Guidelines for Managing Menopausal Symptoms
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Conflicts of Interest: None

Overview
• Natural history of menopause
• Hormone therapy: Risks and Benefits
• Menopausal symptoms
• Current role of hormone therapy for menopausal symptoms
• Non-hormonal treatment of menopausal symptoms

MENOPAUSE IS NOT A DISEASE

“Feminine Forever”
• Dr. Robert Wilson, 1966
• Replacing estrogen is like diabetics replacing insulin
• Women “will be much more pleasant to live with and will not become dull and unattractive.”
• Wyeth-Ayerst funded all expenses
Menopause Is A Positive Step

• Gallup poll 1997: Most middle aged American women “welcome menopause as a new and fulfilling life stage.”
• Goal: Support women in achieving a successful transition

Natural History of Menopause

• Average age is 51
• Predictors of age at menopause
  – Genetics
  – Family history
  – Ethnicity
    • Earlier in Latino and later in Japanese American compared to Caucasians
  – Smoking: about two years earlier
  – Reproductive history
    • Earlier menopause in women never having children and with shorter cycle length

Menopausal Symptoms: Prevalence

• Hot flushes (50% or more)
  • Often with perspiration
• Night sweats (50% or more)
• Sleep disturbance (40-60%)

OTHER SYMPTOMS

• Other symptoms happen at the time of menopause but are less clearly related to menopause
  – Mood changes
  – Cognition
  – Changes in sexual function
  – Urinary complaints
  – Joint pain
Vasomotor Symptoms

- Minnie Pause is a 53 year old woman who had her last menstrual period 18 months ago. She is still having hot flashes and awakens at least twice a night with them. She is considering taking estrogen but wants to know how much longer this will last. What do you tell her?

What do you tell her about when they will go away?

- Average duration is about 2 years and so they should be gone in about 6 months.
- Average duration is about 4 years
- Average duration is about 7 years
- They will never go away

Background

- Treatment for menopausal symptoms is based on their transitory nature
- Many clinical guidelines suggest that symptom duration is approximately 2 years
  - Many studies do not follow women more than 2 years
- Risks and benefits of hormone therapy depend on duration of use
  - “Use lowest dose for shortest duration”
Duration of Vasomotor Symptoms

• Objective: to estimate the natural progression of menopausal symptoms

Vasomotor symptoms

• Rigorous meta-analysis included 10 studies with over 35,000 participants
• Clear definition of vasomotor symptoms
• Assessed prevalence of symptoms and “bothersome symptoms”

Results

• Percent of women with symptoms increased in the two years before the final menstrual period (FMP), peaked one year after the FMP and did not return to premenopausal levels until 8 years after the FMP
• 50% of women had symptoms during the 4 years after FMP
• 10% of women had symptoms up to 12 years after FMP
Results: Bothersome Symptoms

- Avis NE et al. Duration of menopausal vasomotor symptoms over the menopause transition.
- Objective: to determine total duration of frequent vasomotor symptoms (VMS) during menopause transition, to determine how long frequent VMS persist and to identify risk factors for longer VMS duration

SWAN Study

- Multi-ethnic, multi-racial observational study of menopausal transition in 3302 women at 7 sites
  - 13 visits over 17 years
  - Analyses of 1449 women with frequent VMS
- Assessed VMS duration and persistence after FMP

Duration of Vasomotor Symptoms

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- JAMA Int Med 2015

Results

- Median duration of VMS was 7.4 years
  - FMP persistence 4.5 years
- Longer VMS duration in women who were pre or perimenopausal when symptoms began
  - Median 11.8 years
- Women who were postmenopausal when symptoms began had shortest duration
  - Median 3.4 years
- Longer VMS duration
  - African American, younger age, lower educational level, greater perceived stress and symptom sensitivity and higher depressive symptoms and anxiety
Impact
• Frequent VMS lasted more than 7 years for more than half of women
• The earlier VMS started the longer they were likely to last
• This can be included in decision making about menopausal symptom management

Minnie Pause….continued
• Now that Minnie knows that the symptoms could last for a while more, she definitely wants to do something about her intolerable hot flashes. Her only medical history is hypertension well controlled on lisinopril. She would like to hear your thoughts on hormones and whether they are a safe option for her.
• What do you tell her?

What do you tell her?
• Why don’t you try black cohosh- that will work just as well
• Venlafaxine is as effective as hormones and it is a lot safer
• Hormone therapy is probably ok, if you don’t take it for too long
• Absolutely not- no one takes hormones any more

Should I use hormones?
• Ok, so they may help my symptoms……but are they safe?
Background

• WHI trials designed to determine benefit/risk of hormone therapy when taken for chronic disease prevention
  – Primary efficacy outcome: CHD
  – Primary safety outcome: invasive breast cancer
• Combination trial stopped early due to increased breast cancer risk and unfavorable risk-to-benefit ratio

The News

• Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Post-stopping Phases of the Women’s Health Initiative Randomized Trials
• Aims:
  – Provide a comprehensive, integrated overview of findings from the 2 WHI hormone therapy trials with extended post-intervention follow-up and stratification by age and other important variables

Methods

• Post-intervention follow up through Sept 30, 2010 based on 81% surviving participants
• Utilized time to event methods based on intention-to-treat, global index calculated
  – CHD, invasive breast cancer, stroke, PE, colorectal cancer, endometrial cancer, hip fracture, and death
Results

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<tr>
<th>Post-intervention</th>
<th>CEE + MPA</th>
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<tr>
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<td>Diff/10,000 PY</td>
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<tr>
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</tr>
<tr>
<td>Breast CA</td>
<td>10</td>
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<tr>
<td>All-cause mortality</td>
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<td>Global index</td>
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- Global index HR was not modified by age (p>0.99 for trend)
- Absolute risks of adverse events were lower in younger than older women

Post-Intervention

<table>
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- Women in 50s had fewer events per 10,000 PY compared with women in 70s (p for trend, 0.02)

Conclusions

- Neither CEE + MPA nor CEE alone significantly affected all-cause mortality during or after the intervention phase
  - HT has a harmful effect on CHD risk among older women, results in younger women are inconclusive
- Risk–benefit ratio of HT is most favorable when initiated in younger menopausal women
  - Most risks and benefits from hormone therapy dissipate after stopping

Take Home Messages

- For women early in menopause, risks are lowest for hormone therapy and once therapy is stopped these risks wane
- Minnie is young and healthy and would be a candidate for hormone therapy for her vasomotor symptoms; would recommend revisiting the use of hormones annually
ACOG Recommendations

• Management of Menopausal Symptoms, ACOG Practice Bulletin #141, January 2014
  – ACOG. Obstet Gyne. 2014
• Level A Evidence:
  – Systemic HT is the most effective therapy for vasomotor symptoms, low dose has better side effect profile
  – Risks of combined systemic HT include VTE and breast cancer
  – It is recommended that providers individualize care and treat women with lowest effective dose for the shortest duration needed to relieve vasomotor symptoms

Minnie, continued...

• Minnie decides she wants to use hormone therapy and asks what she should start. You have heard that transdermal methods might be safer, but are not entirely sure what to recommend beyond that…

Transdermal Estrogen

• Avoids hepatic first pass metabolism
  – Decreased effect on serum coagulation factors, triglycerides, CRP
• Associated with a lower VTE risk
  – Canonico, 2007
• Associated with a lower risk of stroke
  – Renoux BMJ 2010
• No RCT comparisons of differing HT regimens and clinical CVD outcomes

Key Article

• ACOG Committee Opinion: Postmenopausal Estrogen Therapy: Route of Administration and Risk of Venous Thromboembolism
  – ACOG Committee Opinion #556, April 2013
• Prothrombotic effect of estrogen is possibly related to high concentrations of estrogen in the liver due to first pass effect
• Transdermally administered estrogen has little or no effect in elevating prothrombotic substances
Take home messages

• Transdermal estrogen has been associated with decreased risks of VTE compared with oral forms
• For Minnie, transdermal estrogen is safest, and it may be better to recommend it
  – And she needs a progestin as she still has a uterus

HT for Symptomatic Relief

• Any form of estrogen is highly effective
• Generally can be taken for a few years and gradually stopped
• A progestin should be added for women with a uterus
• Therapy can be tailored to a woman’s preference
• “Lowest dose for shortest duration”

Effective Dose Equivalents

• Dose that stops hot flashes in 80% of women
  – 1 mg micronized 17 beta estradiol
  – 50mcg/day transdermal 17 beta-estradiol
  – 0.625 mg conjugated equine estrogens
  – 1.25 mg piperazine estrone sulfate

Lower dose hormone therapy

• Effective in some trials
• Estimates of efficacy after 12 weeks
  – 38% placebo
  – 63% low dose estrogen
  – 83% standard dose estrogen
• Lower doses may take longer for maximal symptom relief
  – 12 weeks vs 4-8 weeks
• Less bleeding and breast tenderness and may require less progestin
Adding Progestins

• Medroxyprogesterone acetate
  – 2.5 mg daily
• Micronized progesterone
  • “Natural”
  • 200 mg for 12 days or 100 mg a day
• Safer for heart and breast?
  – Not proven
• Cyclic vs continuous?
• Levonorgestrel containing IUD?
  – Off label

Bazedoxifene/conjugated estrogen

• Duavee® approved for treatment of menopausal symptoms and prevention of osteoporosis
  – CEE 0.45 mg
  – Bazedoxifene 20 mg
• Bazedoxifene has estrogen agonist effects on bone and antagonist effects on uterine tissue
• Theoretic advantage
  – Relieve estrogen deficiency symptoms while possibly avoiding increased risks of endometrial and breast cancer

Bazedoxifene/conjugated estrogen

• Medication improved indices of vaginal atrophy and reduced daily number of hot flashes compared with placebo
  – (-9 vs -2.4)
• Similar incidence of VTE between groups
• May be useful for women who can’t tolerate progestin

Estee Jenn

• Estee Jenn is a 60 year old woman who has been on HT for 10 years. You have been trying to encourage her to stop it for a while but she has not wanted to do it. Her best friend has recently developed breast cancer; she has now decided to stop, and wants your advice on the best way to do it. What do you recommend?
**QUESTION**

- Taper by decreasing the daily dose over 6-12 months
- Taper by decreasing the number of days a week HT is used over 6-12 months
- Just stop

**Discontinuing hormone therapy**

- Symptoms will recur in up to 25% of women with stopping therapy
- Unclear if it is best to stop “cold turkey” or to taper
- Taper can be by daily dose or number of days per week or strength of transdermal estrogen
- Taper until mild symptoms
  - Maintain that dose until symptoms resolve

**Factors Associated with Successful Discontinuation of HT**

- 2,328 women participated in a survey about HT practices
  - 802/2090 attempted HT discontinuation
- 75% experienced hot flushes after discontinuation
- Factors associated with successful discontinuation:
  - MD advice, lack of symptom relief, vaginal bleeding and learning to cope with symptoms
- Factors associated with unsuccessful discontinuation: trouble sleeping, mood swings or depression
  
  Newton; J Women's Health 2014

**QUESTION**

- Estee has a resumption of her hot flashes after she stops her estrogen. What pharmacologic alternative do you suggest?
  - Paroxitene
  - Escitalopram
  - Venlafaxine
  - Clonidine
  - Gabapentin
OTHER DRUG TREATMENTS

- SSRIs
- Venlafaxine
- Desvenlafaxine
- Clonidine
- Gabapentin
- Overall efficacy:
  - 50-67% reduction in hot flash frequency with these regimens
  - Placebo effects generally large

Paroxitene

- Paroxitene CR led to a significant decrease in hot flash score
  - 62% in 12.5 mg group
  - 65% in 25 mg group
  - 38% in placebo group
- Avoid in women receiving tamoxifen
  - Decreases active metabolite of tamoxifen
  - Cytochrome P450 CYP2D6

Brisdelle

- First non-hormonal treatment approved for treatment of menopausal symptoms
  - Paroxetine Salt 7.5 mg
- “Efficacy”
  - Reduced hot flashes/severe hot flashes compared with placebo
  - 1 to 1.7 fewer severe hot flashes per day at different time points
  - Proportion with >50% reduction in moderate to severe hot flashes at 24 weeks
  - 48% vs 36%

Escitalopram

- Reduction in hot flash frequency
  - 55% in escitalopram group
  - 36% in placebo group
- Effective in African American and Caucasian women
- Effective regardless of coexisting anxiety or depression
  - Freeman, JAMA 2011
Venlafaxine

- Significant reduction in hot flashes
  - 61% vs 27% in placebo (p<0.01)
- 150 mg no more effective than 75 mg
  - Lopinzi, Lancet 2000

Venlafaxine vs low dose estrogen

- MsFLASH
- 339 peri and post-menopausal women with at least 2 bothersome VMS per day
  - Low dose estrogen (0.5 mg estradiol)
  - Venlafaxine extended release (75 mg)
  - Placebo
- Mean VMS frequency after 8 weeks
  - Joffe et al JAMA 2014

Results

- Number of VMS per day at 8 weeks
  - Estradiol 3.9 (2.9-4.9)
  - Venlafaxine 4.4 (3.5-5.3)
  - Placebo 5.5 (4.7-6.3)
- Treatment satisfaction highest for estradiol
- Both interventions well tolerated

Impact

- Both low dose estrogen and venlafaxine reduced symptoms more than placebo
  - No higher dose estrogen comparison
- Treatment satisfaction with estradiol somewhat higher but clinical significance unclear
Desvenlafaxine
• Industry sponsored trial of metabolite of venlafaxine
  – 700 women with severe hot flashes
• 64% reduction in hot flashes at 12 weeks
  – Vs 51% with placebo
• Hot flashes less severe in desvenlafaxine group
• Not currently FDA approved for this indication
  – Speroff, 2008

Clonidine and Gabapentin
• Clonidine
  – Start with 0.1 mg/day transdermal patch
  – 40% reduction in hot flashes
  – Side effects can be limiting
• Gabapentin
  – 45% reduction in hot flashes vs placebo (29%)
  – 900 mg a day more effective than placebo
  – 300-600 mg at bedtime may help with hot flashes that awaken patients from sleep

“Bioidentical” hormone therapy
• Custom-compounded, multi-hormone regimens
  – Dose adjustments based on serial serum or saliva hormone monitoring
  – No evidence that monitoring is useful
• No evidence it is better than conventional HT
  – Safety not established
• FDA has published statement that the claims are false and misleading
• Endocrine Society states that there is no scientific evidence for bioidenticals

Question
• Estee is tired of medications and would like to try an herbal therapy for treatment of her hot flashes. What treatment do you recommend?
  – Black Cohosh
  – Evening primrose
  – Ginseng
  – Dietary soy
  – Wild yam
  – None of the above
The News


• Objective
  – To update and expand the NAMS evidence-based position on nonhormonal management of menopause-associated vasomotor symptoms

Methods

• Systematic review of nonhormonal menopause treatments
• Costs, time, effort and adverse effects weighed against potential effectiveness
• Divided into categories
  – Recommended
  – Recommend with caution
  – Do not recommend at this time

Results

• Recommended
  – Cognitive behavioral therapy and hypnosis
  – Paroxetine is the only FDA-approved non-hormonal treatment
    • Other SSRIs, SNRIs, gabapentin and clonidine have shown efficacy
• Recommend with caution
  – Weight loss
  – Mindfulness-based stress reduction
  – Soequol derivatives of soy isoflavones
  – Stellate ganglion block
• Do not recommend at this time
  – Cooling techniques, avoidance of triggers, exercise, yoga, paced respiration, relaxation, OTC supplements and herbal remedies, acupuncture, chiropractic, calibration of neural oscillations

Impact for practice

• When recommending nonhormonal treatments for menopause, clinicians should be aware of the limited evidence supporting them
• Although many proposed menopause treatments may not have been proven to be beneficial for VMS treatment, some may be relatively benign (e.g., cooling techniques) or have other benefits (e.g., yoga and exercise)
**Guidelines for Hormone Therapy Use**

**Recommendations**

- **USPSTF:** Harmful effects are likely to exceed the chronic disease prevention benefits in most women
- **ACOG, AHA, and Canadian Task Force:** Recommend against use of HT for prevention of chronic disease
- **NAMS 2012:** When alternative therapies not appropriate, extended use of HT appropriate for women at high risk of fracture

**NAMS 2012**

- Focuses on emerging differences between ET and EPT as varying ages and time intervals since menopause
- Individualization in decision to use HT: consider individual health, personal risk factors and quality of life priorities
- ET has a more favorable risk benefit profile which allows for more flexibility in duration of use
- EPT associated with an increased risk of breast cancer incidence and mortality after 3-5 years
- Premature menopause: HT until median age of natural menopause and then reassess

**NAMS Recommendations for Older Women (2015)**

- **Statement:**
  - Provided that the woman has been advised of the increase in risks associated with continuing HT beyond age 60 and has clinical supervision, extending HT use with the lowest effective dose is acceptable under some circumstances, such as for the woman who has persistent bothersome menopausal symptoms and for whom her clinician has determined that the benefits of menopause symptom relief outweigh the risks.
  - Use of HT should be individualized and not discontinued solely based on a woman’s age.
  - Decision to continue or discontinue should be made jointly.
Donna

- Donna is a 67 year old woman with significant vaginal atrophy. She has not been sexually active for some time and when asked if this is bothersome to her she admits it causes difficulties in her relationship with her husband. She is very hesitant to use hormones in any form because she reads a lot of articles about them and doesn’t think they are safe. She has significant pain with intercourse, no other major symptoms.

- What recommendations do you have?

What do you tell her?

- Vaginal moisturizers
- Estrogen crème will work and it is safer than the pills
- Why don’t you try an estrogen vaginal ring? It’s safer than the crème
- There is a new medication called ospemifene that could help

Background

- VVA is associated with physical discomfort, sexual dysfunction, emotional distress, and reduced quality of life
- Incidence of VVA can be ~60%
- Current treatment options are only estrogen or vaginal moisturizer

Treatment Options

- Vaginal moisturizers are used several times a week and vaginal lubricants are used for sexual intercourse
  - Moisturizers: Replens, Vagisil
  - Lubricants: Astroglide, K-Y Jelly, Elegance Women’s
- Can improve symptoms of vaginal dryness or coital comfort but do not reduce vaginal atrophy
Local Estrogen

- Most effective treatment for moderate to severe symptoms of vaginal atrophy
- Can also reduce UTIs and symptoms of overactive bladder
- Typically given daily initially and then twice a week

Local Estrogen Preparations

- Creams
  - Estradiol (100 µg/g) or CEE (0.625 mg/g)
  - 1 applicator qd for 7 days
  - Then ¼ to ½ applicator twice a week
- Tablet
  - Vagifem (10 µg estradiol)
  - 1 tab vaginally for two weeks then one tab twice a week
- Ring
  - Estrin
  - Releases 7.5 µg estrogen daily for 90 days

Ospemifeme

- Novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy
- Trial in over 600 women with moderate to severe dyspareunia
- Severity of vaginal pain improved by 2-3 levels in 52.8% of ospemifene, 38.8% of placebo
- Hot flushes were the most common AE
  - Only 4.6% in treatment group discontinuing due to AE

Key Article

- Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society
  - NAMS. Menopause, 2013.
- <10% of women report their provider initiated a conversation about VVA
- 1st line therapy: lubricant with intercourse and vaginal moisturizer [Level A]
- Mod-severe VVA: low dose vaginal estrogen or ospemifene [Level A]
Take Home Messages

• Screen women for dyspareunia and VVA—it's common and distressing for women

• Ospemifene is a SERM with apparent positive effects on VVA without endometrial or VTE events
  – Vasomotor symptoms are the most common side effect
  – Not for use in women with a history of breast cancer
  – FDA approved for moderate-severe dyspareunia

Treatment of Vaginal Atrophy

• Regular sexual activity helps maintain vaginal health

• Start with moisturizers and lubricants

• Vaginal Estrogen if moisturizers and lubricants are insufficient
  – Type of estrogen dependent on patient preference

• Ospemifene if a woman can't (arthritis, obesity, vulvodynia) or prefers not to use vaginal product

Women with Breast Cancer

• Topical estrogen has minimal systemic absorption but it is not zero

• Start with non-hormonal options

• Women on aromatase inhibitors
  – Probably best to avoid

• Women with low risk of recurrence
  – Probably ok
  – In concert with oncologist and with discussion of pros and cons

Summary

• Average duration of menopausal symptoms is approximately 4-7 years but seems to be longer in younger women

• Estrogen either alone or with a progestin is not recommended for chronic disease prevention in postmenopausal women

• Risks and benefits of estrogen treatment may differ in older and younger women
Summary

• Estrogen works best for symptoms
  – Use lowest dose for shortest duration
• Best method for discontinuation is not known
• Start with lifestyle modifications and nonprescription remedies
• Drug alternatives include SSRIs, SNRIs, gabapentin, clonidine and combined estrogen/SSRI

Vaginal Atrophy

• Regular sexual activity, moisturizers and lubricants
• Topical estrogen: start with higher dose and then decrease to maintenance dose
• Ospemifene: for women who can’t or won’t use estrogen
• Women with breast cancer individualized decision

Questions?

“Having nine lives is cool, but if I have to go through menopause again, forget it!”