCN 2007

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West London Menopause & PMS Centre
Integrating CAMS with prescription medications – a conservative approach to vasomotor symptom management

- Why an integrated approach?
- Phytoestrogens
  - Rationale & Mechanisms of action
  - Evidence
    - Efficacy
    - Safety
- Other CAMs
- The decision-making process
Integrating CAMS with prescription medications – a conservative approach to vasomotor symptom management

- **Why an integrated approach?**
  - Phytoestrogens
    - Rationale & Mechanisms of action
    - Evidence
      - Efficacy
      - Safety
  - Other CAMs
- **The decision-making process**
Why an Integrated Approach

- Patient choice and individualisation
- Medical contraindication to HRT
- Alternatives may be better than HRT
- Media terror!
Hormone Replacement Therapy – Where are we now?
From euphoria to panic and the need to find equilibrium

1990s Euphoria

The Wall Street Journal
Menopause-Treatment Market Begins to Grow
By Melanie Trollman, The Wall Street Journal, 1157 words

The Washington Post
Death Rate Is Lower for Estrogen Users, Study Finds
[FINAL Edition]
The Washington Post (5-97 Фуллтон) - Washington, D.C.
Jan 1, 1995

The Washington Post
Hormone Combination Protects Heart, Study Finds
[FINAL Edition]
The Washington Post (5-97 Фуллтон) - Washington, D.C.
Aug 15, 1996

2002 - Panic

Mirror.co.uk
An About-Face On Hormone Therapy
Nature Medicine, Vol 12;1, January 2006

The New York Times
Läkarlarm: Öestrogen kan göra dig sjuk
Kraftigt ökar bröstcancer studie
Östrogenbehandlin

To the Editor:
Re “Study Is Halted Over Rise Seen in Cancer Risk” (front p.
has been tested and found risky is one particular drug. Pre
malignant with a

Nature Medicine

What is so surprising about the latest hormone news is where it comes from. While hormone advocates have long criticized the findings of the WH, the new Journal of Women’s Health report doesn’t come from this well-intentioned. It’s written by Robert Bradford, a researcher at New York University School of Medicine.

The milti-nuclator theory of hormone replacement therapy (HRT) has been gaining popularity in recent years. It suggests that by using lower doses of hormones, women can reduce their risk of breast cancer while still experiencing the benefits of estrogen therapy.

This approach, known as microdosing, involves using much smaller amounts of hormones than traditional HRT regimens. Proponents argue that microdosing can help prevent the side effects associated with higher doses, such as increased risk of blood clots and stroke.

However, recent research has raised concerns about the effectiveness and safety of microdosing. A study published in the Journal of the American Medical Association found that women who took microdosed hormones were no less likely to develop breast cancer than those who did not take any hormones at all.

These findings suggest that the milti-nuclator theory of HRT may not be as effective as previously thought. It is important for women to carefully consider the risks and benefits of any hormone therapy regimen before making a decision.

In conclusion, while microdosing may offer potential advantages, it is crucial to approach this approach with caution. Women should consult with their healthcare providers to determine the best course of action based on their individual needs and circumstances.

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The information provided is for educational purposes only and should not be considered medical advice. It is important to consult with a healthcare professional before making any decisions about hormone therapy.

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References:

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Image credit:
Mirror.co.uk: An About-Face On Hormone Therapy
Nature Medicine: Vol 12;1, January 2006
The New York Times
The Washington Post
CNN.com
The Wall Street Journal
The Journal of the American Medical Association
Change in Attitudes towards HRT

• HRT use has fallen by 50%

• Use of complementary therapies rose 9.6% to 18%
  • Hoffman et al Maturitas Sept 2005

• Huge growth in use of unregulated products worth over $27 billion dollars/annum in US

• Recent controversies have polarised views on HRT between epidemiologists and clinicians and have stifled rational debate

• Many women and health professionals remain confused about the benefits and risks of HRT and alternatives
Alternatives to HRT
The controversy in the Daily Mail, September 2006

Risks of ‘herbal HRT’

By Jenny Hope
Medical Correspondent

WOMEN who ditch HRT in favour of unproven alternative therapies risk damaging their health, experts warned last night.

Hundreds of thousands stopped hormone replacement therapy after health scares and started using complementary treatments to treat menopausal symptoms instead.

But the Royal College of Obstetricians and Gynaecologists yesterday issued an unproven directive warning against many herbal remedies and supplements, which are not properly tested and can cause serious harm.

But clove, evening primrose oil, ginseng and St John’s wort may improve quality of life, it said.

Some treatments do not have sufficient scientific evidence to support their claims of relieving menopausal symptoms or of being able to equal the benefits of conventional therapies, said a college report.

College secretary Richard Warren said: “The current interest and enthusiasm directed towards alternative treatments for menopausal symptoms is understandable, but the full risks and benefits of these therapies are not yet known.Each case needs to be considered individually. Women must do thorough research and not rush into treatment decisions.”

Consultant gynaecologist Nick Paranjpe of Queen Charlotte’s Hospital in London, and co-author of the report, said: “Many women use alternatives to HRT to help control menopausal symptoms believing them to be safer and ‘more natural’.

‘But in many cases appropriate research into their safety has not been done.

‘I’m a strong supporter of an integrated approach using lifestyle, alternatives and HRT but it must be evidence-based to ensure both efficacy and long-term safety.”

J hope@dailymail.co.uk
Women can do more

To warn doctors

Interest and warnings about harm to hertiage endometrial cancer patients have been ignored, but new research is cause for concern.

Consultant gynaecologist Nick Panay, of Queen Charlotte’s Hospital, London, said: ‘Women use alternatives to HRT to help control menopausal symptoms believing them to be safer and “more natural”.

Many women mix alternatives to HRT to help control the health risks could outweigh the benefits.

HRT, which results in 80-90 per cent fewer symptoms.

The report also points out that the herb black cohosh has been linked to liver toxicity.

It cites one instance in which ‘a patient subsequently required a liver transplant after a severe adverse reaction’.

Consultant gynaecologist Nick Panay, of Queen Charlotte’s Hospital, London, and co-author of the report, said: ‘Many women use alternatives to HRT to help control menopausal symptoms believing them to be safer and “more natural”.

‘But in many cases appropriate research into their safety has not been done.

‘I’m a strong supporter of an integrated approach using lifestyle, alternatives and HRT but it must be evidence-based to confirm both efficacy and long-term safety.’

j.hope@dailymail.co.uk
Call for Clearer Information

- 413 women questionnaire survey on women using CAMS

- Poor information quality, lack of information, poor clarity of packaging

- Suggested to make available brochures of evidence, patient testimonials, website info etc

Armitage et al Climacteric 2007
MacLennan & Sturdee Climacteric 2007
The Regulatory Guidelines
Implications for prescribing
October 2004 MHRA

• Short term use: minimum effective dosage for shortest duration

• Long term use: consider alternatives as increased incidence of some conditions

• Decision regarding HRT use: discussed on individual basis taking into account her risk factors
European Menopause Survey
symptom prevalence

- Hot flushes: 94% of all women have experienced one or more menopausal symptoms
- Sleeplessness
- Mood swings
- Reduced sex drive
- Headaches/migraine
- Depression
- Involuntary loss of urine
- Vaginal pain

Only 6% have not experienced any symptoms at all
64% of women have experienced one or more severe menopausal symptoms

Genazzani, Schneider, Panay, and Nijland. *Gyne Endocrinol* 2006

Question: Are you currently experiencing or have you experienced any of the following symptoms in the past five years? Can you state them as mild or severe?
84% of women agree that menopause needs to be treated. Do women suffer in silence?

<table>
<thead>
<tr>
<th></th>
<th>Symptoms don't need to be treated</th>
<th>Symptoms need to be treated</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong> n=4201</td>
<td>84</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td><strong>Current HRT user</strong> n=809</td>
<td>94</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td><strong>Past HRT user</strong> n=822</td>
<td>86</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td><strong>Non HRT user</strong> n=2570</td>
<td>80</td>
<td></td>
<td>17</td>
</tr>
</tbody>
</table>

Only 22% of women used an appropriate treatment for menopause related symptoms.

Genazzani, Schneider, Panay, and Nijland *Gyne Endocrinol* 2006

Question: Severe menopausal symptoms need to be treated instead of accepting them just as they are. Do you agree or disagree?
HRT versus alternatives

• Prevalence and satisfaction surveys

  – Vashisht and Studd 2001
    • 68% UK menopause clinic had ever tried alternative
    • 66% regular users
    • 62% satisfied with the results

  – Panay, Thompson, Bellone, Horner and Davis 2007
    • 84% had tried alternative (increased compared with 2001)
    • 35% regular users of alternatives (reduced compared with 2001)
Comparative satisfaction ratings

Panay, Thompson, Bellone, Horner and Davis (2007)
Integrating CAMS with prescription medications – a conservative approach to vasomotor symptom management

- Why an integrated approach?

- Phytoestrogens
  - Rationale & Mechanisms of action
  - Evidence
    - Efficacy
    - Safety

- Other CAMs

- The decision-making process
1926

the discovery of estrogenic activity of plant compounds

Loewe S, Lange F, Spohr E. Biochem Zeitschr 1927;180:1-26
Phytoestrogens

- Naturally occurring compounds from plants
- 100-1000x weaker than oestradiol
- Many classes
  - isoflavones
    - soybeans, chickpeas, red clover
  - lignans
    - cereals, vegetables, legumes, flaxseed & linseed
Incidence of Menopausal Symptoms In Peri- and Postmenopausal Women

Relative Isoflavone Content


<table>
<thead>
<tr>
<th>Isoflavone</th>
<th>Red Clover Extract</th>
<th>Soy</th>
<th>Chinese Peas</th>
<th>Green Split Peas</th>
<th>Chick Peas</th>
<th>Broad Beans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genistein</td>
<td>▢</td>
<td>▢</td>
<td></td>
<td>▢</td>
<td></td>
<td>▢</td>
</tr>
<tr>
<td>Biochanin</td>
<td>▢</td>
<td>▢</td>
<td></td>
<td>▢</td>
<td>▢</td>
<td>▢</td>
</tr>
<tr>
<td>Daidzein</td>
<td>▢</td>
<td>▢</td>
<td></td>
<td>▢</td>
<td>▢</td>
<td>▢</td>
</tr>
<tr>
<td>Formononetin</td>
<td>▢</td>
<td>▢</td>
<td></td>
<td>▢</td>
<td>▢</td>
<td>▢</td>
</tr>
</tbody>
</table>

Total Isoflavones Per Serving
- 40mg 1 tablet
- 20mg 1 cup
- 13mg half cup
- 10mg half cup
- 2mg half cup
- 2mg half cup
Molecular binding of isoflavones

- Oestradiol ER α ER β
- Genistein ER β 7 to 30 fold greater binding affinity
- Biochanin & Daidzein also ER β but lower affinity
- Formononetin ? ER α binding

Turner et al J Pharm Science 2007
Molecular binding of isoflavones

- Cautions for isoflavones in breast cancer

- Formononetin ? ERα binding

- May be ER α binding when ER β receptors saturated

Panay Maturitas 2007
Integrating phytoestrogens with prescription medications – a conservative approach to vasomotor symptom management

- Why an integrated approach?

- Phytoestrogens
  - Rationale & Mechanisms of action
  - Evidence
    - Efficacy
    - Safety

- Other CAMs

- The decision-making process
Phytoestrogens
Red clover

• 5 RCTs thus far – only 2/5 have shown benefit compared to placebo
  – Jeri et al. Climacteric 1999
  – van de Weijer. Maturitas 2002

• Recent meta-analysis of all 5 studies showed small but significant reduction versus placebo

• Meta analyses of isoflavones (soy and red clover) – small benefit
  • Howes et al. Maturitas 2006
  • Coon Ernst Phytomedicine 2006
Phytoestrogens
Red clover

• Coon Ernst Phytomedicine 2006

• 17 trials identified

• 5 suitable for analysis

• Reduction in hot flush frequency in treatment group (40-82mg isoflavones daily)

Weighted difference of -1.5 hot flushes daily (95% CI -2.94 - 0.03) p=0.05
Phytoestrogens
Red clover

- Other Meta analyses state limited efficacy has been demonstrated and suggest better trials required
  - Evidence based practice centre – Oregon
  - Nedrow et al Arch Internal Med 2006
  - Nelson et al JAMA 2006
Phytoestrogens
Red clover

Safety

• Breast
  No evidence of increased breast density
  Atkinson et al Breast Canc Res 2004

  No data on safety after breast cancer diagnosis
  Antoine et al Climacteric 2007
  Panay & Rees SAC Opinion Paper 6 RCOG 2006

• Endometrial
  No evidence of endometrial hyperplasia (biopsy and scan data)
  Clifton-Bligh Menopause 2001 (USS)
  Hale Menopause 2001 (Biopsy)
Phytoestrogens
Soy

• Meta-analysis 178 full text articles
  – “inconsistent results” – stronger evidence soy isoflavone products

• 12 RCTs thus far
  • Only 4 have shown benefit versus placebo

• Faure et al. Menopause 2002
  – 61% symptom reduction in active versus 21% in placebo group
Phytoestrogens
Soy

Safety

• Breast
  – No effect on mammographic density

• Endometrium
    – Low risk of endometrial hyperplasia with long-term use
Integrating phytoestrogens with prescription medications – a conservative approach to vasomotor symptom management

• Why an integrated approach?

• Phytoestrogens
  • Rationale & Mechanisms of action
  • Evidence
    • Efficacy
    • Safety

• Other CAMs

• The decision-making process
Other alternatives to conventional HRT
Black cohosh (*cimicifuga racemosa*)

- Native to North America, from the buttercup family

- Four recent placebo-controlled RCTs
  - Wuttke *et al*. *Maturitas* 2003 +ve
  - Pockaj *et al*. J Clin Onc 2006 -ve

- Certified by the German Medicines Control Agency
Other alternatives to conventional HRT
Black cohosh

Safety

- No breast data
- Appears safe on endometrium
  - Huntley and Ernst 2003
- Seven reports of liver toxicity
  - ?autoimmune mechanism
  - MHRA *Curr Prob Pharmac* October 10th 2004
  - Black box warning
Other alternatives to conventional HRT
Transdermal progesterone

• ↓ Menopausal symptoms compared with placebo
  – but no ↑ bone mineral density
    – Leonetti et al. Obstet Gynecol 1999
    – Komesaroff et al. Climacteric 2001
    – Wren et al. Menopause 2003

• Insufficient absorption to transform endometrium

• Absorption may take 6 weeks
Other alternatives to conventional HRT
Acupuncture

- Insertion of needles along ‘meridians’ or energy channels

- One RCT v estrogen in 45 women
  - Wyon et al Climacteric 2004

- Estrogen superior in relieving symptoms
Other alternatives to conventional HRT
Reflexology

- Little research

- Pilot RCT
  - 76 women, non specific foot massage or reflexology
  - ↓ symptoms but no difference in groups

- Williamson BJOG 2002
Other alternatives to conventional HRT

- Evening primrose oil - 2 RCTs – no benefit
- Sage – no RCTs
- Ginseng – no RCTs
- Homeopathy – no RCTs
- Kava Kava – caution!
- Chinese Herbs – caution!
- Mixed preparations e.g. menopace, flash fighters – no data
She found if administered correctly, evening primrose oil had a remarkably calming effect.
Integrating phytoestrogens with prescription medications – a conservative approach to vasomotor symptom management

- Why an integrated approach?

- Phytoestrogens
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    - Safety

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- The decision-making process
The decision-making process
Vasomotor symptom treatment algorithm

- Five stepwise phases

1. General health assessment of patient
2. Exclusion of other pathology
3. Discussion of all available treatment options
   - Efficacy and safety of HRT
   - Efficacy and safety of alternatives
   - Taking into account individual’s risk factors
4. Severity rating of symptoms
5. Treatment allocation

Vasomotor Symptom Treatment Algorithm: A conservative, clinical approach

- **Monopausal patient**
- **General health assessment**

**Symptomatic**
- Exclude other possible causes of symptoms e.g. thyroid, depression, diabetes, iron deficiency

Discuss all available treatment options for vasomotor symptoms including lifestyle, CAM and prescription medications (hormonal and non-hormonal).

Patient to rate severity of vasomotor symptoms from mild to severe

- **Mildly Symptomatic**
  - **Lifestyle and Complementary**
    - **Lifestyle Modifications**
      - Core body temp
      - Exercise
      - Non-smoking
      - Relaxation
    - **Complementary Therapies**
      - Red clover isoavones
      - Soy isoavones
      - Black cohosh
  - **First Line**
    - Lifestyle and Complementary
  - **Review after 6-12 weeks**
    - If treatment is not satisfactory within 12 weeks, discuss second line options
  - **Second Line**
    - **HT**
    - **Non-HT prescription medications**
    - **AND/OR**
      - Lifestyle and Complementary

- **Moderately Symptomatic**
  - Averse to or contraindicated to HT.
  - Patient understands risks and benefits of HT

- **Severely Symptomatic**
  - Patient understands risks and benefits of HT
  - **HT**
    - Low dose estrogen +/- progesterone
    - Lifestyle modifications
    - Complementary Therapies such as red clover isoavones, soy isoavones, black cohosh

Review after 3 months then annually, or as required by patient.

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Vasomotor treatment algorithm: conservative, clinical approach

**Mildly symptomatic**

**Lifestyle and complementary**

**Lifestyle modifications**
- Core body temperature
- Exercise
- Non-smoking
- Relaxation

**Complementary therapies**
- Red clover isoflavones
- Soy isoflavones
- Black cohosh

Review after 3 months then annually, or as required by patient
Vasomotor treatment algorithm: a conservative, clinical approach

**Moderately symptomatic**

**First line**

Lifestyle and complementary
- Lifestyle modifications
- Complementary therapies such as red clover isoflavones, soy isoflavones, black cohosh

**Review after 8–12 weeks**

If treatment is not satisfactory within 12 weeks, discuss second line options

- Averse or contra-indicated to HT
- Patient understands risks and benefits of HT

**Second line**

Non-HT prescription medications and/or Lifestyle and complementary

HT
- Low dose est +/- prog

Review after 3 months then annually, or as required by patient
Vasomotor treatment algorithm: a conservative, clinical approach

**Severely symptomatic**

- Averse or contra-indicated to HT

**Non-HT prescription medications**

*Trial non-HT prescription therapies for symptoms*

- Antidepressants
- Gabapentin
- Antihypertensives

and/or

**Lifestyle and complementary**

- Lifestyle modifications
- Complementary therapies such as red clover isoflavones, soy isoflavones, black cohosh

**HT**

- Low dose estrogen +/- progesterone

Review after 3 months then annually, or as required by patient
The decision-making process
Exclusions from algorithm

- Algorithm intended for healthy women with vasomotor symptoms only
- Inappropriate for algorithm
  - Premature menopause
  - Osteoporosis risk
  - Psychological or urogenital symptoms
The decision-making process

• Specific risk categories

• **Potential Side Effects**
  • Intolerance to soy / lignanes
  • Reduction of libido through increased SHBG/reduced free testosterone

• Breast / Ovarian cancer
  – High dose isoflavones prescribed with caution – possible E2 alpha effect of formononetin

• CHD / VTE risk
  – Prescription of phytoestrogens with caution
  – No effect on Factor VII, von Willebrand factor of Isoflavones
    – Nestle Curr Opin Lipido
What are the problems with use of alternatives?

- Little formal testing
  - efficacy
- **safety**
  - interactions
  - post-marketing surveillance
- Poor quality control
- Delay in evidence based treatments

- Is the therapist suitably qualified?
- Who retains overall clinical responsibility?
Integrating CAMS with prescription medications – a conservative approach to vasomotor symptom management

THE ‘SAFE’
4-POINT QUALITY CODE

• **Standardised levels of active ingredient**

• **Absence of drug interactions and contaminants**

• **Found to be an effective and a safe product**

• **Effective levels of active ingredient**
Integrating CAMS with prescription medications – a conservative approach to vasomotor symptom management
This week the House of Lords Committee recommended that acupuncture and herbal medicine should be legally regulated to protect the public from quack practitioners. Experts claim that current regulation of complementary and alternative medicine (CAM) is inadequate and fragmented, with only two of them, osteopathy and chiropractics, currently regulated as professions by Acts of Parliament.
Regulation of CAMS – the big 5

- Osteopathy – regulated
- Chiropractic – regulated
- Acupuncture – consultation phase
- Herbalism – consultation phase
- Homeopathy
Perceived drawbacks with the current proposals

- Potential loss of an indigenous traditional medical system and its medicines
- Discrimination against an indigenous traditional medical system
- The loss of traditional community based herbalists
- Reduced choice and diversity for the public to decide on their healthcare options
- State regulation does not ensure public safety
- How will the new legislation be policed, when existing regulation has not been policed adequately, leading to current problems?
Integrating CAMS with prescription medications – a conservative approach to vasomotor symptom management

Take Home Messages

- Integrated approach involving lifestyle, complementary and traditional therapies should be evidence based both in terms of efficacy and safety

- Data for efficacy and safety of phytoestrogens still poor - larger RCTs required

- Products recommended should ideally be registered, strictly quality controlled and appropriately labelled

- SAC Alternatives Panay & Rees www.rcog.org.uk
Its not all bad news!

- **NHS R&D Programme 2007** -

In response to the House of Lords Select Committee's desire to foster high-quality research into the CAM genre, and surveys which indicate that on average a third of patients with cancer had used some form of CAM, the Department provided funding for research in CAM (£1.3 million for the first round of a research capacity building scheme, and £324,000 for three qualitative research projects on CAM in the care of patients with cancer). This will help develop the evidence base for CAM in healthcare.
Thank you for your attention!