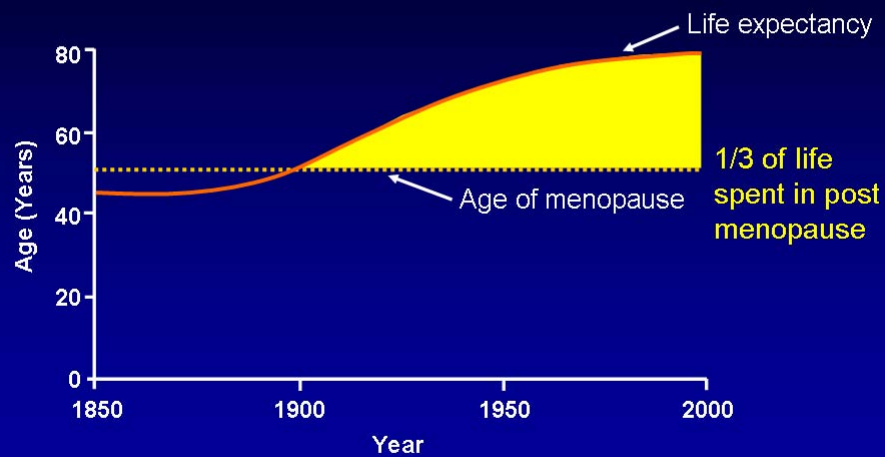


# What every woman should know about Bioidentical Hormones

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## Gap Widens Between Life Expectancy and Menopausal Age



Soules MR, et al. *J Am Geriatr Soc.* 1982;30:547-561.

## Menopause: Uncharted Waters...

- Only in last 100 years have women been routinely surviving beyond age of menopause
- The statement "I don't want to take hormones because women 1000 years ago did not take them. I just want what is natural." is therefore invalid.
- The human female body has not been evolutionarily designed to survive beyond menopause...we have extended lifespan due to medical advances (most notably reduction of infectious diseases), not because of development of genetic changes (evolution) that provide survival advantage; we have developed a multitude of "lifestyle diseases" – conditions due to poor nutrition / sedentary lifestyle / stress - eg. heart disease, diabetes, etc...

## Goal of Menopause Management

- Optimize Quality of life
  - Reducing hot flashes
  - Sexual health
  - Quality sleep
  - Healthy mood
  - Healthy weight
- Prevent chronic diseases
  - Heart disease
  - Osteoporosis
  - Diabetes
  - Cancers

# Menopausal Symptoms

## The Seven Dwarves of Menopause

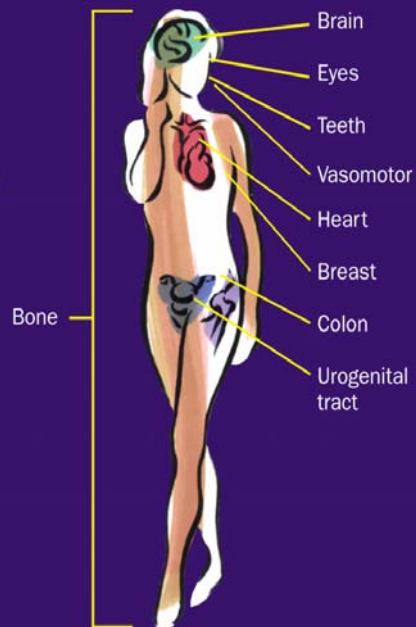


Itchy, Bitchy, Sweaty, Sleepy, Bloating, Forgetful & Psycho

Graphic courtesy of Cathy Nonas, RD.

## Effect of Estrogen in Target Tissues

Each woman should weigh her potential risks and benefits to make her own individual decision regarding HRT.



## Symptoms Associated with Perimenopause

- Change in menstrual flow and cycle
- Vasomotor (hot flashes, night sweats)
- Vaginal dryness / dyspareunia
- Change in libido
- Mood swings, irritability, anxiety, depression
- Stiffness / soreness / paresthesiae
- Forgetfulness
- Insomnia / sleep disturbance
- Palpitations
- Urine incontinence
- fatigue / lack of stamina
- Headaches

## WHI Study Overall Conclusions

- Over one year, 10,000 women taking estrogen plus progestin compared with placebo might experience:
  - 7 more CHD events
  - 8 more strokes
  - 18 more thromboembolic events
  - 8 more invasive breast cancers
  - 6 fewer colorectal cancers
  - 5 fewer hip fractures

## What is the Real Story about WHI?

- 16,608 ? “healthy” postmenopausal women
- Average age 63
- Average 12 years post-menopause
- ~70% were 60-79 years old (all participants in the memory substudy were 65-79 years old!!)
- Only ~ 10% were symptomatic ( ~15% in the first 5 years post-menopause)
- Women assigned to HRT (?primary vs secondary prevention?)
  - Smokers > 40%
  - Overweight (BMI 25-29) 35%; obese (BMI ≥ 30) 34%
  - Hypertension 36%
  - 42% discontinued treatment (intention to treat analysis used)
  - Doubts exist about validity of statistical analyses

## The Real Story about WHI...

- The question that needs to be answered:
  - Does estrogen replacement starting at the time of menopause help preserve function?
- The question that has been addressed by WHI:
  - Does hormone replacement therapy repair the damage that may have been done in the years without estrogen? – is this a fair question?....

## What can we conclude from WHI?

- Can a cardio-protective effect of starting HRT at the time of menopause be ruled out by WHI? **NO!!**
- Can the cardiovascular consequences of stopping HRT that began at the time of menopause be forecasted by WHI? **NO!!**
- Can the results of WHI be generalized to healthy women going through menopause? **NO!!**
- Can the results of WHI (on Premarin and PremPro) be generalized to other preparations of ERT/HRT? **NO!!**

## WHI: Main Criticisms

- Study participants:
  - older age range
  - Presence of cardiovascular risk factors
  - Presence of subclinical cardiovascular disease
- Validity of Statistical analysis
- Choice of HT regimen

## HT Breast Cancer Paradox

- HT and Breast Cancer Paradox:
  - ↑ Risk ↓ Mortality
- Potential explanations:
  - Unlikely to be initiation of cancer:
    - Premammographic → Preclinical → 1cm Clinical cancer takes 10 years
  - Detection/Surveillance Bias: Women on HT more likely to get mammograms
  - HT effects on preexisting tumors (think of hormone therapy as fertilizer)

## HT and Breast Cancer (cont'd)

- Contrasting Example
  - Cigarette smoking and Lung Cancer: RR=20-30
  - Family history, overweight, alcohol more significant risk factors for breast cancer than HT
- WHI Premarin-only arm actually showed reduction in breast cancer in participants who were compliant with therapy
- Women with BRCA gene can take estrogen therapy after oophorectomy without compromising the protective effect of oophorectomy against breast cancer

## Breast Cancer Rates Decline! MD Anderson News Release 12/14/2006

- Overall 7 percent relative decline in breast cancer incidence between 2002 and 2003, with 12% decline in women between ages 50-69 diagnosed with estrogen receptor positive (ER-positive) breast cancer
- Potential explanations:
  - Menopause hormone use was down by 30% since 2001 (this rapid decline is not a biologically plausible explanation of HT as cause of breast cancer; it supports hypothesis that HT increases growth of preexisting tumor, and removal of this "fuel" may make the difference between detectable or not by mammogram)
  - Mammograms fell 3% in 2003 among 50-64 years old
  - Calcium use went up by 40% from 2000 to 2003
  - Raloxifene use (to treat and prevent osteoporosis) increased by 12% from 2001 to 2003
  - Anti-inflammatory drugs use more than doubled from 1999 to 2003

## The HRT-Ovarian Cancer Scare (Lancet April 19,2007 e-publication)

- The Million Women Study, a trial in the United Kingdom of postmenopausal women, has found that those receiving HRT were, on average, 20% more likely to develop and die from ovarian cancer than women who never received therapy.
- The total incidence of ovarian, endometrial, and breast cancers in the study population is 63% higher in current users of HRT than in never users.



## HRT-Ovarian Cancer Scare (cont'd)

- many reservations concerning the MWS methodology
- Most epidemiologists would consider a relative risk of 1.2 is of minimal clinical significance but will inevitably reach statistical significance with very large numbers.
- Risk is far better reported in absolute numbers rather than relative risk or percentage. The absolute risk for ovarian cancer in the MWS was only one extra case per 2500 women after 5 years and mortality was one per 3300 over 5 years.
- It is most regrettable that the risks for all gynecological cancers have been added together to produce an estimated increase in risk of 63% for hormone users. Endometrial cancer should be prevented by combined hormone therapy, and adding percentages is inappropriate and will inevitably cause further unnecessary distress to the many women who are benefiting from HRT.

## "Critical Time Window" Hypothesis

- Initiation of HT early in menopause would confer cardiovascular and neural protection; whereas late initiation of HT would not be effective in disease prevention and may even be harmful
- Recent analysis of Nurses Health Study showed women who started HT early in menopause had significantly lower risk of heart disease
- "REMEMBER" pilot study of women aged 70-79 who started HT early in menopause performed significantly better in cognitive testing compared to never users

Grodstein, F. et al. *Journal of Women's Health* 2006; 15 (1): 35-44.  
MacLennan, A. H. et al. *Menopause* 2006; 13 (1): 28-36

## Recommendations by the International Menopause Society

- Use of HRT indicated for the relief of menopausal and urogenital symptoms, avoidance of bone wasting and fractures, and atrophy of connective tissue/epithelia
- There are not new reasons to place mandatory limitations on the length of treatment, including arbitrary cessation of HRT in women who started replacement during the menopausal transition and remain symptom-free while on HRT.
- HRT has been associated with a small absolute increase in deep vein thrombosis and pulmonary embolism, and apparent smaller increase in breast cancer, and reduction in the risk of colorectal cancer and fractures.

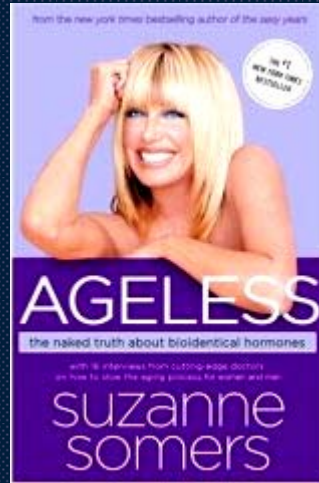
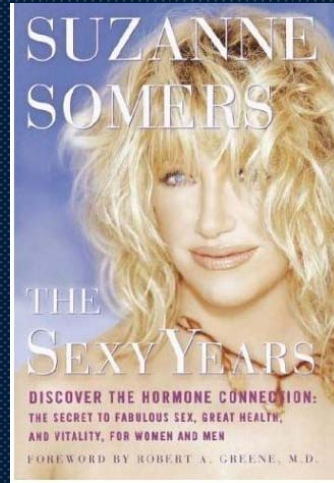
Maturitas. 2005 May 16;51(1):15-20

## Recommendations by the International Menopause Society

- Prevention, not treatment, is the most feasible goal...use of HRT should be part of overall strategy including lifestyle modification and other preventive measures...
- There is not evidence that HRT is beneficial for existing heart disease or dementia, but the initiation of hormones during the menopausal transition appears to provide protection
- The dose and regimen of HRT should be individualized
- the different types and regimens of HRT do not have the same tissue and metabolic effects and should not be grouped together as having a class effect
- Evidence from population studies cannot be generalized to individual patients...

Maturitas. 2005 May 16;51(1):15-20

## Bioidentical Hormones: Hope or Hype?



### The Bioidentical Hype...

- Misleading information regarding "Bioidentical Hormones" abound in lay literature and internet
- Bioidentical should mean identical to human version of the hormones – ie. Estrogens and progesterone and androgens that are found in a young woman's blood stream
- Bioidentical does not mean "compounded"! Many pharmaceutical hormones are bioidentical!!
- Compounded hormones are also synthesized from precursor hormones from plants
- Compounded hormones are made from same "raw material" as pharmaceutical bioidentical products
- If natural means unaltered from nature, there are no natural bioidentical hormones!!! (we cannot use desiccated human ovaries!)

## The Bioidentical Hype, and some Hope☺

- There is no valid evidence to support use of salivary hormone measurements for adjustment of HT dosages
- Popular Myths: Estriol is most important/abundant estrogen (NOT TRUE!!! Estriol is only found in significant levels in circulation during pregnancy); Estriol is safer and protects against breast cancer risk conferred by estradiol (NOT TRUE!!! Estriol is much weaker than estradiol, when used in equipotent doses, estriol stimulates breast and endometrium)
- Bioidentical hormones are not “risk-free” as promoted by certain individuals
- Most requests for Bioidentical hormones are driven by desire to improve quality of life – combine appropriate health-promoting strategies and individualized hormone therapy

## Pharmaceutical vs Compounding

- |   |   |
|---|---|
| ■ <b>Pharmaceutical hormones</b>                | ■ <b>Compounded hormones</b>                                      |
| ■ <b>Advantages:</b>                            | ■ <b>Advantages:</b>  |
| ■ Quality control / consistency                 | ■ Flexible combinations   |
| ■ Customized doses                              | ■ Customized doses  |
| ■ <b>Disadvantages:</b>                         | ■ <b>Disadvantages:</b>   |
| ■ Fixed doses (less flexibility for adjustment) | ■ Lack of regulation  |
|   | ■ Dependent on individual pharmacist for accuracy and consistency |

## Risks and Benefits of HRT

### Benefits

- Reduce menopausal symptoms
  - Hot flashes
  - Mood / sleep
  - Sexuality
  - Skin health
- Improves bone density
- Improves cholesterol
- Potentially decrease risk of dementia
- Reduces macular degeneration
- Decreases colon cancer

### Who should not take estrogen:

- Breast cancer
- Uterine cancer
- Undiagnosed vaginal bleeding
- Pregnancy
- History of thromboembolism\*
- Severe liver / gallbladder disease
- Severely elevated triglycerides\*

\*route of administration may make a difference

## Hormone Replacement Delivery Strategies

### Estrogen

1. Oral
2. Transdermal (patch, cream, gels) – advantage of less increase in clotting risk due to avoidance of first pass through the liver
3. Vaginal (cream, tablet, ring)
4. Nasal / sublingual / buccal (produce burst of serum level, not physiologic)

### Progestins

1. Oral
2. Transdermal (patch, cream)
3. Vaginal
4. Intrauterine device releasing progestin (#3 & 4 may be associated with less systemic side effect)

## Types of Estrogen and Progestin

### Estrogens

"Natural" (unaltered from nature)

- Premarin

Synthesized from plant source

- Plant based conjugated / esterified estrogen; eg. Ogen, Menest

Synthesized (bioidentical)

- Estriol
- Estrone
- Estradiol (oral, patches, gels, creams)

Synthetic

- Custom design; eg. Ethinyl estradiol

### Progestin (to protect against endometrial cancer)

"natural" (unaltered from nature)

- None

Synthesized from plant source (bioidentical)

- Prometrium
- Compounded progesterone

Synthetic

- Custom design – progestins have different effects and different potencies in tissues; eg. Provera, norgestimate, NETA, etc.

## Pros and Cons of Androgen Therapy (Testosterone and DHEA)

### Potential Benefits

- Improvement in mood / sense of well-being
- ? Improvement in muscle strength and stamina
- Bone formation
- Reduce hot flashes
- Increased bioavailable T correlates with sexual interest & responsiveness
- ? Effect on breast cancer

### Potential risks

- Skin side effects
  - Acne
  - Oily skin
  - Hirsutism
  - Scalp hair loss
- Lipids: lower HDL (transdermal does not appear to affect lipoprotein concentrations)

## Serum Levels of Sex Hormones: Replete, Deplete?

- A woman may be estrogen- or testosterone-replete even with low “laboratory values” if she is not experiencing symptoms reflecting a deficiency
- Serum hormone levels do not necessarily correlate with tissue levels, which may only be variably predictive of symptoms of deficiency
- Serum hormone levels are at best a crude guide
  - The relationship between serum hormone levels and physiologic function are currently not well understood

Alexander, JL et al. In press. *Menopause*, November 2004.

## Other Strategies to Manage Menopausal Symptoms

### Lifestyle modifications

- Diet (low fat, low glycemic / high fiber)
- Avoid excess caffeine / alcohol
- Regular exercise
- Stress reduction
- Acupuncture
- Mind-body / behavioral therapy
- Paced breathing
- Biofeedback and pelvic PT for incontinence

### Other meds:

- Low dose antidepressants for hot flashes

### Complementary approaches

- Phytoestrogens (eg. Soy, Red Clover)
- Chastetree berry
- Black cohosh
- Dong quai
- DHEA
- St. John’s Wort (beware of interaction with drugs)
- Important considerations when using alternative approaches: safety, efficacy and reliability of preparations

## The Bottom Line about HRT...

- Know your own risk factors
- Know what your goals are
- Practice the healthiest lifestyle you can...
- EACH WOMAN IS AN INDIVIDUAL WHO DESERVES A PERSONALIZED AND INTEGRATED STRATEGY TO SUPPORT A HEALTHY MENOPAUSAL TRANSITION!!

## Individualize Therapy!!!



"It's always best to start with a low dose and closely monitor the results."



## Resources

- American Association of Clinical Endocrinologists:  
[www.aace.com](http://www.aace.com)
- The Hormone Foundation: [www.hormone.org](http://www.hormone.org)
- American Society of Reproductive Medicine:  
[www.asrm.org](http://www.asrm.org)
- Society for Women's Health Research:  
[www.womenshealthresearch.org](http://www.womenshealthresearch.org)
- North American Menopause Society:  
[www.menopause.org](http://www.menopause.org)
- International Menopause Society:  
[www.imsociety.org](http://www.imsociety.org)

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