Menopause management after breast cancer
Disclosures

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• Beneficiary: Novo, Lilly
  • Pfizer/Wyeth
  • MSD
  • Bayer
  • Janssen-Cilag
  • Adcock-Ingram

• Honoraria/ travel/ Advisory Boards

• Former president SAMS

• Member of SAMS, NAMS, IMS, SASOG, RCOG, SAMA, SAUGA, IUGA

• LOC RCOG 2017
Menopause Matters

Over the past century, postmenopause life expectancy has increased by 30 years\(^1,\)\(^2\)

100 years ago
Menopause was at the end of lifespan (~51 yr)\(^1\)

50 years ago
Women were living 20 yr after menopause (<1/4 of lifespan)\(^3\)

Now
Women are living nearly 30 yr after menopause\(^3\)

How do we now contribute to improved wellness of those 30 years of life that women did not have 100 years ago?

Number of Women Reaching Menopause Continues to Grow

- In the United States, ~6000 women reach menopause each day\(^1\)
- By 2020, an estimated 78 million US women will be 45 years of age or older\(^2\)

### Consequences and Symptoms of Menopause and Estrogen Deficiency

<table>
<thead>
<tr>
<th>Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor disturbances¹</td>
<td>• Hot flushes</td>
</tr>
<tr>
<td></td>
<td>• Night sweats</td>
</tr>
<tr>
<td>Loss of bone mass²</td>
<td>• Increased risk of osteoporotic fracture</td>
</tr>
<tr>
<td>Sleep, mood, and cognitive changes¹</td>
<td>• Sleep disturbances</td>
</tr>
<tr>
<td></td>
<td>• Mood swings</td>
</tr>
<tr>
<td></td>
<td>• Anxiety, depression, cognitive symptoms (reduced concentration, impaired memory)</td>
</tr>
<tr>
<td>Urogenital atrophy¹</td>
<td>• Vaginal dryness</td>
</tr>
<tr>
<td></td>
<td>• Urinary symptoms</td>
</tr>
<tr>
<td></td>
<td>• Dyspareunia and other sexual concerns</td>
</tr>
</tbody>
</table>

Menopausal Symptoms Are Prevalent and Bothersome

Vasomotor symptoms
• 65% of postmenopausal women have hot flushes\(^1\)
  - Moderate to severe in up to 60% of symptomatic women\(^2\)
• Hot flushes persist for an average of 4 to 5 years\(^3-5\)
• Women with more bothersome hot flushes are more likely to report anxiety and depression\(^6\)
• Night sweats may be associated with sleep deprivation and increased daytime sleepiness
  - Can negatively affect mood, social relationships, and productivity\(^7\)

Vulvovaginal atrophy
• Symptoms reported in 45% of postmenopausal women\(^8\)
• Dyspareunia increases with increasing age\(^9\)

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Symptoms May Begin Even Before the Last Menstrual Period


CI=confidence interval; FMP=final menstrual period.
Symptoms May Persist Long After Menopause

- **Hot flushes**: Sudden onset of an uncomfortable sensation of heat, accompanied by skin flushing and sweating, usually of the chest and face
- **Night sweats**: Hot flushes that occur during sleep\(^1,2\)
- Frequency of hot flushes varies, but tends to remain consistent for an individual\(^3\)
  - Daily, infrequently (weekly or monthly), or as often as every hour
- Meta-analysis of 10 studies involving 35,445 women\(^4\)
  - Nearly 50% reported VMS 4 years after their FMP
  - 10% reported symptoms continuing to 12 years after their FMP
  - Median duration of VMS symptoms = 4 years among symptomatic women

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VMS=vasomotor symptoms

Meet the Super Flasher: Some Menopausal Women Suffer Years of Hot Flashes

By TARA PARKER-POPE   JULY 25, 2016 1:08 PM

410
Prevalence of VMS by Ethnicity During the Menopausal Transition

Population included 3188 women enrolled in the Study of Women’s Health Across the Nation from 1996 through 2002.

Presence and Increased Severity of VMS Associated With More Physician Visits

<table>
<thead>
<tr>
<th>Menopause-related physician visits</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 yr since FMP</td>
<td>0.42</td>
<td>0.67</td>
<td>1.31</td>
<td>1.30</td>
</tr>
<tr>
<td>5-10 yr since FMP</td>
<td>0.66</td>
<td>1.33</td>
<td>1.28</td>
<td>4.39</td>
</tr>
<tr>
<td>Cost (2010) associated with menopause-related physician visits</td>
<td>$257.02</td>
<td>$573.89</td>
<td>$834.43</td>
<td>$961.18</td>
</tr>
</tbody>
</table>

- Women with severe VMS had 2 more physician visits in the past 6 months vs those without VMS.
- Women with mild VMS had 1 more physician visit in the past 6 months vs those without VMS.
- The cost associated with physician visits increased by 123% for the Mild group, by 224% for the Moderate group, and by 274% for the Severe group, vs the No VMS group.

National Cancer Registry (NCR):

CANCER REALITY CHECK

Every year 14 million people world-wide hear the words:
"You have cancer"

Top 5 cancers among
Stats as per National Cancer Registry (2008)

SA Women
Lifetime risk 1:9
1. Breast
2. Cervical
3. Origin Unknown*
4. Kaposi Sarcoma
5. Colorectal

SA Men
Lifetime risk 1:8
1. Prostate
2. Origin Unknown*
3. Lung
4. Kaposi Sarcoma
5. Colorectal

*‘Origin unknown’ means that it is not possible to determine where the cancer originated in the body

90% of cancers are caused by environmental & lifestyle factors such as smoking, diet & exercise

- More than 100 000 South Africans are diagnosed with cancer every year
- South African cancer survival rate is 6/10
- One in 4 South Africans is affected by cancer through diagnosis of family, friends or self

CANCER ⇒ TB + AIDS + MALARIA

Globally cancer kills more people than TB, AIDS and Malaria combined

Centre for Disease Control and Prevention (CDC)
Roughly 1 in 8 U.S. women will develop invasive breast cancer sometime during her life. (American Cancer Society, 2015)
Globally, breast cancer is the most prevalent cancer in women.

New cancer cases (all ages), females 5,060,657:

- Breast: 1151289 (22.7%)
- Cervix uteri: 493243 (9.7%)
- Colon and rectum: 472687 (9.3%)
- Lung: 386991 (7.6%)
- Stomach: 330518 (6.5%)
- Liver: 204499 (4.0%)
- Esophagus: 198783 (3.9%)
- Ovary, etc.: 184043 (3.6%)
- Corpus uteri: 146723 (2.9%)
- Other: 1491972 (29.5%)

ASR (incidence): 37.7
ASR (deaths): 13.2

http://www-dep.iarc.fr/
Globocan 2002, IARC
Breast cancer

- The most frequent cancer in women
- Incidence: 124 cases / 100,000 women/years
- Lifetime risk: 12.1%
- Risk between 50 and 60 years: 2.4%

National Institutes of Health,
http://seer.cancer.gov,
accessed April 2010
LEADING CAUSE OF DEATH: PERCEIVED

- 38% Breast cancer
- 18% Heart disease
- 13% Ovarian cancer
- 16% Other cancers
- 1% Lung cancer
- 2% Other cancer
- 1% Smoking
- 1% Stress
- 1% Don’t know/other
- 2% Old age

Source: Gallup poll
LEADING CAUSES OF DEATH: ACTUAL

- Heart disease: 45%
- Breast cancer: 4%
- Ovarian cancer: 5%
- Lung cancer: 11%
- Other cancer: 4%
- Pneumonia: 4%
- COPD: 2%
- Other: 5%
Breast cancer has a favorable prognosis
10-year survival rate:

80%
Survivorship - A New Paradigm

“Survivor: An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also impacted by the survivorship experience and are therefore included in this definition.”

Medical and social condition with major economic implications

NCI 2004
“The Three Seasons of Survival”

- Acute
- Extended
- Permanent

Fitzhugh Mullan NEJM 1985
Symptom Management

- Women with breast cancer have many adverse symptoms, of which some are specific to premenopausal patients

- Hot flushes: non-hormonal drugs, such as antidepressants and anti-seizure compounds

- Vaginal dryness and dyspareunia- Non-estrogenic vaginal lubricants

- Cancer-related fatigue- exercise

Special Issues for Cancer Survivors

• Chemotherapy often leads to temporary/permanent loss of ovarian function

• Unpredictable as far as who will regain function. Younger women tend to have a greater chance of regaining function than older women

• Medications used as ongoing therapy: tamoxifen and aromatase inhibitors exacerbate hot flushes.
Hot Flushes

Osteoporosis

MSK

Cardiovascular Disease

COPYRIGHT OF SPE
Bone Loss Can Lead to Osteoporosis

- Women experience rapid acceleration in bone loss during the first few years after menopause

Adapted from Finkelstein JS. In: Cecil Textbook of Medicine; 1996;1379-1384.

Postmenopausal Osteoporosis: Rationale for Prevention*

• Osteoporosis, the most common bone disease in humans, becomes a serious health threat in postmenopausal women

• Bone effects of lower levels of estrogens at menopause
  - Decrease in bone mass and architectural deterioration of bone tissue
  - Bone remodeling, which can lead to substantial loss of bone over time
  - Asymptomatic bone loss, resulting in reduced bone strength

• Approximately 50% of women in the US ≥50 years of age have low bone mass, putting them at risk for osteoporosis
  - By age 80 years, many women have lost ~30% of their peak bone mass

*Estrogen-based therapies are indicated only for the prevention of postmenopausal osteoporosis.

Accelerated Bone Loss in Early Menopause

• Begins during menopausal transition\textsuperscript{1}
  - VMS are associated with increased risk of bone loss\textsuperscript{2}
  - Women with hot flushes may have lower BMD compared with women without hot flushes\textsuperscript{2}
    • Consequently, younger women with VMS may be at an increased risk of osteoporosis and osteoporotic fractures

• >50\% of women aged 50-59 yr have either low bone mass or osteoporosis\textsuperscript{3}

• Low bone mass and osteoporosis increase fracture risk\textsuperscript{4}

\begin{itemize}
\end{itemize}
Age-related fractures

Incidence/100,000 person-year

Age group, year

MEN

WOMEN

Colles'

Vertebrae

Hip

Vertebrae

Colles'

Hip

>85

>85

Burden of Disease

- 1 out of 4 osteoporotic hip fractures result in long-term nursing home care
- One half of these are unable to walk without assistance
- 24% greater risk of dying within one year
Significant Burden of Fractures Resulting From Low Bone Mass

- Projected annual direct costs of osteoporosis (includes both men and women)\(^1\)
  - $25.3 billion by 2025 and ~$50 billion by 2040

- Osteoporotic fractures account for
  - ~$17 billion in direct medical costs\(^1\)
  - >400,000 hospital admissions\(^2\)
  - ~2.5 million physician visits\(^2\)
  - >180,000 nursing home admissions\(^2\)

- Among women who experience osteoporotic hip fracture\(^3\)
  - 20% die within 1 year
  - 50% never regain their previous level of function
  - 25% require assisted living

*Estrogen-based therapies are indicated only for the prevention of postmenopausal osteoporosis.

HIP FRACTURES

50% Likely to become permanently disabled

20% are likely to die

http://www.osteoporosis.ca/english/About
VMS Associated With Decreased BMD

• Bone substudy of SWAN (Study of Women’s Health Across the Nation)
  - A prospective study characterizing women’s health status across the menopause transition
  - Age range, 42-52 yr; mean age, 46 yr at entry; n=2213

• BMD was consistently lower among women with any VMS vs women without VMS, regardless of menopausal stage

Depression as a Risk Factor for Osteoporosis

✓ Association between depression and low bone mineral density

✓ Depression may induce bone loss and osteoporotic fractures
  ✓ Via specific immune and endocrine mechanisms
  ✓ Potential effect of specific antidepressants
  ✓ Possible role of poor lifestyle

SSRIs, Bone Mineral Density & Risk of Fracture

✓ Experimental data have identified a functional 5-HT system in bone

✓ SSRIs may have a direct negative influence on bone regulation

✓ Risk of fractures seems to be greater with SSRIs than with tricyclic antidepressants

Management = Fracture Prevention

Prevent / Treat Falls Risk

<table>
<thead>
<tr>
<th>TYPICAL PATTERNS OF FALLING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture</td>
</tr>
<tr>
<td>Wrist fracture</td>
</tr>
</tbody>
</table>

Prevent / Treat Osteoporosis
MSK effects of AIs: Arthralgia

• Arthralgia is a class effect with treatment with AIs (10-15% incidence)

• Lack of standardized definition and toxicity assessment methods of MSK symptoms and arthralgias may be a reason for variable reported incidence of arthralgia in AI treated women

• Arthralgia and other forms of MSK pain are common even among healthy older women; their incidence rises substantially during the perimenopause, with some evidence of a subsequent decline in postmenopausal women
ATAC: First Arthralgia Event—Time to Onset

Treatment first received

Tamoxifen
Anastrozole

6-month first event rate = D/S, where D is the decrement in the Kaplan-Meier (KM) event-free estimate over the previous 6 months, and S is the KM estimate 6 months prior to the time point.
Management MSK Health: Women on Adjuvant AI therapy

• Nutritional supplementation
  – Adequate protein consumption
  – Appropriate intake of other vitamins and minerals
    • Calcium (1200 mg/day)
    • Vitamin D (800-2000 IU/day)

• Lifestyle advice
  – Minimum of 30 minutes of physical activity of modest intensity on most, if not all, days of the week
  – Patient education material with specific exercises and instructions for exercise, moving safely, maintaining optimal posture
  – Smoking cessation
  – Limiting alcohol
  – Undertaking steps to minimize falls
Management of Arthralgia
Pharmacological Approaches

• Pain may be relieved with:

  – Oral medications:
    • Acetaminophen (<4 g/day)
    • NSAIDs → ie, naproxen (500-750mg/day)
    • COX2 Inhibitors
      – especially in patients with increased risk for GI & lower risk of CV complications
    • Dose and duration are important!
      – Therapeutic dose for a minimum of 2 weeks

• Consider referral to rheumatologist for complicated cases
AIs vs. Tamoxifen

• **AIs** offer superior efficacy with regard to disease-free survival rates

• **AIs** are well tolerated

  • Lower risk of…
    – Deep vein thrombosis (DVT)
    – Uterine malignancies
    – Hot flushes
    – Vaginal discharge

• Higher risk of MSK disorders
  – Bone and joint pain (arthralgia)
  – Loss of bone mineral density
  – Increased incidence of fractures
MSK effects of AIs: Increase of fracture in phase III trial of AIs

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidences of fractures (%)</th>
<th>Aromatase inhibitor</th>
<th>tamoxifen</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC (68 months)</td>
<td>11</td>
<td>7.7</td>
<td>3.1</td>
<td>2.0</td>
</tr>
<tr>
<td>IES (31 months)</td>
<td>3.1</td>
<td>2.3</td>
<td>5.3</td>
<td>4.0</td>
</tr>
<tr>
<td>MA17 (30 months)</td>
<td>5.3</td>
<td>4.6</td>
<td>5.7</td>
<td>1.0</td>
</tr>
<tr>
<td>BIG 1-98 (26 months)</td>
<td>5.7</td>
<td>4.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>ABCSG/ARNO (28 months)</td>
<td>2.0</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

• Aromatase inhibitors are recommended as adjuvant therapy in women with hormone receptor-positive breast cancer and have proven superiority over tamoxifen

• Arthralgia and bone fragility are class effects which can be managed by non-pharmacological and pharmacological means

• Consider a multifaceted approach for management of MSK health:
  – Lifestyle changes
  – Nutritional supplementation
  – BMD monitoring
  – Pharmacological intervention
  – Referral to Rheumatologist when is appropriate
BMD Results from ATAC

• For both a steroidal and a non-steroidal aromatase inhibitor, normal baseline BMD seems to identify patients at low risk of developing osteoporosis
  – In the ATAC study, no patient with normal BMD at baseline became osteoporotic after 5 years of anastrozole

• Regular monitoring of BMD is essential in aromatase inhibitor-treated patients with pre-existing osteopenia, to target bone protection strategies directly to patients at particular risk

ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial was an international randomised controlled trial of 9366 women with localized breast cancer : Lancet. 2005
Monitoring Bone Health

• Low initial BMD increases risk of AI induced bone loss

• Management should include:
  – Baseline and regularly scheduled bone density measurements

• Initial assessment of a breast cancer patient should include:
  – Detailed review of risk factors for osteoporosis
  – History of fragility fracture
  – Baseline BMD
Management of MSK health

Women starting aromatase inhibitor therapy

Baseline DXA scan of hip and spine (T score)

- Normal
- Low Bone Mass
- Osteoporotic

Nutritional supplement
Lifestyle choices
BMD measurement: every 1-2 years

Nutritional supplement
Lifestyle choices
Annual BMD measurement
Candidate for bisphosphonate treatment
Refer to rheumatologist or endocrinologist
Conclusion

- AIs improve DFS compared with tamoxifen in postmenopausal women with HR+ breast cancer

- AIs are generally associated with improved side effect profile improved vs. tamoxifen except for BMD loss and arthralgia

- Adequate monitoring of baseline bone density and any changes associated with treatment appears to be crucial for reducing the risk of fracture

- The appropriate management of arthralgia and other bone-related symptoms of aromatase inhibitor treatment is crucial for AI patient compliance
First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women

Based on GRADE A evidence*

<table>
<thead>
<tr>
<th>Type of Fracture</th>
<th>Antiresorptive Therapy</th>
<th>Bone Formation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bisphosphonates</td>
<td>Denosumab</td>
</tr>
<tr>
<td></td>
<td>Alendronate</td>
<td>Risedronate</td>
</tr>
<tr>
<td>Vertebral</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Hip</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Non-Vertebral†</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

† In Clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.

*For postmenopausal women, indicates first line therapies and Grade A recommendation. For men requiring treatment, alendronate, risedronate, and zoledronic acid can be used as first-line therapies for prevention of fractures (Grade D).

**Hormone therapy (estrogen) can be used as first-line therapy in women with menopausal symptoms.
Appropriate medical therapy
Cardiovascular Disease
Mortality Rates in Women

At Every Age, More Women Die of Heart Disease Than Breast Cancer


<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mortality Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-49</td>
<td>800</td>
</tr>
<tr>
<td>50-54</td>
<td>1200</td>
</tr>
<tr>
<td>55-59</td>
<td>1600</td>
</tr>
<tr>
<td>60-64</td>
<td>2500</td>
</tr>
<tr>
<td>65-69</td>
<td>4500</td>
</tr>
<tr>
<td>70-74</td>
<td>6500</td>
</tr>
<tr>
<td>75-79</td>
<td>800</td>
</tr>
<tr>
<td>80-84</td>
<td>400</td>
</tr>
<tr>
<td>85+</td>
<td>0</td>
</tr>
</tbody>
</table>

Coronary Artery Disease
Stroke
Lung Cancer
Breast Cancer
Colon Cancer
Endometrial Cancer
Prevalence of coronary vascular disease (CVD) and some risk factors
USA females 2004

- Total CVD
- CHD
- Hypertension
- Smokers
- Hypercholesterolemia
- Overweight
- Obese
- Diabetes

% of Population

www.americanheart.org
CVD and menopausal status

Adapted from the Framingham Study, DHEW No 74, 1974
CVD risk factors

• Lipids and lipoproteins
• Glucose and insulin metabolism
• Body fat distribution
• Coagulation and fibrinolysis
• Homocysteine
• Inflammatory markers
• Blood pressure
• Arterial function
Management

- Diagnose
- Support/Encouragement
- Diet
- Exercise
- Weight loss
- Refer
Hot Flushes
Hot flushes

- Hot flushes are most common menopausal symptom.
- Major impact on quality of life.
- Estrogen is best and most logical treatment— but what about the breast cancer survivor?
- Of currently available alternatives, SSRIs or gabapentin seem best.
Lifestyle Modifications

<table>
<thead>
<tr>
<th>Avoid triggers: stress, caffeine, alcohol, spicy foods, beverages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce stress: meditation, yoga, massage, paced breathing</td>
</tr>
<tr>
<td>Keep cool: drink cold drinks, bathe in cool water, use fans and cotton sheets, wear appropriate clothing</td>
</tr>
<tr>
<td>Exercise: aerobic and weight-bearing exercises</td>
</tr>
</tbody>
</table>

The effects of these measures have not been evaluated in randomized trials.
Hot Flushes: Demographics, Lifestyle, Health

- Symptoms vary by race/ethnicity
  - More African Americans and Hispanics than Caucasians affected
  - Fewer Chinese than Caucasian affected

- Significant association with
  - BMI
  - Passive smoke exposure
  - History of premenstrual symptoms
  - Use of OTC pain medication
  - History of comorbidities
  - Perceived stress
  - Age

Alternative Approaches for Vasomotor Symptoms: Lifestyle Adaptations

- Limited effectiveness
  - Cooling body core temperature
  - Exercise
  - Paced respirations (catecholamine control)
  - Relaxing activities
    - yoga, massage, meditation,
    - paced respiration, leisurely bath
  - Avoid Triggers
    - spicy food, hot drinks, caffeine, alcohol

NAMS Position Statement (Treatment of menopause-associated vasomotor symptoms)
For mild vasomotor symptoms

- Encourage lifestyle changes
- Non-prescription remedies tested short term with little efficacy over placebo but no evidence of harm
  - Dietary isoflavones
  - Black cohosh
  - Vitamin E
NEW YORK (MarketWatch) — DNA tests on some store-brand herbal supplements showed that nearly four of five didn’t have the ingredients listed on the labels, and a large number didn’t have a botanical substance of any kind, according to findings from the New York state attorney general’s office.
Nonprescription Products Have Limited Data to Support Efficacy in Relieving Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study Design</th>
<th>Efficacy</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy-derived isoflavones(^1)</td>
<td>Systematic review of 25 randomized controlled trials of phytoestrogens (≥4 weeks) involving 2,348 symptomatic women</td>
<td>7 of 8 soy food trials, 3 of 5 soy extract trials, and 3 of 5 red clover trials showed no significant difference from placebo.</td>
<td>Most common adverse events were gastrointestinal disorders.</td>
</tr>
<tr>
<td>Black cohosh(^2)</td>
<td>N=80 late perimenopausal or postmenopausal women; 160 mg/day</td>
<td>No significant difference from placebo</td>
<td>Both groups reported gastrointestinal symptoms, nausea and vomiting, fatigue, asthenia, or malaise; and headaches.</td>
</tr>
<tr>
<td>Evening primrose oil(^3)</td>
<td>N=56 menopausal women; 4000 mg/day for 6 months</td>
<td>No significant difference from placebo</td>
<td>Minimal side effects, including slight nausea.</td>
</tr>
<tr>
<td>Dong quai(^4)</td>
<td>N=71 menopausal women; 4.5 g/day for 6 months</td>
<td>No significant difference from placebo</td>
<td>Both treatment groups reported burping, gas, and headaches.</td>
</tr>
<tr>
<td>Ginkgo biloba(^5,6)</td>
<td>N=87 menopausal women; 120 mg/day for 6 weeks; N=31 menopausal women; 120 mg/day for 1 week</td>
<td>No significant difference from placebo</td>
<td>None reported.</td>
</tr>
<tr>
<td>Ginseng(^7)</td>
<td>N=384 menopausal women; 100 mg/day for 4 months</td>
<td>No significant difference from placebo</td>
<td>Both treatment groups reported influenza or colds, headaches or migraines, and gastrointestinal disorders.</td>
</tr>
<tr>
<td>Vitamin E(^8)</td>
<td>N=120 women with a history of breast cancer; 800 IU/day for 4 weeks in a crossover design</td>
<td>No significant difference from placebo</td>
<td>Both groups reported headaches, fatigue, and nausea.</td>
</tr>
</tbody>
</table>

# Nonhormonal Treatments for Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Study Design*</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMs (black cohosh, St. John’s Wort, red clover, acupuncture, exercise)</td>
<td>Duration, 4-52 wk OL and RPL trials Entry criteria – mostly &gt; 14 HF/wk</td>
<td>Mixed results, mostly with no sustained improvement</td>
</tr>
<tr>
<td>SSRI† (paroxetine, fluoxetine sertraline, citalopram, escitalopram)</td>
<td>Duration, 4-36 wk RPL trials with all agents N = 20-90 active arm Entry criteria – mostly, &gt; 14 HF/day</td>
<td>Reduction in VMS (frequency, composite scores), 28%-55%</td>
</tr>
<tr>
<td>SNRI† (venlafaxine, desvenlafaxine)</td>
<td>Duration, 12-52 wk RPL trials with all agents N = 22-66 in VEN; N = 120-200 in DVS Entry criteria - &gt; 14 HF/wk for VEN &gt; 50 HF/wk for DVS</td>
<td>Reduction in VMS (frequency, composite scores), 35%-58% for VEN 55%-68% for DVS</td>
</tr>
<tr>
<td>Gabapentin†</td>
<td>Duration, 4-12 wk RPL trials , N = 20-100 Entry criteria - &gt; 14-50 HF/wk</td>
<td>Reduction in VMS (frequency, composite scores), 50%-70%</td>
</tr>
</tbody>
</table>

*Menopausal, nondepressed women; † Treatment is off label
Clinical Management

Mod-Severe Vasomotor Symptoms

• Hormone therapy is only FDA approved treatment
  – “gold standard” - but contraindicated

• SSRI’s and gabapentin
  – have efficacy in early studies

• Progestogens effective
  – however large doses required

• Clonidine (oral or transdermal)
Efficacy of Therapies for Hot Flushes

% Hot Flash Score Reduction (Mean)

Week

0 1 2 3 4 5 6

Black Cohosh (n = 58)
Placebo (n = 420)
Soy (n = 78)
Vitamin E (n = 53)
Clonidine (n = 75)
Venlafaxine (n = 74)
Venlafaxine (vs MPA) (n = 94)
Megestrol (n = 74)
Venlafaxine (n = 48)
MPA 400 mg (n = 94)
MPA 500 mg x 3 (n = 7)

aCL Loprinzi, unpublished data.
Courtesy of C.L. Loprinzi, MD.
Efficacy of Gabapentin for Hot Flushes

Hot Flash Severity

HT and Antidepressant Prescription Patterns: A Reciprocal Relationship

Number of Prescriptions

Period 1
Period 2

HRT
SSRIs

WHI Publication, July 17, 2002

Jan 01  Feb 01  Mar 01  Apr 01  May 01  Jun 01  Jul 01  Aug 01  Sep 01  Oct 01  Nov 01  Dec 01  Jan 02  Feb 02  Mar 02  Apr 02  May 02  Jun 02  Jul 02  Aug 02  Sep 02  Oct 02  Nov 02  Dec 02  Jan 03  Feb 03  Mar 03  Apr 03  May 03  Jun 03  Jul 03  Aug 03  Sep 03  Oct 03  Nov 03

SA = serotonergic antidepressants.
Use of Antidepressants for Management of Hot Flashes

- **paroxetine, venlafaxine**
  - Studied more extensively than any of the other antidepressants.
  - Reduce the frequency and severity of hot flashes
- **citalopram, desvenlafaxine, escitalopram, fluoxetine, sertraline**
  - Second- or third-line options if patients fail therapy with or cannot tolerate paroxetine or venlafaxine
- **duloxetine, fluvoxamine, mirtazapine**
  - More studies needed

Breast Cancer and Depression: Tamoxifen and Antidepressants via Cytochrome P450 2D6

✓ Women taking tamoxifen for the treatment or prevention of recurrence of breast cancer are likely to take antidepressants either for a psychiatric disorder or for hot flushes.

✓ Some antidepressants inhibit the metabolism of tamoxifen to its more active metabolites by the cytochrome P450 2D6 (CYP2D6) enzyme, thereby decreasing the anticancer effect.

### Interactions between tamoxifen and antidepressants via cytochrome P450 2D6

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>2D6 Interaction</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>+++ Strong</td>
<td>:to be avoided</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+++ Strong</td>
<td>:to be avoided</td>
</tr>
<tr>
<td>Citalopram</td>
<td>+ Mild</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>+ Mild</td>
<td>: studies lacking</td>
</tr>
<tr>
<td>Bupropion</td>
<td>+++ Strong</td>
<td>: to be avoided</td>
</tr>
<tr>
<td>Sertraline</td>
<td>++ Moderate</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>++ Moderate</td>
<td>2D6 and 3A4: studies lacking</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>- Minimal</td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td></td>
<td>Minimal: studies lacking</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>+</td>
<td>Minimal: studies lacking</td>
</tr>
</tbody>
</table>


Trials of AI versus tamoxifen suggest a very modest difference in menopausal side-effects, with tamoxifen users reporting slightly more hot flushes.

Since vaginal dryness is more common with AIs, changing to tamoxifen may be helpful.

Postmenopausal women who received a single injection of bupivacaine to the stellate ganglion reported half as many bothersome hot flashes in the 6 months after the nerve block than those who received sham therapy.
Review

Stellate ganglion block for treating hot flashes: A viable treatment option or sham procedure?^1

Thomas Guttuso Jr.^1

University at Buffalo, 3435 Main St., Buffalo, NY 14214, United States
Figure 1. Therapeutic effect of the stellate ganglion block on generation of hot flashes. Neural connections between the stellate ganglion and the hypothalamus, amygdala and regions of the prefrontal cortex, in particular the insular cortex may be involved in the interruption of the sympathetic nervous system allowing the body’s temperature-regulating mechanisms to reset.
Stellate ganglion block for treating hot flashes: A viable treatment option or sham procedure?*

Thomas Guttuso Jr.*

University at Buffalo, 3435 Main St., Buffalo, NY 14214, United States

Table 1
Summary of reports of SGB for treating hot flashes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total n</th>
<th>SGB1/SGB2/SGB3</th>
<th>Median subject age</th>
<th>Main outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hendy et al. [11]</td>
<td>(1)</td>
<td>1/0/0</td>
<td>-</td>
<td>?</td>
<td>&quot;abolished ipsilateral sweating during attacks&quot;</td>
</tr>
<tr>
<td>Lipov et al. [2]</td>
<td>(6)</td>
<td>1/3/2</td>
<td>53</td>
<td>Subjects' verbal reports</td>
<td>Subjectively, all 6 subjects were &quot;asymptomatic&quot; for 2–5 weeks after SGB1 with more prolonged benefit after SGB2 &amp; 3.</td>
</tr>
<tr>
<td>Lipov et al. [7]</td>
<td>(13)</td>
<td>5/8/0</td>
<td>54</td>
<td>Daily hot flash diary</td>
<td>90% reduction in HFF from BL to week 12</td>
</tr>
<tr>
<td>Pachman et al. [8]</td>
<td>(9)</td>
<td>9/0/0</td>
<td>53</td>
<td>Daily hot flash diary</td>
<td>44% reduction in HFF from BL to week 6</td>
</tr>
<tr>
<td>Haest et al. [10]</td>
<td>(25)</td>
<td>6/16/3</td>
<td>53</td>
<td>Daily hot flash diary</td>
<td>40% reduction in HF scores from BL to week 12</td>
</tr>
<tr>
<td>van Gastel et al. [9]</td>
<td>(19)</td>
<td>19/0/0</td>
<td>58 (females)</td>
<td>Daily hot flash diary</td>
<td>34% &amp; 28% reductions in HF scores and HFF, respectively, from BL to week 4.</td>
</tr>
</tbody>
</table>

SGB1, 2, 3, number of subjects receiving 1, 2, or 3 stellate ganglion blocks, respectively; HFF, hot flash frequency; HF scores, hot flash scores, which is a combination of HFF and hot flash severity into 1 score. BL, baseline.
COMPLICATIONS:

<table>
<thead>
<tr>
<th>Misplaced needle</th>
<th>Spread of local anaesthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematoma from vascular trauma</td>
<td>Intravascular injection:</td>
</tr>
<tr>
<td>Carotid trauma</td>
<td>Carotid artery</td>
</tr>
<tr>
<td>Internal jugular vein trauma</td>
<td>Vertebral artery</td>
</tr>
<tr>
<td>Neural injury (recurrent laryngeal nerve)</td>
<td>Internal jugular vein</td>
</tr>
<tr>
<td>Vagus injury</td>
<td></td>
</tr>
<tr>
<td>Brachial plexus roots injury</td>
<td>Neuraxial/brachial plexus spread:</td>
</tr>
<tr>
<td>Pulmonary injury</td>
<td>Epidural block</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Intrathecal</td>
</tr>
<tr>
<td>Haemothorax</td>
<td>Brachial plexus anaesthesia or injury (intraneural injection)</td>
</tr>
<tr>
<td>Chylothorax (thoracic duct injury)</td>
<td></td>
</tr>
<tr>
<td>Oesophageal perforation</td>
<td>Local spread:</td>
</tr>
<tr>
<td></td>
<td>Horseness (recurrent laryngeal nerve)</td>
</tr>
<tr>
<td></td>
<td>Elevated hemidiaphragm (phrenic nerve)</td>
</tr>
</tbody>
</table>

Infection

- Soft tissue (abscess)
- Neuraxial (meningitis)
- Osteitis
Vaginal Dryness
Pre-menopause (n = 172)
Early Perimenopause (n = 148)
Late Perimenopause (n = 106)
Post-menopause 1 year (n = 72)
Post-menopause 2 years (n = 54)
Post-menopause 3 years (n = 31)

Vaginal Dryness With Menopause

Vaginal symptoms

• Unlike hot flushes, which tend to improve over the course of time, dryness usually gets worse

• “Use or lose it” has some truth to it
Vulvovaginal Atrophy Treatment

• Smoking cessation
• Continued vaginal coitus provides protection by increasing blood flow
• Vaginal stimulation
• Avoid antihistamines
• Vaginal moisturizers polycarbophil gel (Replens)
• No evidence dietary estrogen or supplements help
HRT is linked to breast cancer.

HRT rail cancer a stroke risk.

HRT attack for women.

HRT dang for woman.
• Vaginal estrogen has low systemic absorption and has not been associated with an increased risk of breast cancer

Rosenberg LU, Magnusson C, Lindstrom L, Wedelin S, Hall P, Dickman PW. Menopausal hormone therapy and other breast cancer risk factors in relation to the risk of different histological subtypes of breast cancer: a case-control study.

Breast Cancer Res 2006;8:111.
One retrospective cohort study evaluated 13,479 women with a history of estrogen receptor-positive breast cancer and who had used varying formulations of vaginal estrogen, including cream, pessary and tablet. Over a mean follow-up of 3.5 years, no significant difference in recurrence rates was noted among patients using vaginal estrogen relative to controls (Relative Risk [RR] 0.78, 95% CI 0.48–1.25).

Le Ray I. Dell’Aniello S, Bonnetain F, Azoulay L, Suisse S.

2016 IMS Recommendations on women’s midlife health and menopause hormone therapy
Baber RJ, Panay N, Fenton A for the IMS Writing group

• There is a lack of safety data supporting the use of MHT (ET or EPT) in breast cancer survivors.

• So, the research has focused on non-hormonal alternatives for menopause symptoms in breast cancer survivors.
Breast Cancer-MHT

- Very limited amount of data available.
- Most survivors too anxious to even consider therapy.
- In US: major trials by DiSaia and Creasman, do not show increased risk of recurrence in survivors administered estrogen.
- European data, primarily from Sweden, does show increased risk of recurrence, in range of 2 to 3 fold, in women given hormone therapy.
- Novel approach: stay tuned: administration of estrogen plus a SERM.
POSITION STATEMENT

South African Menopause Society revised consensus position statement on menopausal hormone therapy, 2014

F Guidozzi, A Alperstein, J S Bagratee, P Dalmeyer, M Davey, T J de Villiers, S Hirschowitz, T Kopenhager, S P Moodley, P Roos, A Shaw, O Shimange, T Smith, C Thomas, J Pitus, J van der Spuy, J van Waart, on behalf of the Council of the South African Menopause Society
3.15.1 Breast cancer survivors

- At present, it is prudent not to offer HT routinely to breast cancer survivors for management of menopausal symptoms, even though the data are somewhat controversial.

- Three randomised trials have addressed this issue, two of which showed an increase in cancer recurrences, while the other did not. None of the three studies showed an increase in death from the disease. Data derived from observational studies, including two large meta-analyses, do not show an increase in recurrences or death rate in breast cancer survivors using HT.
3.15.1 Breast cancer survivors

- HT should be prescribed only when patients are fully informed of the current available data and wish to use this therapeutic modality.

- There is no evidence to suggest that transvaginal topical oestrogen increases recurrence, so it may be prescribed to patients with intractable symptoms associated with urogenital atrophy.
Although there is controversy related to the risk of topical estrogen therapy and breast cancer recurrence, the Committee Opinion notes that data show there is no increased risk of cancer recurrence with the use of topical vaginal estrogen.
Diana Nancy Contreras, MD, Chair of ACOG's Subcommittee on Gynecologic Oncology, stated,

"These new recommendations are especially important and helpful because they provide the patient with the information needed to make an informed decision with the input of her health care provider."
Data regarding the risks of systemic HRT in survivors of breast cancer are varied, and an increase in breast cancer recurrence with the use of systemic HRT has been demonstrated in randomised controlled trials.

Limited data exist regarding the use of vaginal estrogen, however, no effect on recurrence has been demonstrated.

The decision regarding the use of HRT in women with cancer must be individualised and should take into account issues regarding quality of life.
CONCLUSION

As the number of breast cancer survivors increases, menopause has become an increasingly important issue for women with breast cancer, with both short- and long-term health consequences and significant impacts on physical and emotional well-being. Recognition of the importance of these issues has led to increased research and identification of potential therapeutic strategies, especially for the management of vasomotor symptoms. However, further high-quality research is needed to improve understanding of symptom etiology and clarify therapeutic options. Management of menopause in breast cancer survivors is complex and can be challenging for the clinician, and therefore a multidisciplinary approach is recommended.

A. J. Vincent

CLIMACTERIC 2015;18:1–12
Ethical issues

How to balance the risks of HRT with quality of life concerns in survivors of gynaecological and breast cancer when evidence to guide our recommendations is limited?
Age 57
Ex NZ

Breast Cancer 9 months prior to coming to SA

“I have no quality of life”

Long discussion

Mirena and TD E2

6 weeks later

“I would rather live life short and well rather than miserable and unhappy”
“I feel empowered that I made a strong choice that in no way diminishes my femininity”
Approach to the Symptomatic Breast Cancer Survivor

• Life style management

• Herbal/botanical approach

• Consider non hormonal medication

• Discuss risk/benefit ratio of MHT-no data
WHEN DEALING WITH WOMEN REMEMBER

The word "NO" means "NO"

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