Non hormonal medical treatment of vasomotor symptoms

Caroline Antoine
Menopause Clinic
Department of Gynaecology and Obstetrics
CHU Saint-Pierre

Belgian Menopause Society Symposium – November 14, 2015
• No conflict of interest to declare.

• Unrestricted research funding from IRIS Research Fund, Vesalius Research Fund, Amgen and MSD.
Is there a need?

- Some patients may not use MHT.
- For others the timing is inappropriate.
- Some patients do not want to use MHT.
Alternatives to estrogen

Prescribed drugs:
- Clonidine
- SSRI/SNRI
- Gabapentin

Non-estrogenic hormones:
- Progestins
- Progesterone

Complementary and alternative treatment (CAM):
- Phytoestrogens
  - Soy
  - Red clover
- Cimicifuga racemosa

Other
- Stellate-ganglion block
- Acupuncture
- Lifestyle

In the center of the city, in the center of life, with passion for care
Non hormonal drugs

- Clonidine
- SSRI/SNRI
- Gabapentin
Clonidine

- Centrally acting α2 adrenergic agonist
- Decreases sympathetic tone
  - ! Other antihypertensive drugs

- Dixarit® (0.025 mg)
  - Vascular headache
  - Hot flushes

afmps – AMM BE106102
In the center of the city, in the center of life, with passion for care

Clonidine – Meta analysis

Nelson et al. JAMA 2006
Clonidine

- **Side effects**
  - Mouth dryness
  - Sleep disturbances
  - Drowsiness
  - Constipation
  - Hypotension

- **Safety**
  - Long term use in other indications
  - Approved for hot flushes
  - No data in BC survivors

Buijs et al; Br Cancer Res Treat 2009
Boekhout et al. J Clin Oncol 2011

Hickey et al. Lancet Oncol. 2005
Antoine et al. Climacteric 2007
SSRI / SNRI

- **SSRI (Selective Serotonin Reuptake Inhibitors)**
  - Citalopram (Citalopram®, Cipramil®)
  - Escitalopram (Escitalopram®, Sipralexa®)
  - Fluoxetine* (Fluoxetine®, Prozac®)
  - Paroxetine*§ (Paroxetine®, Seroxat®)
  - Sertraline (Sertraline®, Serlain®)

- **SNRI (Serotonine and Noradrenaline Reuptake Inhibitors)**
  - Venlafaxine (Venlafaxine®, Efexor®)
  - Desvenlafaxine (not available in Belgium)

* Strong CYP2D6 inhibitors
§ FDA approval for hot flushes (June 2013)
Endoxifen concentration according to CYP2D6 activity.

Sideras K et al. JCO 2010;28:2768-2776
In the center of the city, in the center of life, with passion for care

Forest plots of hot flash reduction in newer antidepressant studies.

Loprinzi C L et al. JCO 2009;27:2831-2837

-13%
-13 to 41%
(10-25mg/d)
-18% (50mg/d)
-3% (100mg/d)
-33% (75mg/d)
Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials

James A. Simon, MD, CCD, NCMP, IF, FACOG,1 David J. Portman, MD,2 Andrew M. Kaunitz, MD,3 Hana Mekonnen, MA,4 Kazem Kazempour, PhD,4 Sailaja Bhaskar, PhD,5 and Joel Lippman, MD5
Maintenance of the efficacy of desvenlafaxine in menopausal vasomotor symptoms: a 1-year randomized controlled trial

JoAnn V. Pinkerton, MD,¹ David F. Archer, MD,² Christine J. Guico-Pabia, MD, MBA, MPH,³ Eunhee Hwang, PhD,³ and Ru-fong J. Cheng, MD³

FIG. 2. A: Adjusted mean (SE) change in the number of moderate and severe HFVs on months 3, 6, and 12 (MITT efficacy substudy population, n = 365; observed cases). B: Adjusted mean (SE) change in the average daily HF severity score on months 3, 6, and 12 (MITT efficacy substudy population, n = 365; observed cases).*P < 0.001, desvenlafaxine 100 mg/day versus placebo. †P < 0.01, desvenlafaxine 100 mg/day versus placebo. HF, hot flush; MITT, modified intent to treat (≥1 dose of study drug and ≥1 day of baseline and on-therapy HF data).

Desvenlafaxine -66% HF/day
Placebo -41% HF/day
SSRI / SNRI

• Side effects
  – GI problems
  – Insomnia
  – Loss of libido
  – Headache
  – HTA

• Safety
  – Interaction with tamoxifen (fluoxetine and paroxetine)
  – HTA and cardiomyopathy (venlafaxine and desvenlafaxine)
  – Suicide risk

Sideras et al. JCO 2010
Neil et al. Heart Lung Circ 2012
Gabapentin

• γ-aminobutiric acid (GABA) analog
• Decreases noradrenergic hyperactivity (?)

• Indications
  • Epilepsy
  • Neuropathic pain
Gabapentin – Meta analysis

4 Weeks

Gabapentin 900-2400 mg - 35 to 38%

Loprinzi et al. J Clin Oncol 2009
## Gabapentin – Meta analysis

**Gabapentine 900 mg: -20 to 30% in frequency and severity of HF**

**Toulis et al. Clinical Therapeutics 2009**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean (SD)</th>
<th>WMD (random), 95% CI</th>
<th>Weight (%)</th>
<th>WMD (random), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guttuso et al</td>
<td>30</td>
<td>44.60 (31.50)</td>
<td>13.70 (15.70, 11.93)</td>
<td>83.70</td>
<td>-18.50 (-27.69, -2.81)</td>
</tr>
<tr>
<td>Pandy et al</td>
<td>144</td>
<td>48.00 (6.50)</td>
<td>43.02 (28.70, 30.31)</td>
<td>83.70</td>
<td>15.70 (31.93, 0)</td>
</tr>
<tr>
<td>Butt et al</td>
<td>99</td>
<td>45.70 (3.50)</td>
<td>22.00 (9.99, 22.61)</td>
<td>90.00</td>
<td>23.72 (15.46, 30.97)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>273</td>
<td>254</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 90.82$, df = 2 ($P &lt; 0.001$), $p = 97.8%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 6.41$ ($P &lt; 0.001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 1. Percentage reduction in the frequency of hot flashes in women who received gabapentin or placebo.*

---

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean (SD)</th>
<th>WMD (random), 95% CI</th>
<th>Weight (%)</th>
<th>WMD (random), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guttuso et al</td>
<td>30</td>
<td>53.50 (35.90)</td>
<td>8.21 (2.20, 4.11)</td>
<td>83.70</td>
<td>-18.50 (-41.16, -1.14)</td>
</tr>
<tr>
<td>Pandy et al</td>
<td>144</td>
<td>46.00 (6.00)</td>
<td>45.55 (37.00, 29.47)</td>
<td>83.70</td>
<td>22.10 (31.93, 0)</td>
</tr>
<tr>
<td>Butt et al</td>
<td>99</td>
<td>51.00 (3.74)</td>
<td>46.00 (24.50, 23.40)</td>
<td>90.00</td>
<td>27.26 (21.24, 33.29)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>273</td>
<td>264</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 45.97$, df = 2 ($P &lt; 0.001$), $p = 95.6%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 8.87$ ($P &lt; 0.001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 2. Percentage reduction in the composite score for hot flashes in women who received gabapentin or placebo.*
Gabapentin

• Side effects
  – Dizziness
  – Drowsiness
  – Headache
  – Ataxia
  – Weight gain
decrease with time

Butt et al. Menopause 2008

• Safety
  – No data in BC patients
  – Interactions with tamoxifen unlikely

Hickey et al. Lancet Oncol. 2005
Antoine et al. Climacteric 2007
Pregabalin

Median changes from baseline for (A) hot flash scores and (B) hot flash frequencies for the three study arms.

- 50% placebo, - 65% 75 mg bid, -71% 150 mg bid

Loprinzi et al. J Clin Oncol 2010
Comparative studies
Venlafaxine is superior to clonidine as treatment of hot flashes in breast cancer patients—a double-blind, randomized study

S. Loibl¹*, K. Schwedler¹, G. von Minckwitz¹,², R. Strohmeier¹, K. M. Mehta² & M. Kaufmann¹

¹Department of Obstetrics and Gynecology, University Hospital Frankfurt am Main, Frankfurt am Main, Germany; ²German Breast Group, Schleussnerstr. 42, 63263 Neu-Isenburg, Germany

Figure 2. Median hot flash frequency per day from baseline to treatment week 4 for the first part of the trial (n = 64). There was a 57% reduction with venlafaxine compared with 37% with clonidine (P = 0.025; two-sided t-test). Dotted lines represent clonidine and solid lines venlafaxine.

Clonidine -37% (-4.85 HF/d) (n=33)

Venlafaxine -57% (-7.6 HF/d) (n=31)
Venlafaxine versus clonidine for the treatment of hot flashes in breast cancer patients: a double-blind, randomized cross-over study

Ciska Buijs · Constantijne H. Mom · Pax H. B. Willemse · H. Marike Boezen · J. Marina Maurer · A. N. Machtedt Wymenga · Robert S. de Jong · Peter Nieboer · Elisabeth G. E. de Vries · Marian J. E. Mourits

Table 3 Change in hot flash score from baseline to week 8

<table>
<thead>
<tr>
<th>% of Baseline score</th>
<th>Venlafaxine (n = 43)</th>
<th>Clonidine (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>1–24</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>25–49</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>50–74</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>75–100</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>&gt;100</td>
<td>11</td>
<td>26</td>
</tr>
</tbody>
</table>

-49% -55%

Fig. 2 Changes in hot flash frequency from baseline for venlafaxine and clonidine (%)

In the center of the city, in the center of life, with passion for care
Management of Hot Flashes in Patients Who Have Breast Cancer With Venlafaxine and Clonidine: A Randomized, Double-Blind, Placebo-Controlled Trial

Anneleen H. Boekhout, Andrew D. Vincent, Onilia R. Dalesio, Joan van den Bosch, Joke H. Fockema-Töns, Sandra Adriaanse, Sylvia Sprangers, Bastiaan Nuijen, los H. Reimer, and Jan H.M. Schellens

Weeks 1-4: Venlafaxine vs placebo p=0.01

Weeks 9-12: Clonidine vs placebo p=0.02

4 time periods:
Clonidine vs venlafaxine = NS
12 weeks:
Venlafaxine > Clonidine

Important placebo effect
4 weeks

Mean daily hot flash scores plotted by study week.

-66%

Bordeleau L et al. JCO 2010;28:5147-5152
56 patients provided a preference:

18 (32%) Gabapentin
38 (68%) Venlafaxine

<table>
<thead>
<tr>
<th>Preference</th>
<th>Prefer Gabapentin (n = 18)</th>
<th>Prefer Venlafaxine (n = 38)</th>
<th>Total (N = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How much better was the preferred treatment?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Much better</td>
<td>12 (66.7%)</td>
<td>22 (57.9%)</td>
<td>34 (60.7%)</td>
</tr>
<tr>
<td>A little better</td>
<td>6 (33.3%)</td>
<td>16 (42.1%)</td>
<td>22 (39.3%)</td>
</tr>
<tr>
<td>Reasons for preference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased severity of hot flashes</td>
<td>17 (94.4%)</td>
<td>36 (94.7%)</td>
<td>53 (94.6%)</td>
</tr>
<tr>
<td>Decreased frequency of hot flashes</td>
<td>17 (94.4%)</td>
<td>32 (84.2%)</td>
<td>49 (87.5%)</td>
</tr>
<tr>
<td>Few adverse effects</td>
<td>11 (61.1%)</td>
<td>22 (57.9%)</td>
<td>33 (58.9%)</td>
</tr>
<tr>
<td>Future plans for hot flash treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Would like to continue with preferred drug</td>
<td>10 (55.6%)</td>
<td>29 (76.3%)</td>
<td>39 (69.6%)</td>
</tr>
<tr>
<td>Would like to try other drug</td>
<td>3 (16.7%)</td>
<td>2 (5.3%)</td>
<td>5 (8.9%)</td>
</tr>
<tr>
<td>Do not want to be on any treatment</td>
<td>3 (16.7%)</td>
<td>7 (18.4%)</td>
<td>10 (17.9%)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (11.1%)</td>
<td>0 (0%)</td>
<td>2 (3.6%)</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Treatment</td>
<td>Control</td>
</tr>
<tr>
<td>--------------</td>
<td>----</td>
<td>--------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Reddy 2006</td>
<td>46</td>
<td>Gabapentin 2400 mg</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gabapentin CE 0.625 mg</td>
<td></td>
</tr>
<tr>
<td>Aguirre 2010</td>
<td>45</td>
<td>Gabapentin 600 mg</td>
<td>Estradiol patch 25μg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allameh 2013</td>
<td>84</td>
<td>Gabapentin 100 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gabapentin 300 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gabapentin CE 0.625 mg</td>
<td></td>
</tr>
<tr>
<td>Rahmanian 2015</td>
<td>79</td>
<td>Gabapentin 300 mg</td>
<td>Fluoxetine 20 mg</td>
</tr>
</tbody>
</table>
Pooled analysis of Six Interventions for Vasomotor Symptoms

8 Weeks – Pharmacologic Interventions

Guthrie et al. Obstetrics & Gynecology 2015
Randomized Controlled Trial of Low-Dose Estradiol and the SNRI Venlafaxine for Vasomotor Symptoms

8 Weeks

Estradiol -53%  
Venlafaxine -48%  
Placebo -29%

Estradiol vs Venlafaxine = NS

Joffe et al. JAMA 2014
Placebo effect

• Strong placebo effect common in vasomotor symptoms trials (14 – 50%)
  • Natural resolution of symptoms?
  • True physiologic response to placebo?
  • Fatigue with symptoms recording over time?

• An intervention for vasomotor symptoms needs to be compared to a placebo

Conclusions

- **SNRI**
  - Venlafaxine 75 mg/day
  - Desvenlafaxine 100 mg/d

- **SSRI**
  - Escitalopram 10-20 mg/day
  - Citalopram 10-20 mg/day
  - Paroxetine 7.5-12.5 mg/day
Conclusions

• Gabapentin (100 and 300 mg)
  3 times/day, to introduce gradually

• Dixarit® (0.025 mg)
  2 pills twice/day (max 3 pills twice/day), to introduce gradually (side effects), stop after 8 weeks if ineffective
Conclusions

• Are the side effects acceptable?
• The price of the drug
• Off label use of a drug
  • Information
  • Controls
• Long-term use / efficacy
• No other ‘estrogenic’ effects (vagina/bone)
• Comparative studies with MHT
• Safety in BC patients
Pooled estimates of proportion of vasomotor symptoms by year to/from final menstrual period. Six studies provided data for the main meta-analysis. One was longitudinal, and the others were cross-sectional.

Patterns of Estradiol, Progesterone, Luteinizing and Follicle-stimulating Hormones

Patterns of estradiol, progesterone, luteinizing hormone, and follicle-stimulating hormone levels in a sample of 8 midreproductive-aged (MRA) and 14 older reproductive-aged (ORA) women. Error bars indicate mean ± 1.0 standard error.

Atherosclerosis¹