University of Nebraska Medical Center

# Modern Menopause:

## Optimizing Mental and Physical Wellness

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## From 1887:

" The ovaries, after long years of service, have not the ability of retiring in graceful old age, but become irritated, transmit their irritation to the abdominal ganglia, which in turn transmit the irritation to the brain, producing disturbances in the cerebral tissue exhibiting themselves in extreme nervousness or in an outburst of actual insanity."

• A.M. Farnum, 1887

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## Learning Objectives:

1. Discuss perimenopause and menopause, and the common physical and mental changes women experience during these periods.
2. Examine current data regarding mental health during the menopause transition.
3. Identify strategies to promote mental and physical wellness during this time of life.

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## Definitions

**Menopause** is the point at which menstruation permanently ceases.

**Perimenopause** is the period of years where a transition occurs between normal ovulatory cycles and cessation of ovulation and menses, characterized by irregular menses.

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## Defining Menopause & Perimenopause

A woman's lifetime

Perimenopause
First signs of change

Menopause
Diagnosed 12 months retrospectively

NAMS. Menopause Curriculum Study Guide. 2002.
Utian, WH. *Menopause*. 2001.

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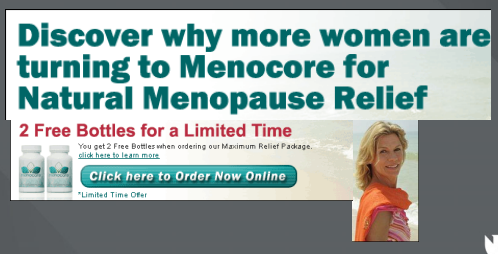
## Cultural Definition

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## Cultural Definition


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## Hormonal Changes

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## Two Key Physiological Changes

Menopause

- Loss of primary ovarian follicles
- Resulting decrease in serum and tissue estradiol levels

Gruber CJ, et al. *N Eng J Med.* 2002

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## Perimenopause

Overall estrogen levels are *increased* during early perimenopause, generally still within the normal range.

Menstrual cycles are initially shorter, with the nadir at age 42.

As long as ovulation is continuing, progesterone levels should be unchanged (indicated by regular menstrual cycles.)

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## Perimenopause

Over the next 8-10 years, average cycle length increases, then ovulation becomes more sporadic.

Follicle stores are depleted at an accelerated rate.

However, estrogen levels do not notably decline until within one year of menopause.

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## Menopause

After menopause, ovarian estrogen production is negligible.

However, postmenopausal women maintain estrogen production at lower levels through peripheral conversion of androgens to estrogen.

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## Estrogen

| Premenopausal: | | Postmenopausal: | |
|---|---|---|---|
| Estradiol | 40-400 pg/ml | Estradiol | 10-20 pg/ml |
| Estrone | 30-200 pg/ml | Estrone | 30-70 pg/ml |

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## Androgens

Produced by the ovaries and adrenal glands.

Ovaries still make testosterone, even after menopause! (for a while….)

Total androgen production decreases in the postmenopausal period.

However, the androgen to estrogen ratio increases dramatically.

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## Androgens

Net result: similar to somewhat diminished total androgen production in early postmenopausal period.

However, with decreased sex hormone binding globulin levels, free androgen may be increased, resulting in mild hirsutism or hair loss.

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## Androgens: Later Years

In the later postmenopausal period, ovarian androgen production stops.

All androgen is adrenally derived.

Net result: decreased total androgen.

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## Menopause-related Symptoms

| Vasomotor | Genitourinary | Other Systemic |
|---|---|---|
| Hot Flashes | Vaginal dryness | Fatigue |
| Headache | Dyspareunia | Reduced sexual desire/arousal |
| Palpitations | Vaginal itching/burning | Anxiety, irritability and depression |
| Night sweats | Urinary frequency, dysuria, urgency | Cognitive difficulties |
| Insomnia/sleep disturbance | | Backache/ stiffness |

Nevin JE, Pharr ME. *Prim Care*. 2002.
Stenchever MA, et al. Comprehensive Gynecology, 4th ed. 2001.

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## The Hot Flush

10% of women experience prior to menopause.

50-85% of women after menopause.

Usually last only 1-2 years, but may last for 5 or more years in up to 25% of patients.

Physiology not completely understood.

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## Medical Conditions More Common After Menopause

- Osteoporosis
- Atherosclerotic disease
  - Heart disease, stroke

Stenchever MA, et al. Comprehensive Gynecology, 4th ed. 2001.
Wenger NK. *Brit Med J.* 1997.

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## Does menopause cause depression?

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## Involutional Melancholia

During the early and mid-twentieth century, it was widely accepted that menopause was a time of poor psychological health.

In the Diagnostic and Statistical Manual, edition 2, depression during menopause was given a unique diagnosis.

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## Involutional Melancholia

However, in the 1970s, longitudinal studies demonstrated that depression during this time was not unique, and was not experienced by the majority of women.

This diagnosis was therefore excluded in DSM, edition 3, published in 1980.

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## Depression

Persistent sad, anxious, or empty mood.
Loss of interest or pleasure in activities.
Restlessness, irritability, or excessive crying.
Feelings of guilt, worthlessness, hopelessness.
Sleeping too much or too little.
Changes in appetite and weight.
Decreased energy.
Thoughts of death or suicide.
Difficulty concentrating, remembering, or making decisions.
Somatic (physical) complaints.

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## Incidence

- 12% of women will be diagnosed with major depression in their lifetimes.
- 20% of visits to primary care providers are related to depression.
- Women are twice as likely as men to be affected.

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## Incidence

- Mood disorders are more common during the perimenopausal years than pre- or post-menopause.
- New onset depression ~30%
- If prior history of depression ~60%.
- Decrease in the postmenopausal years.

Risk for new onset depression during the menopause transition: the Harvard Study of moods and cycles. Cohen et al. *Arch Gen Psychiatry* 2006

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## Menopause and Depression

U.S. National Health Examination Follow-up Study

No evidence of association between psychologic distress and menopause.

Decline in depression with age.

» C.M. Busch, et al, *Journal of Aging Health*, 1994

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## Menopause and Depression

Clinic based population surveys have revealed an increased rate of mood disturbance in perimenopausal and menopausal women presenting for care.

» Soares, et al, *Archives of General Psychiatry*, June 2001

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## Menopause and Depression

Conclusions:

- Menopause is not a time of adverse mental health for the majority of women.
- No reason to fear or expect a poor outcome in the majority of women.
- Good treatments are available.

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## Who is affected? Perimenopause

In Massachusetts Women's Health Survey, women with prolonged perimenopause were at slightly increased risk of depression.

Older studies showed an increase in psychiatric complaints in the period immediately proceeding menopause.

Possibly due to acute hormonal shift.

» D. Becker, et al, *Psychosomatics*, 2001
» P.A. Kaufert, The Modern Management of Menopause, 1994

29

## Who is affected? Life Stressors

In Massachusetts Women's Health Survey, the greatest predictor of a positive depression screen from one survey to the next was relationship issues.

The most likely predictor of successive positive screens was poor health and the number of chronic illnesses.

» N.E. Avis, et al, *Annals of Epidemiology*, 1994
» P.A. Kaufert, The Modern Management of Menopause, 1994

30

## Who is affected? Patient History

Past history of depression may predict depression in menopause.

60-77% of women with a past history of depression complained of depressive symptoms at menopause.

» D. Becker, et al, *Psychosomatics*, 2001

Risk for new onset depression during the menopause transition: the Harvard Study of moods and cycles. Cohen et al. *Arch Gen Psychiatry* 2006

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## Who is affected? Patient History

Prior history of premenstual dysphoric disorder (PMDD) and postpartum depression are positively correlated with depression at menopause.

» N.E. Avis, et al, *Annals of Epidemiology*, 1994

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## Common Symptoms

Emotional lability.
Fatigue, sleep complaints.
Vasomotor symptoms.
Somatic complaints.

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## Estrogen Deprivation Theory

Hypothesizes that the sudden change in estrogen levels preceding the menopause biochemically precipitates mood changes.

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## Estrogen Deprivation Theory

Accounts for increased mood symptoms in perimenopause.

Explains association between menopausal mood changes and PMDD and postpartum depression.

Unclear why women would not be universally susceptible to mood disorder in menopause.

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## The Domino Affect

Hypothesizes that mood changes in menopausal patients are a consequence of excessive vasomotor symptoms and sleep disturbance.

Benefit in mood with hormone therapy is a direct result of decreased vasomotor symptoms.

» L. Speroff, Clinical Gynecologic Endocrinology and Infertility, 7th ed.

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## The Domino Affect

Heart and Estrogen/Progesterone Replacement Study (HERS):

Women who had vasomotor symptoms had improvements in emotional measures of quality of life on HRT.

» M. Hlatky, et al, *JAMA*, Feb. 2002

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## Life Stressors

Onset of illness.
Illness or death of parents, spouse.
Empty nest syndrome.
Relationship stressors.
Bleeding irregularities.

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## Menopause and Cognition

Another common complaint during menopause is a change in cognitive performance.

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## Menopause and Cognition

Current research on cognition around the time of menopause is split regarding occurrence of cognitive decline and potential benefit of HRT.

Weakness: many ways to assess mental functioning.
Some differences have been detected based on free estradiol levels.

» L. Speroff, Clinical Gynecologic Endocrinology and Infertility, 7th ed.

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## The Domino Affect

Hypothesizes that cognitive changes in menopausal patients are a consequence of excessive vasomotor symptoms and sleep disturbance.

Benefit in cognition with hormone therapy is a direct result of decreased vasomotor symptoms.

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## Menopause and Cognition

Estrogen Benefits on CNS:

Protects against neuronal cytotoxicity.
Reduces serum concentration of amyloid P.
Increases synapses and neuronal growth.

» L. Speroff, Clinical Gynecologic Endocrinology and Infertility, 7th ed.

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## Menopause and Cognition

Primary Prevention of Alzheimer's:

"Hormone replacement therapy and incidence of Alzheimer disease in older women. The Cache County Study."

» P. Zandi et al, *JAMA*, 288:2123, 2002

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## Menopause and Cognition

Primary Prevention of Alzheimer's:

Any use of HRT decreased risk by 41%, and ten or more years of use reduced risk by 83%.

HRT had to be used ten or more years **before** the development of symptoms.

» P. Zandi et al, *JAMA*, 288:2123, 2002

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## Menopause and Cognition

Women's Health Initiative Memory Study (WHIMS)

- Enrolled women aged 65+ also participating in WHI
- Had to be off HRT for 5+ years
- Average time in study ~4 years
- Evaluating diagnosis of dementia and cognitive function

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## Menopause and Cognition

Women's Health Initiative Memory Study (WHIMS)

- Women on HRT were 2 times more likely to be diagnosed with dementia.
- No significant difference in cognitive function for women on HRT vs. placebo.

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## Menopause and Cognition

Cochrane Database Systematic Review 2008:

- 16 studies, ~10,000 women
- HRT does not prevent cognitive decline in older postmenopausal women
- Not known if there are subgroups that may benefit from HRT

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## Menopause and Cognition

WHIMSY: RCT of hormone therapy in women aged 50-55 showed neither benefit nor harm to cognitive function 7 years after stopping treament.

global cognitive function--memory, problem-solving skills

specific cognitive functions—verbal memory, attention, executive function, verbal fluency and working memory

JAMA Internal Medicine 2013

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# Management of Menopause Symptoms

The Hormone Therapy Controversy

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# Overview of HERS

Heart and Estrogen/progestin Replacement Study (HERS)

- Secondary prevention in women with CHD
- Found CEE with MPA does not reduce MIs
- More CHD events in hormone group during Year 1

Coope J. Management of the Menopause and Post-Menopausal Years. 1976. Baumgardner SB, et al. *Obstet Gynecol.* 1978.; Stampfer MJ, et al. *N Engl J Med.* 1985.; Wilson PWF, et al. *N Engl J Med.* 1985.; Hulley S, et al. *JAMA.* 1998.

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# Overview of WHI

Women's Health Initiative (WHI )

- Primary prevention in healthy women
- Age 50-79 (mean 63 y)
- Post-menopause (mean 12 y)
- Treated with CEE with (or without) MPA
- Primary outcome rate of fatal or non-fatal MI
- E-P arm terminated July 2002
- E-only arm terminated March 2004

Rossouw JE, et al. *JAMA.* 2002.
Anderson GL. Press conference remarks. 2004.

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## WHI Results: CHD

| E-P arm | E-only arm |
|---|---|
| HT neither protected nor worsened<br>Risk of CHD was 24% higher in E-P group<br>Not statistically significant<br>39 cases versus 30 cases per 10,000 p-y<br>Time trend existed | No increased risk |

Manson JE, et al. *N Engl J Med*. 2003.; WHI Steering Committee. *JAMA*. 2004.; Pradham AD, et al. *JAMA*. 2002.

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## WHI Results: Breast Cancer

| E-P arm | E-only arm |
|---|---|
| More invasive breast cancers<br>More total breast cancers<br>No difference in in situ breast cancers<br>Invasive cancers larger and more advanced<br>Time trend existed | 23% decrease<br>Approached statistically significant |

Chlebowski, RT. *JAMA*. 2003.
WHI Steering Committee. *JAMA*. 2004.

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## WHI Results: VTE

| E-P arm | E-only arm |
|---|---|
| Statistically significant increased risk<br>Hazard ratio for PE=2.13<br>8 additional cases of PE per 10,000 person-years | Rate also increased |

Rossouw JE, et al. *JAMA*. 2002.
WHI Steering Committee. *JAMA*. 2004.

54

## WHI Results: Stroke

| E-P arm | E-only arm |
|---|---|
| Statistically significant increased risk of ischemic stroke<br>Hazard ratio=1.44 | Slightly increased risk |

Wassertheil-Smoller S, et al. *JAMA*. 2003.
WHI Steering Committee. *JAMA*. 2004.

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## WHI Results: Osteoporotic Fractures

| E-P arm | E-only arm |
|---|---|
| Statistically significant lower risk<br>Hazard ratio=0.76 | Statistically significant reduction in hip fractures |

Cauley, JA. *JAMA*. 2003.
WHI Steering Committee. *JAMA*. 2004.

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## WHI Results: Colorectal Cancer

| E-P arm | E-only arm |
|---|---|
| Statistically significant decreased risk<br>Hazard ratio=0.61<br>Diagnosed cancers more advanced in HT group | No overall reduction<br>Significant age effect with lower rate in 50-59 age group |

Chlebowski RT, et al. *N Engl J Med*. 2004.
WHI Steering Committee. *JAMA*. 2004.

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## WHI Results: Quality of Life

| E-P arm | E-only arm |
|---|---|
| Subgroup of about 1,500 tested<br>No significant difference<br>In 574 who were 50-54 and symptomatic, improvement in sleep disturbance | No data available (study ended) |

Hays J, et al. *N Engl J Med*. 2003.

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## WHI Results: Gynecologic Cancers

| E-P arm | E-only arm |
|---|---|
| Rates low<br>No differences between groups | No data available (study ended) |

Anderson GL, et al. *JAMA*. 2003.

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## WHI Results: Dementia

| E-P arm | E-only arm |
|---|---|
| In subgroup over age 65, no protective effect seen with HT<br>Decrease in MMSE scores in HT group<br>When segmented by age, risk seen only in 75-80 age group | Non-significant trend toward increased risk |

Rapp SR, et al. *JAMA*. 2003.
Shumaker SA, et al. *JAMA*. 2003.; NIH. 2004.

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## Understanding WHI Results

What WHI results do not tell us

- Benefits and risks of beginning HT at menopause
- Benefits and risks for treatment of menopause-related symptoms
- Use of other doses, formulations, regimens, durations, and routes of administration of HT
- Information on events after cessation

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## Putting WHI Results into Context

- Well-designed study of mostly asymptomatic women distant from menopause
- Results have been generalized to other groups and to other HT formulations
- Not yet known if findings apply

Lobo RA. *Arch Intern Med.* 2004.

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## Counseling Patients About HT

1. Each woman must weigh risks and benefits in light of her circumstances
2. Women must put risks into perspective to make fully informed decision
3. Each woman must clarify her purpose and goal for using HT

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## Understanding Risk

| Relative Risk | Absolute Risk |
|---|---|
| Helps investigators identify causes | Helps assess impact on an individual |

- WHI: 26% increase in breast cancer in E-P arm
- This does not mean 26% chance of getting breast cancer

International Food Information Council. 2004.; Nurse Practitioners in Women's Health. 2004.; Rossouw JE, et al. *JAMA*. 2002.

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## Absolute Risk Quantified by WHI

| Outcome | Risk or benefit of E-P per 10,000 women |
|---|---|
| MI | 7 more cases |
| Stroke | 8 more cases |
| Breast cancer | 8 more cases |
| VTE | 18 more cases |
| Colorectal cancer | 6 fewer cases |
| Hip fractures | 5 fewer cases |

WHI. *June 2002 HRT Update*. 2002.

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## Absolute Risk Quantified by WHI

| Risk factor | Risk per 1,000 women | Extra breast cancers |
|---|---|---|
| Baseline risk | 45 | -- |
| HT 5 y | 47 | 2 |
| HT 15 y | 57 | 12 |
| Menopause after 54 | 58 | 13 |
| BMI > 31 | 59 | 14 |
| Lifetime excess alcohol | 72 | 27 |
| Lack of exercise | 72 | 27 |

Huang Z. *JAMA*. 1997.; LaCroix AZ. *Lancet*. 1997.; Longnecker MP. *Cancer Epidemiol Biomarkers Prev*. 1995.; Smith-Warner SA. *JAMA*. 1998.; Thune I. *N Engl J Med*. 1997.; WHI. 2002.

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## Hormone Therapy

Both WHI and HERS trials showed no improvement in measures of depression or quality of life in women on hormone replacement.

The exception: HERS women with vasomotor symptoms showed some mild improvement in depression symptoms.

» M. Hlatky, et al, *JAMA*, Feb. 2002
» J. Hays, et al, *NEJM*, May 2003

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## Hormone Therapy

- The KEEPS trial (Kronos Early Estrogen Prevention Study)
- Women 45-54 years
- Lower depression and anxiety scores on HT versus placebo
- Addition of SSRI provides additional benefit for perimenopausal depression.

Effects of hormone therapy on cognition and mood….Gleason et al. *PLoS Med.* 2015

Efficacy of citalopram as monotherapy or adjunctive treatment….Soares et al. J Clin Psychiatry 2003

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## Hormone Therapy

Double blind, randomized, placebo-controlled trial
Age between 40-55 years.
History of irregular menses or amenorrhea for <12 months. (Perimenopause)
Diagnoses of MDD, dysthymic disorder, or minor depression disorder by DSM-IV.
Transdermal patches of 17B-estradiol for 12 weeks.
Remission of depression in 68% of subjects treated with estradiol vs. 20% of women on placebo. (p=.001)
Similar improvement in physical complaints.

» Soares et al, *Archives of General Psychiatry* 2001

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## Psychiatric Approach

Treat depression as it would be treated at any other time.

Combination of pharmacotherapy and psychotherapy.

Refer to psychiatrist early.

This is the preferred treatment for women with isolated mental health symptoms and/or minimal vasomotor symptoms.

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## When do we use HT?

Treatment of hot flashes/night sweats.

Treatment of vaginal symptoms.

Treatment of mood changes in select patients.

In early years after menopause.

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## When do we avoid HT?

Women at high risk of complications of HT.

Women many years past menopause.

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## Alternatives

SNRIs such as venlafaxine:

Decrease hot flashes by ~50%.

May have additional benefits for mood symptoms.

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## What about compounded HT?

- No data to suggest this is safer or more effective than FDA approved hormone therapy options.
- North American Menopause Assoc, American College of Ob/Gyn, and the Endocrine Society advise against use of custom compounded HT.
- Endocrine Society 2016:
  - Numerous approved products available
  - No RCT demonstrating efficacy or safety
  - Not subject to regulatory oversight.

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## Lifestyle Changes

- Exercise.
- Improving sleep hygiene.
- Weight loss.

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## Physical Activity & Mental Health

- 169 women around menopause transition
- Previously low activity
- Baseline psychological battery
- Assigned to walking, yoga, or control

- Both walking and yoga associated with:
  - Increases in positive affect
  - Improved QOL
  - Decreased negative mental health outcomes

Elavsky, S. & McAuley, E. ann. behav. med. (2007) 33: 132.

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## Physical activity and VMS

Review of 24 studies on menopausal VMS and exercise:

Overall decrease in VMS with exercise.

Sternfeld, Dugan Obstet Gyn Clinics North AM Sept 2011

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## In Conclusion:

Even in situations where HRT is indicated, a comprehensive treatment strategy is the best approach.

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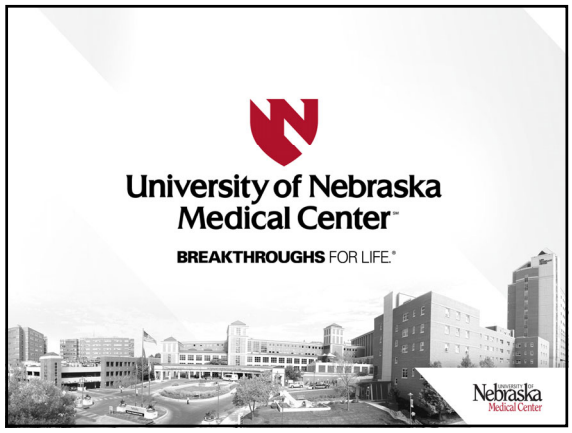
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