Efficacy and Tolerability of Antidepressant Duloxetine for Treatment of Hot Flushes in Menopausal Women

Irina Shestakova, MD, PhD

Research Center of Obstetrics, Gynecology and Perinatology
Department of Gynecological Endocrinology
Out-patient “Climacteric Clinic”
Moscow, Russia

Training Course in Reproductive Health Research
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Hot flushes - Background and Significance

- The most bothersome symptom of menopause
- May last up to 15 years after menopause
- Are more severe in women who underwent ovarectomy
- Associated with a diminished sense of well-being as a result of fatigue, irritability, poor concentration and anxiety
- Severely affect quality of life

Hot Flushes

- Overall incidence

Premenopause	25%
Perimenopause	69%
Late postmenopause	39%

- Large cross-cultural variability in prevalence

North American women (black>white)	70%
Dutch women	80%
Chinese women	18%
Mayan women in Mexico	0%

No data in Russian population

(personal experience - up to 60% of women who visit “Climacteric Clinic”)

Patient Population

- Mean age of menopause is 51 years
- Life expectancy for women is 67 years
- Career goals are achieved
- Loss of spouse - life expectancy for men 59 years
- This age is related to the first grand child
- Most patients seeing neurologists and psychiatrists for depression are menopausal women

History of Treatment of Hot flushes in Russia

Before 1990	"Wait and it will go away"
	Very rarely methyltestosterone
	Low doses of contraceptive pills
	Belladonna alkaloids
	Neuroanalgesia
Early 1990s	First clinical experience with hormone replacement therapy in Russia
1996	
- Russian Menopause Society founded	
- Clinical recommendation on treatment of menopausal symptoms	Hormone therapy – gold standard Alternative therapy – herbal meds
2002	First anecdotal experience with antidepressants
- Publication of WHI results	Searching for evidence of its efficacy and safety

Hot Flashes Treatment

- Hormone therapy (Estrogens, progestins) - “Gold standard”
- Different non-hormonal agents:

  - methyldopa
  - propranolol
  - vitamin E
  - belladonna alkaloids
  - clonidine
  - gabapentin
  - soy and different herbal preparations
  - antidepressants (SSRIs and SNRIs)

Antidepressants

SSRIs (serotonin reuptake inhibitors)

- citalopram
- fluoxetine
- fluvoxamine
- paroxetine
- sertraline
- dapoxetine

SNRIs (serotonin-norepinephrine reuptake inhibitors)

- venlafaxine
- duloxetine

Candidates for Alternative Treatment

- Women with clear contraindications to hormone therapy

  - breast cancer survivals
  - significant cardiovascular pathology
  - varicose vein disease,
  - diabetes
  - obesity
  - history, including familial, of GYN malignancies

- Women with negative attitude towards “hormones”

Literature Search Results
(PubMed, Cochrane Database)

- No systematic review were found in Cochrane Library
- 2 Cochrane Database protocols for review on this topic is currently being developed in general menopausal women and breast cancer survivals populations
- 1 systematic review and meta-analysis
- 13 original articles on 6 antidepressants were retrieved and reviewed.
- No trials were found on such antidepressants as dapoxetin or duloxetine.

REVIEW CLINICIAN'S CORNER

Nonhormonal Therapies for Menopausal Hot Flashes

Systematic Review and Meta-analysis

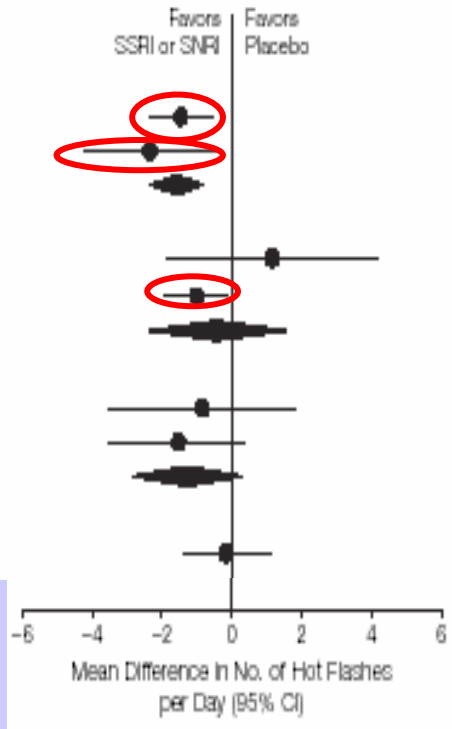
JAMA. 2006;295:2057-2071 www.jama.com

Conclusion The SSRIs or SNRIs, clonidine, and gabapentin trials provide evidence for efficacy; however, effects are less than for estrogen, few trials have been published and most have methodological deficiencies, generalizability is limited, and adverse effects and cost may restrict use for many women. These therapies may be most useful for highly symptomatic women who cannot take estrogen but are not optimal choices for most women.

JAMA. 2006;295:2057-2071 www.jama.com

Figure 2. Trials of Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Source	Dose	No. of Participants	Duration of Trial	Quality	Mean Difference (95% CI)
Paroxetine Trials					
Stearns et al,[29] 2003	12.5 or 25 mg/d*	165	6 wk	Good	−1.52 (−2.36 to −0.69)
Stearns et al,[30] 2005	10 or 20 mg/d	151	4 wk	Fair	−2.43 (−4.43 to −0.42)
Combined					−1.66 (−2.43 to −0.89)
Venlafaxine Trials					
Evans et al,[22] 2005	75 mg/d*	80	12 wk	Fair	1.10 (−1.94 to 4.14)
Loprinzi et al,[31] 2000	37.5 or 75 mg/d*†	167	4 wk	Good	−1.09 (−1.99 to −0.18)
Combined					−0.49 (−2.40 to 1.41)
Fluoxetine Trials					
Loprinzi et al,[32] 2002	20 mg/d	81	4 wk	Fair	−0.90 (−3.78 to 1.98)
Suvanto-Luukkonen et al,[23] 2005	20 mg/d‡	100	3 mo	Fair	−1.60 (−3.63 to 0.43)
Combined					−1.37 (−3.03 to 0.29)
Citalopram Trials					
Suvanto-Luukkonen et al,[23] 2005	20 mg/d‡	100	3 mo	Fair	−0.20 (−1.45 to 1.05)



Therapy	No. of Trials in Review	Trial Quality	No. of Comparisons in Meta-analysis	Effects on Hot Flashes vs Placebo: Mean Difference in No. of Daily Hot Flashes vs Placebo (95% CI)*	Effects on Hot Flashes vs Placebo: Severity or Composite Score (% Difference)†
SSRIs or SNRIs	6	Fair-good	7	−1.13 (−1.70 to −0.57)	Improved in 4 of 6 trials (10-36)

Menopause: The Journal of The North American Menopause Society
Vol. 11, No. 1, pp. 11-33
DOI: 10.1097/01.GME.0000108177.85442.71

POSITION STATEMENT

Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society

Prescription therapies: nonhormonal options

In women with hot flashes for whom hormones are not an option, nonhormonal prescription drugs have shown some effectiveness in relieving hot flashes. However, there are no comparative trials in similar patient populations to guide clinicians in selecting a particular option.

If there are no contraindications, NAMS recommends the antidepressants venlafaxine (at dosages of 37.5-75 mg/day), paroxetine (12.5-25 mg/day), or fluoxetine (20 mg/day) as options for women with hot flashes who are not candidates for HT, including breast cancer survivors. The additional antidepressant effect may benefit some women who suffer from mood disorders.

Hot flash relief, if any, is almost immediate with these therapies, whereas for depression, effects often are not observed for 6 to 8 weeks. This rapid onset of action can be a powerful reinforcement for women who do not find relief from other, simpler methods. A brief trial of 1 week may determine if these agents are going to be effective.

Side effects, especially nausea and sexual dysfunction, should be monitored. Women who experience drowsiness should take the drug at night. Venlafaxine is the most likely in its class to promote weight loss (by causing anorexia), and may be preferred by overweight women. Paroxetine has similar side effects, although less nausea and anorexia. It can also cause blurred vision, although this is rare. Fluoxetine is less likely to cause acute withdrawal side effects because of its longer half-life.

To minimize side effects, very low doses of these antidepressants can be used when starting therapy. If not effective, the dose can be increased after 1 week. Higher doses than those used in trials do not seem appropriate, given the lack of additional efficacy and the potential for increased toxicity. Taking the drugs with food may lessen nausea.

These antidepressant medications should not be stopped abruptly, as sudden withdrawal has been associated with headaches and anxiety. Women who have been using an antidepressant for at least 1 week should taper off the drug. Tapering may require up to 2 weeks, depending on the initial dosage.

INTERNATIONAL MENOPAUSE SOCIETY
THE SOCIETY FOR THE STUDY OF ALL ASPECTS OF THE CLIMACTERIC IN MEN AND WOMEN

PRESS STATEMENT

ISSUED ON BEHALF OF THE BOARD OF THE INTERNATIONAL MENOPAUSE SOCIETY BY
Amos Pines, *President*, David Sturdee, *General Secretary*, Martin Birkhäuser, *Treasurer*, Marco Gambacciani and Nick Panay

Recommendations on postmenopausal hormone therapy

February 27, 2007

ALTERNATIVE TREATMENTS

The efficacy and safety of complementary alternative medicines have not been demonstrated and further studies are required.

Selective serotonin reuptake inhibitors, selective noradrenaline reuptake inhibitors and gabapentin are effective in reducing vasomotor symptoms in short-term studies. Their long-term safety needs further evaluation.

Reasons for Selection of Duloxetine

- Few trials in general population of menopausal women
- No trial on direct comparison of antidepressants versus hormone therapy for hot flushes
- Duloxetine is a member of SNRIs (as Venlafaxine)
- Duloxetine has shown appropriate safety in women with stress urinary incontinence

Mariappan P, Ballantyne Z, N'Dow JMO, Alhasso AA. Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. Cochrane Database of Systematic Reviews 2005

Study Outline

- Population: Menopause women with hot flushes
- Intervention: Duloxetine
- Comparison: Estrogen-progestogen hormone therapy
- Outcomes:

  Primary: Frequency and Severity of hot flushes

  - Assessed using Climacteric Scale

  Secondary: - Intensity of depression symptoms

  - Assessed using Hamilton's Depression Scale

  - Drop-out rate, reasons for drop-out

  - Tolerability

Clinical Trial Design

- Pilot
- Randomized
- Open
- 50 menopausal women with hot flashes
- Randomly assigned to receive:

Antidepressant - Duloxetine, 60 mg, PO, once daily
OR
Cyclic hormonal therapy - Estradiol 1mg + Dydrogesterone 10mg, once daily

Eligibility Criteria

Inclusion criteria

- Healthy menopausal women who are presented with the main complain of moderate or severe hot flushes and are seeking therapy for this reason
- Age 40-55, no history of hysterectomy or ovarectomy

Exclusion criteria

- Treatment with other antidepressants, somnoleptics, any herbal or other complementary products for alleviating hot flushes
- Treatment with warfarin, sibutramine or tramadol (drug interaction)
- Contraindications to sex steroids

Conclusion

- This pilot trial will be the first experience of using evidence based medicine methodology to determine the alternative treatment options for menopausal hot flushes
- It will provide a therapeutic alternative for women with contraindications for conventional hormone therapy, non-responders to hormone therapy as well as general gynecologists, endocrinologists, oncologists and neurologists who are involved in medical care of this population
- We do not treat hot flushes, we treat women with hot flushes

Thank you !!!