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A Review of Non-hormonal Treatment Options for the Vasomotor Symptoms of Menopause with Emphasis on Brisdelle® (*Paroxetine mesylate*) and Serada® (*Gabapentin ER)*

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Vasomotor symptoms, hot flashes and night sweats, are a common and disturbing symptoms associated with menopause. Vasomotor symptoms (VMS) are characterized as a sudden sensation of heat centered on the face and chest that can become generalized throughout the body. Hot flashes are not only a significant cause of discomfort, but have also been linked to sleep disturbances, changes in mood, cognitive dysfunction, and decreased quality of life.[1] Complaints of hot flashes are the most frequent menopausal complaint, and are one of the main reasons for menopausal women to seek treatment.[2] Hot flashes occur in 14-51% of women prior to perimenopause, 35-50% of women in perimenopause, and 30-80% of women after menopause.[3] They vary based on frequency, severity, duration, and onset. Episodes usually last 2 -4 minutes, and can occur up to 24 times per day in severe cases.[4] Risk factors for increased severity include obesity, older age, smoking, depression, and personal history of breast cancer.[7]

Treatment for VMS focuses on a combination of non-pharmacological and pharmacological treatments. Non-pharmacological therapy should be implemented prior to pharmacological treatment and includes avoidance of triggers, maintaining a cool environment, and relaxation therapy.[9] Hormonal therapy has been the standard treatment for the reduction of both the frequency and severity of hot flashes. Recent studies have raised concern with the safety of hormonal treatments in these patients. The Women's Health Initiative Trials for Estrogen and Progestin therapy, and Estrogen Only therapy have highlighted potential consequences of hormonal therapy, and started the trend toward increased reluctance to hormonal therapy options.[5,6] This has led to changes in the way hot flashes are treated, with an increased utilization of non-hormonal therapy options. This article provides an evidence-based summary of the non-hormonal treatment options for VMS. Two new non-hormonal therapies will be more extensively reviewed.

History of Management and Current Therapeutic Options

Hormonal therapy (HT) is the most effective therapy for the management of VMS.[4,7,9] Prior to the recent approval of Brisdelle (*Paroxetine mesylate*), HT

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was the only FDA-approved therapy for VMS. Hormonal treatments contain estrogens alone or the combination of estrogens plus progestins. Trials such as the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) Estrogen/Progestin Trial highlighted the significant risks that hormone therapy possess.[5] The WHI trials found that there is an increased risk of coronary heart disease in the first 6 years of therapy, increased risk of stroke after 2 years of therapy, increased risk of thrombosis in the first year of therapy that continues throughout therapy duration, increased breast cancer risk after 4 years of therapy, and increased risk of cholecystitis.[5,9] Risk of coronary heart disease also varies based on the timing of HT. Risk increases if HT is initiated ten or more years after menopause, but appears to have decreased risk if started prior to ten years after menopause.[9] FDA reported a list of relative contraindications for HT. These include personal history of breast cancer, active liver disease, history of idiopathic or current venous thromboembolism, active or recent arterial thromboembolic disease, untreated hypertension, estrogen-sensitive malignant conditions, or untreated endometrial hyperplasia.[9,19] Current recommendations for HT therapy are to treat with the lowest doses of hormones for the shortest duration possible.[4,19,24] Progestin therapy alone is being used more due to the negative adverse effects of estrogen therapy.[9] Oral, intramuscular and topical formulations are being used for the management of VMS. These therapies are very efficacious with efficacy ranging between 74-86%.[9] Progestin therapies are associated with use limiting side effects such as weight gain, and withdrawal bleeding.

Evidence supports the efficacy of certain selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, and clonidine for the management of VMS. The majority of evidence for SSRIs and SNRIs lies with paroxetine, venlafaxine, and desvenlafaxine.[8,9,10] Fluoxetine, citalopram, escitalopram, and sertraline have also been studied for the management of VMS. SSRIs and SNRIs are effective in VMS treatment earlier than what is typically seen for depression and psychiatric symptoms.[12] Disadvantages with non-hormonal options include lack of direct comparative studies between the agents, inferior efficacy to HT, and lack of long-term safety and efficacy data.[8,10,11,12] Over the counter options and nutritional supplements such as red clover, soy isoflavone extracts, and vitamin E have limited evidence of efficacy and are not supported in the literature.[7,9,10] Black cohosh has more evidence of efficacy compared to other over the counter products, however it has been linked to liver toxicity and has limited safety data.[9,10]

In recent years more attention has been given to non-hormonal options for patients. This gives women who are not candidates for HT, or those who wish to avoid HT, options to treat their VMS. Non-hormonal therapies have been used off-label for years to treat VMS, however they are overall less effective than HT for VMS management. Most recent advances in the treatment of VMS have focused on non-hormonal therapies. Brisdelle®, low-dose mesylate salt of paroxetine (LDMP), was approved in July 2013 for the treatment of moderate to severe VMS. Serada®, an extended-release (ER) formulation of gabapentin, is currently under review by the FDA for the management of VMS.

Table 1 summarizes some of the non-hormonal treatment options for VMS management. Current guidelines do not specifically recommend one non-hormonal therapy over another. The American Association of Clinical Endocrinologists (AACE) Guidelines for the Treatment of Menopause recommend SSRIs/SNRIs over other non-hormonal therapies.[9] They conclude that venlafaxine may be the most beneficial in the class. The North American Menopause Society (NAMS) do not recommend one non-hormonal option over another.[4] NAMS recommends venlafaxine, paroxetine, fluoxetine, or gabapentin with the same level of recommendation. A meta-analysis of the trials studying non-hormonal therapies summarized the mean difference in number of hot flashes per day.[12] The investigators concluded that gabapentin was the most effective, with a mean value of 2.05 less hot flashes per day. The composite score, which takes into account both the reduction in frequency and severity of hot flashes, was improved in 2/2 trials for gabapentin. A Cochrane review of the non-hormonal therapies concluded that the choice between SSRIs/SNRIs should be guided by cost and preference since they did not conclude one was significantly better over another.[18] The Cochrane review also concluded that gabapentin was only beneficial in high doses greater or equal to 900 mg/day in divided doses. A recent 2013 review of all of the SSRIs used in VMS management found that all SSRIs studied were more effective than placebo, but escitalopram may be superior to other SSRIs.[11] Escitalopram has recently been studied more for the management of VMS, and direct comparative studies would need to be completed to be able to clearly recommended one SSRI over another based on efficacy alone.

Table 1 | Comparison of Treatment Options in Reduction of Frequency and Severity of Hot Flases[7,8,9,13]

Medication	Reduction of events*	Side Effects	Studies	Pros	Cons
Hormonal therapy (E+P or E alone)	75-79% 2-3 HF/day	Breast tenderness, uterine bleeding, nausea, vomiting, headache, weight changes, cholecystitis	——	Most effective therapy for hot flashes Osteoporosis prevention Effective for urogenital symptoms	Increase risk of stroke, VTE Must contain progestins to prevent endometrial hyperplasia if intact uterus present Tolerability
Paroxetine mesylate ¤	61%	Headache, dizziness, nausea, nasopharyngitis	Simon 2012, Kaunitz 2012	FDA approved for treatment of hot flashes Assessed in moderate-severe cases (≥50/week)	Cost Interaction with tamoxifen CYP-related drug interactions Serotonin syndrome risk
Paroxetine HCl CR §	62-65% 1-2 HF/day	Headache, nausea, drowsiness, and insomnia	Stearns 2003	Shown to have higher efficacy than other SSRIs/SNRIs	Interaction with tamoxifen CYP-related drug interactions Serotonin syndrome risk
Venlafaxine ER	35-61% ~1 HF/day	Decreased appetite, anxiety, constipation, xerostomia, nausea, headache	Loprinzi 2000, Evans 2005, Carpenter 2007	Recommended by AACE guidelines	Possible drug interactions Serotonin syndrome risk Possible increase in blood pressure
Desvenlafaxine	61-69% ~1 HF/day	Dizziness, insomnia, hyperhidrosis, nausea, xerostomia, decreased appetite, constipation, somnolence	Archer 2013, Sun 2013	Assessed in moderate-severe cases (≥50/week)	Cost Possible drug interactions Serotonin syndrome risk
Gabapentin	50-70% ~2 HF/day	Somnolence, fatigue, nausea, vomiting, dizziness, peripheral edema	Guttuso 2003, Pandya 2005, Reddy 2006	Assessed in moderate-severe cases (≥50/week) Improvement of sleep Compared with HT in Reddy 2006cite	Tolerability Frequent dosing Studied up to 12 week duration
Gabapentin ER	~1-2 HF/day	Somnolence, dizziness, nausea, headache, sedation	BREEZE 1, BREEZE 2, BREEZE 3	Less somnolence compared to short-acting gabapentin Studied up to 6 month duration Once or twice daily dosing Improvement of sleep	Currently under review for FDA approval Cost
Clonidine	38-78% ~1 HF/day	Drowsiness, dizziness, dry mouth, hypotension, constipation, skin irritation from patches	Edington 1980, Nagamani 1987, Pandya 2000, Laufer 1982,	Oral and transdermal option Dual benefit for women with hypertension	Less evidence to support effectiveness than other therapies Tolerability

*Placebo effect in reduction of hot flashes ranges between 20-50%, Composite (%) score factors in both severity and frequency.

¤Low dose mesylate salt of paroxetine, 7.5 mg

§Based off of controlled release (CR) paroxetine HCl 12.5-25 mg

E: estrogen, **E+P:** estrogen and progesterone, **CR:** controlled release, **ER:** extended-release, **HF:** hot flash, **HT:** hormone therapy

What is New in Non-hormonal VMS Management?

Brisdelle® (*Paroxetine mesylate*)

LDMP is the first and only FDA-approved non-hormonal therapy for the treatment of moderate to severe vasomotor symptoms of menopause. LDMP comes as a 7.5 mg capsule. Paroxetine is considered to be one of the most promising SSRIs for the management of VMS. Studies have found superior efficacy with paroxetine versus other SSRIs including fluoxetine and sertraline.[7,8,9,11]

Pharmacology

LDMP is a SSRI, but its mechanism of action for the treatment of VMS is unknown. One theory is that the neurotransmitters, like norepinephrine and serotonin, play a role in the central thermoregulatory center dysfunction that are thought to be involved in VMS pathophysiology.[11]

Pharmacokinetics and Drug Interactions

A phase 1, open-label, single and multiple-dose study evaluated the pharmacokinetics and safety of LDMP in 24 postmenopausal women.[22] The authors reported a half-life of 17.3 hours, time to max concentration (t_{max}) of 6 hours, and a mean area under the curve (AUC) at steady state that was ~3 fold greater than AUC on day one. On day 14, the AUC was ~5 fold greater than on day 1. This indicates that LDMP exhibits nonlinear pharmacokinetics, and can accumulate after multiple doses. Accumulation is thought to be due to the fact that CYP2D6 is readily saturable. The bioavailability and rate of absorption are not significantly affected by food. LDMP can be taken without regard of meals. There is very minimal (2%) renal excretion of the parent compound. Liver metabolism accounts for approximately 62% of the metabolism, and 36% is excreted in the feces. There are no dosing adjustments for renal or hepatic impairment.[14]

LDMP is a strong CYP2D6 inhibitor, and co-administration with other drugs that rely on CYP2D6 for metabolism can lead to potentially significant drug interactions.[14] One important drug interaction is between LDMP and tamoxifen. Tamoxifen is used for the treatment and prophylaxis of breast cancer, and relies on CYP2D6 for conversion to an active metabolite. A trial of 1298 patients with breast cancer compared the rate of breast cancer recurrence in patients treated with tamoxifen with or without a CYP2D6 inhibitor.[15] Patients who were also on a CYP2D6 inhibitor had significantly higher rates of breast cancer recurrence at 2 years, 13.9% versus 7.5%. A retrospective study found that patients on paroxetine and tamoxifen had a significant increase in risk of death from breast cancer.[16] This finding was not observed among other SSRIs that do not cause CYP2D6 inhibition. It is important to consider this drug interaction because patients with a history of breast cancer, and patients on tamoxifen, tend to report increased rates of hot flashes.[7,18] Another potentially serious drug interaction occurs between SSRIs and anticoagulants due to platelet serotonin depletion.[14] Signs of bleeding should be monitored for anyone on a SSRI and medications like NSAIDS, warfarin, aspirin, heparin, and other anticoagulants. Life-threatening serotonin syndrome is more likely to occur when LDMP is administered with other serotonergic medications, or medications that impair the metabolism of serotonin.[14] Other potential interactions include drugs that rely on CYP2D6 for conversion to active metabolites. Codeine, for example, relies on CYP2D6 for conversion to morphine so pain relief may be impeded when combined with LDMP.

Adverse Effects and Safety

The most common adverse effects reported among the study participants were fatigue, constipation, headache, abnormal dreams, insomnia, and hyperhidrosis.[22] No deaths or serious side effects occurred in the study, and no subjects withdrew due to adverse events. In phase 2 and 3 clinical trials, the common adverse effects decreased with increased duration of therapy, and only 4.7% of women discontinued the medication due to side effects.

Like other SSRIs, LDMP has a potential for serious side effects and potentially life-threatening adverse reactions. LDMP has a black box warning for the potential to increase risk of suicidal thinking and behavior, similar to all SSRIs and SNRIs.[14] LDMP was not tested in women who have a history of depression, suicide, or psychiatric conditions.[14,25,26] Other adverse effects linked to SSRI use include SIADH, bone fractures, seizures, akathisia, acute angle closure glaucoma, and cognitive/motor impairment.[14]

Serada® (*Gabapentin ER*)

Gabapentin has been used off label for the management of VMS for many years. Drawbacks with the use of immediate release gabapentin are frequent dosing and CNS-related side effects. Recently, gabapentin ER has been evaluated for its potential role in VMS management, and is currently under review by the FDA for this indication. Benefits for the use of

gabapentin include a positive safety profile, lack of drug interactions, and its possible benefit on sleep in postmenopausal women with VMS.[17]

Pharmacology

Gabapentin binds to the α2δ subunit of voltage -gated calcium channels that are present in the central and peripheral nervous system. The exact mechanism of action for VSM is not known, but one theory is that the ventromedial part of the hypothalamus may be a target of gabapentin. This area has a high concentration of substance P, which may stimulate the hypothalamic cooling center.[17]

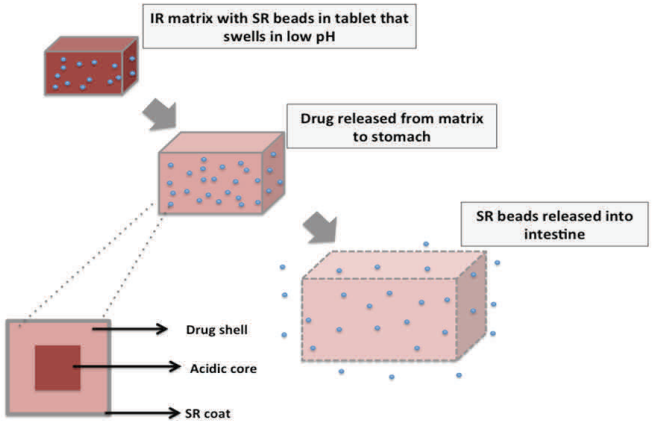
Pharmacokinetics and drug interactions

The pharmacokinetics and safety of gabapentin ER were studied among 124 postmenopausal women experiencing at least 7 moderate-severe hot flashes per day in a multicenter, randomized, double-blind, dose-escalating, placebo-controlled trial.[20] The mechanism of the extended release formulation of gabapentin ER is through the use of a novel gastroretentive formulation (Figure 1). The tablet swells when it comes into contact with gastric secretions, and prevents passage past the pyloric sphincter. The drug is slowly released over about 10 hours. Immediate-release gabapentin has saturable absorption in the small intestine via the L-amino transport system. This limits the bioavailability at higher doses. However, the slow release of the ER formulation attenuates the saturation of the receptors in the small intestine so the ER versions of gabapentin do not exhibit the same inverse relationship between bioavailability and dose. The extended-release and immediate-release versions of gabapentin both have similar half-lives of 5-7 hours, and have similar renal clearance.[17,21] Gabapentin ER should be taken with food to maximize the bioavailability and release of the medication.[17,20,21] The fat content of the meal is directly proportional with the time to max concentration (t_{max}) and bioavailability of gabapentin ER. Cmax of gabapentin increases 33-84% and AUC of gabapentin increases 33-118% with food depending on the fat content of the meal.[21]

Gabapentin ER is excreted unchanged in the urine and is minimally bound to plasma proteins. Since gabapentin does not undergo liver metabolism, and does not have extensive protein binding, there are relatively few drug interactions.[17,21] Certain medications can limit or increase the absorption of gabapentin ER.[21] Antacids can reduce the absorption, while medications like hydrocodone and morphine can enhance the absorption. The depressive CNS side effects of gabapentin can be amplified when given with other medications that cause CNS depression like benzodiazepines, alcohol, opioids, muscle relaxers, antiparkinsonian agents, and antipsychotics.[21]

Adverse Effects and Safety

Figure 1: Gastroretentive mechanism for Gabapentin Extended-release[32]



Adapted from the Patent Application Publication US 2011/0287096 A1
SR: sustained release, **IR:** immediate release

The most common adverse effects are headache, dizziness, nausea, and somnolence.[20,27,28,29] These side effects are thought to be less in the extended release version than in the immediate release product. Less common side effects reported in phase 3 trials were nasopharyngitis, weight gain, flatulence, and vomiting.[27,28,29]

Safety considerations for gabapentin include increased risk for suicidal thoughts or behavior, and the risk of seizures with rapid discontinuation.[21] Gabapentin ER undergoes renal clearance so the safety profile can be affected by the renal function of the patient taking the medication. Dosing adjustments for renal impairment have not been set for Serada®. The lowest creatinine clearance studied among postmenopausal women was 66 ml/min. Gralise®(*Gabapentin ER*) is approved for use in postherpatic neuralgia. Doses must be renally adjusted for creatinine clearance between 30-60 mL/min. Use in creatinine clearance below 30 mL/min is not recommended.[21] No dosing adjustments are required for hepatic impairment.

Clinical Trials

The safety and efficacy of both LDMP and gabapentin ER have been studied in multiple clinical trials. LDMP was evaluated in 2 phase 3 placebo-controlled clinical trials. The results from these trials enabled LDMP to gain FDA approval for moderate to severe VMS.[23,26] Both trials found that LDMP achieved reduction in both frequency and severity of hot flash-

es. Treatment benefits were seen as early as week 1 and persisted through week 24.[25] Gabapentin ER was evaluated in 3 phase 3 placebo-controlled clinical trials.[27,28,29] The results from these trials are being evaluated in hopes of gaining FDA approval for moderate to severe VMS. Table 2 and table 3 summarize the clinical trials for LDMP and Gabapentin ER.

The results of the two phase three clinical trials for LDMP showed that LDMP was effective at lowering both the frequency and severity of VMS for patients with moderate-severe VMS. Benefits were seen in the reduction of frequency in as early as the first week of therapy, and as early as 2 weeks for reduction of severity. Benefits were higher at week 12 than at week 4 for both frequency and severity. The benefit in frequency and severity persisted until 24 weeks. The persistence of benefit is assessed by showing a statistically significant difference of 50% or more reduction at week 24 between study groups.[14] The most common side effects reported were nausea (3.8% vs 1.4%), fatigue (3.4% vs 1.5%), and dizziness (2% vs 0.8%). No clinically significant changes in lab values, vital signs or electrocardiograms were observed.

Two of the studies for gabapentin ER evaluated two different dosing strategies.[27,28] The dosing regimens evaluated were 1,200 mg once daily, and 600 mg in the morning plus 1,200 mg in the evening (1,800 mg total/day). The BREEZE 1 trial for gabapentin ER was not able to show statistically significant reductions of frequency or severity at week 12 for either treatment group compared to placebo. The BREEZE 2 trial was only able to show statistically significant reductions in severity with the 1,800 mg/day group. The BREEZE 3 trial only evaluated the 1,800mg/day group versus placebo. This study was able to show statistically significant reductions in both the frequency and severity of VMS at weeks 4 and 12. These results were maintained out to week 24, but did not reach statistically significant reductions from placebo. BREEZE 3 also evaluated the impact that gabapentin ER has on sleep. This was assessed using the Insomnia Severity Index score (ISI) and the daily sleep interference score (S/I). At baseline the mean ISI scores in the treatment and placebo group were 17.54 and 17.33, respectively. This indicates moderate insomnia at baseline among the participants in the study. The S/I scores also indicated baseline moderate-severe insomnia with scores of 7.3 and 7.4. After 12 weeks the ISI score in the gabapentin ER and placebo groups were 8.7 and 6.3 (P=0.0044), and the S/I scores were 3.6 and 2.8

Table 2 | Summary of LDMP Clinical Trials

Study	Design and Study Population	Results - Frequency and % Response	Results - Severity and Composite score
Simon 2012	568 postmenopausal women, age 40+ R, DB, MC, PC LDMP 7.5 mg vs P * 12-day SB period with only P 24 wk duration 1⁰ endpoint: ê in frequency and severity of VMS Mean age 54 yr 76% Caucasian, 22% AA Average of more than 7-8 moderate to severe HF/day or 50-60 moderate to severe HF/wk for at least 30 d prior	**Week 4** 28.9 vs 19.0 fewer HF/wk P<0.0001 **Week 12** 37.2 vs 27.6 fewer HF/wk P=0.0001 **Week 24** 47.5% vs 36.3% response P=0.0066	**Week 4** -0.089 vs -0.056 ê in severity P=0.0452 **Week 12** -0.123 vs -0.067 ê in severity P-0.0114 **Week 4** -76 vs -49.5 CS P<0.0001 **Week 12** -97.7 vs -72 CS P=0.0001
Kaunitz 2012	606 postmenopausal women, age 40+ R, DB, MC, PC LDMP 7.5 mg vs P* 12 wk duration 1° endpoint: ê in frequency and severity of VMS Mean age 55 yr 65% Caucasian, 33% AA Average of more than 7-8 moderate to severe HF/day or 50-60 moderate to severe HF/wk for at least 30 d prior	**Week 4** 33 vs 23.5 fewer HF/wk at P<0.0001 **Week 12** 43.5 vs 37.3 fewer HF/wk P=0.009	**Week 4** -0.09 vs -0.05 ê in severity P=0.0048 **Week 12** No significant difference **Week 4** -85.51 vs -60.83 CS P<0.0001 **Week 12** -111.9 vs -96.85 CS P=0.0063

*LDMP (low dose mesylate salt of paroxetine) dosed 7.5 mg at bedtime
P: Placebo, **RC:** randomized, **PC:** placebo controlled, **DB:** double blind, **SB:** single blind, **MC:** multicenter, **Yr:** years of age, **AA:** African american **HF:** hot flashes, **wk:** week, **d:** days, **AE:** adverse event, **LDMP:** Low dose mesylate salt of paroxetine, **CS:** composite score

(P=0.0056). Reductions persisted through week 24 of the study. The most common side effects reported in the trials were nausea, dizziness, somnolence, headache, and sedation. No clinically significant changes in lab values, vital signs or electrocardiograms were observed.

Dosing and Cost

The convenience of dosing can be important for patient compliance. For example, gabapentin, requires up to TID dosing while the majority of the other options are dosed QD. Because some of the therapies do not have generics available, there is a significant variability in cost. Table 4 summarizes the dosing of the non-hormonal therapies, the cost for a 30 day supply, and if the drug is on the 2013 Florida Medicaid preferred drug list.

Place in Therapy for Newer Agents

FDA approval of non-hormonal therapies for VMS management, fulfill a void that has been part of VMS management for many years. There are many women who suffer from VMS who cannot take, or choose not to take hormonal therapy. Having FDA-approval of non-hormonal therapies means that the efficacy and safety of these therapies were studied in randomized-controlled trials among postmenopausal women experiencing VMS, and have dosing that has been studied exactly for the purpose of VMS management. Insurance coverage may be greatly improved for therapies once they are FDA-approved specifically for VMS management.

Brisdelle® is now approved for the management of moderate-severe VMS, and Serada® is currently in review for FDA approval. The drugs differ in their alternative indications, pharmacokinetics, and side effect profile. Having two completely different non-hormonal therapies approved for VMS management allows women to have choices, and is especially beneficial for women who fail or cannot use one of the traditional options.

Table 3 | Summary of Gabapentin ER Clinical Trials

Study	Design and Population*,¤,§	Results - Frequency	Results - Severity
BREEZE 1	541 postmenopausal women Prospective, R, PC, MC, DB 12 wk duration with 6 month assessment Mean age 52.9 yr, ~20% AA, ~70% caucasian	**Week 4** (1)-0.96±0.38, P=.0117 (2)-1.51±0.38, P<.0010 **Week 12** (1)-0.56±0.42, P=0.183 (2)-1.53±0.41, P=0.198	**Week 4** (1)-0.26±0.08, P=.0016 (2)-0.32±0.08, P=.0001 **Week 12** (1)-0.20±0.08, P=.0016 (2)-0.20±0.10, P=.0468
BREEZE 2	565 postmenopausal women Prospective, R, PC, MC, DB 12 week duration Mean age 53.2 yr	**Week 4** (1)-1.61±0.53, P=.0024 (2)-1.51±0.52, P=.0040 **Week 12** (1)-1.56±0.51, P=.0024 (2)-1.12±0.51, P=.0280	**Week 4** (1)-1.15±0.08, P=.0608 (2)-1.28±0.08, P=.0003 **Week 12** (1)-0.21±0.10, P=.0280 (2)-0.29±0.10, P=.0026
BREEZE 3	600 postmenopausal women Prospective, R, PC, MC, DB 600 mg in the morning +1,200 mg at bedtime of G-ER vs P 12 wk duration with 6 month assessment Impact on sleep assessment Mean age 54 yr	**Week 4** -1.69, P<0.0001 **Week 12** -1.14, P=0.0001 **Week 24** -1.08, P<0.0174 Not significant	**Week 4** -0.21, P<0.001 **Week 12** -0.19, P=0.004 **Week 24** -0.22, P=0.0457 Not significant

* Primary outcome in all three studies was hot flash severity and frequency at 4 and 12 weeks

¤ Two treatment groups: (1) 1,200 mg once daily and (2)600 mg in the morning + 1,200 mg at bedtime (1,800 mg) for BREEZE 1 and BREEZE 2

§All women had an average of 7+ moderate-to-severe hot flashes per day or a minimum of 50 per week, along with episodes of sweating, in the 30 days prior

P: Placebo, **RC:** randomized, **PC:** placebo controlled, **DB:** double blind, **MC:** multicenter, **Yr:** years of age, **AA:** African american **HF:** hot flashes, **wk:** week, **d:** days, **, G-ER:** Gabapentin Extended Release

Table 4 | Dosing and Cost of Non-hormonal Treatment Options for Hot Flashes

Medication	Dosing and titration	Cash Price* ($/30-day supply)	Medicaid Preferred Drug¤
Brisdelle® (*Paroxetine mesylate*)	7.5 mg once daily at bedtime	Not yet available	Not yet available
Serada® (*Gabapentin ER*)	1,200 mg once daily or 1800 mg in two divided doses	Not yet available	Not yet available
Paroxetine CR	12.5-25 mg once daily	$71-$110	No
Venlafaxine ER	37.5-75 mg once daily	$27-$65	Yes
Pristiq® (Desvenlafaxine)	100-150 mg once daily	$200-$230	Prior authorization required
Gabapentin	300 mg daily titrated to 300 mg three times daily (Minimum effective dose)	$25-$31	Yes
Clonidine	0.05-0.1 twice daily 0.1 mg at bedtime 0.1 mg/24hr patch	$8-$15.41 $84.14-$94.00	Yes

* Range of lowest to highest cash prices from common pharmacies in Gainesville, FL; www.goodrx.com
¤2013 Florida Medicaid Preferred Drug List

Summary

Hormonal therapy is the most effective option for the management of VMS, and until recently was the only FDA-approved therapy for VMS management. Due to the safety concerns associated with postmenopausal hormonal therapy, there has been a trend in the decrease of its use. More women are relying on non-pharmacological and non-hormonal therapies for the management of their hot flashes. Certain SSRIs and SNRIs, gabapentin, and clonidine have been found to be effective in the management of VMS. Among the SSRIs and SNRIs, venlafaxine, desvenlafaxine, and paroxetine have shown the most promising results in clinical trials. Gabapentin, in higher doses, is effective in VMS management, and has even been shown to have similar efficacy to hormonal therapy.[30] Brisdelle®, a low dose of paroxetine mesylate, was recently FDA-approved for moderate-severe VMS treatment. Serada®, an extended-release version of gabapentin, is currently under review by the FDA for moderate-severe VMS treatment. FDA approval of these non-hormonal therapies allows women to have more options, and ensures that these therapies are adequately studied among postmenopausal women for this indication. More studies are needed that directly compare these therapies to each other, and that show safety and efficacy for longer durations of time.

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Also The American College of Obstetricians and Gynecologist recently published a Practice Bulletin regarding the management of menopausal symptoms. This article can be found at the citation below.

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