

# Actual status of veralipride use

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**Abstract:** During the climacteric period, several symptoms exist that motivate women to seek medical advice; one of the most common is the hot flush, which presents in 75%–85% of these during a variable time span. For the treatment of hot flush, several non-hormonal treatments exist; among them, veralipride has shown to be a useful treatment of vasomotor symptoms during the climacteric period. In recent times, several medical societies have discredited its use. The purpose of this review, therefore, is to define a measured position in relation to the use of this drug. On completion of this review, it was possible to conclude that this drug has an antidopaminergic mechanism of action. The recommended schedule is: 100 mg/day for 20 days, with 10 days drug free. Since the risk of undesirable secondary effects such as galactorrhea, mastodynia, and extrapyramidal can increase with use, no more than 3 treatment cycles are recommended. This drug has a residual effect that can allow drug-free intervals, which permit a longer time between schedules.

**Keywords:** veralipride, hot flushes, climacteric, menopause, symptoms, secondary effects

## Introduction

During the climacteric period, several symptoms exist that motivate women to seek medical advice. One of the most frequent is the hot flush, which presents in 75%–85% of these for a variable time span.

The hot flush is defined as a sudden hot sensation in the face, neck, and chest, which can have different intensity and frequency during the day and night and can be accompanied by sweating, flushing, throbs, anxiety, or irritability.<sup>1</sup> The hot flush has an average duration of 4 minutes but can last from a few seconds to 10 minutes.<sup>2</sup>

For hot flushes to occur, estradiol serum levels need to have decreased. This produces changes in hypothalamic neurotransmitters such as those synthesized in noradrenergic and dopaminergic neurons. The increase in noradrenergic tone modifies the opioid system and in concert with the decrease in dopaminergic tone modifies the release of gonadotrophin-releasing hormone (GnRH) and luteinizing hormone (LH),<sup>3</sup> which traduce an increase in its pulsatility. These neurotransmitters by themselves promote instability of the thermoregulatory center and condition vasomotor symptoms.<sup>4</sup> Also, it has been observed that estrogen deficiency is associated with a decrease in serotonin levels allowing hot flushes to occur, probably due to an interconnection between this neurotransmitter and noradrenaline.<sup>5</sup>

For the treatment of climacteric symptoms, several drugs have been used with different results in relation to their effectiveness and secondary effects.<sup>6</sup> The most representative studies with these drugs are shown in Table 1.

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**Table 1** Hot flushes decrease with several treatments

	Mechanism	Dose	Hot flushes decrease vs placebo	Secondary effects	Withdrawal (%)
<b>Clonidine</b> Carranza-Lira <sup>7</sup>	$\alpha$ -2 adrenergic agonist	0.1 mg e/12 hr	83% vs 50%	Mouth dryness, depression, nausea, insomnia, somnolence	–
<b>Gabapentin</b> Reddy <sup>8</sup>	GABA analog	900 mg/day	54%–71% vs 29	Dizziness, headache, disorientation up to 50%	–
Biglia <sup>9</sup>		900 mg/day	Frequency 57.0% Intensity 66.9%		34.8
<b>Venlafaxine</b> Evans <sup>10</sup> Phillips <sup>11</sup> Ladd <sup>12</sup>	SNRI	75 mg/day 75–225 mg/day	61% vs 20% 60%	Anti-cholinergic effects Hepatitis	– – –
<b>Desvenlafaxine</b> Archer <sup>13,14</sup>	SNRI	100–150 mg/day	63% vs 47% 66.6% vs 50.8%		More than placebo
Speroff <sup>15</sup>		100 mg/day	64%		–
<b>Paroxetine</b> Stearns <sup>16</sup>	SSRI	25 mg/day	65% vs 38%		–
<b>Fluoxetine</b> Loprinzi <sup>17</sup> Oktem <sup>18</sup> Suvanto-Luukonen <sup>19</sup>	SSRI	20 mg/day 20 mg/day 10–30 mg/day	50% vs 36% 62% No better than placebo		– 33 34
<b>Citalopram</b> Suvanto-Luukonen <sup>19</sup> Soares <sup>20</sup> Kalay <sup>21</sup>	SSRI	10–30 mg/day 20–60 mg/day 10–20 mg/day	No better than placebo 86.6% decrease in depression 37% vs 13%		34 – –
<b>Propranolol</b> Carranza <sup>7</sup> Coope <sup>22</sup> Alcoff <sup>23</sup>	$\beta$ adrenergic blocker	20 mg e/12 hr 40 mg e/8 hr	50% vs 50% Similar than placebo Favorable vs placebo		– – –
<b>Vitamin E</b> Barton <sup>24</sup> Biglia <sup>25</sup>		800 IU/day	One hot flush less than with placebo Frequency 10.2% Intensity 7.28%	Clinically similar to placebo	– 34.8
<b>Methyl-dopa</b> Andersen <sup>26</sup> Nesheim <sup>27</sup>	$\alpha$ 2 adrenergic agonist	375–1125 mg/day 250–500 e/12hr	65% vs 38% 85%		– 33
<b>Cimicifuga racemosa</b> Oktem <sup>18</sup> Jacobson <sup>28</sup> Borrelli <sup>29</sup>		40 mg/day Not indicated 4 mg e/12 hr	85% No better than placebo Similar to estrogen		33 Risk of hepatotoxicity <sup>30</sup> –

**Abbreviations:** SSRI, serotonin selective reuptake inhibitors; SNRI, serotonin noradrenalin reuptake inhibitors.

Veralipride is another drug that has shown its effectiveness, and it has been considered a good therapeutic alternative for climacteric-related vasomotor symptoms when a contraindication or non-acceptance of hormone therapy (HT) exists. Veralipride can also be used in association with other drugs that do not confer any control of vasomotor symptoms; for example, raloxifene, whose main indication is for postmenopausal women with risk of or established osteopenia-osteoporosis.<sup>31</sup>

Veralipride has been used for a long time. Recent studies have proved its efficiency in the recommended dose of 100 mg/day;<sup>32</sup> however, at this time some medical societies<sup>33</sup> and government organizations<sup>34</sup> have discredited its use due to its secondary adverse effects. The still in use Mexican Official Norm for the prevention and control of perimenopausal and postmenopausal diseases in women establishes that the drug can be useful in the control of vasomotor symptoms.<sup>35</sup>

For all previously exposed the purpose of this work is to review the current evidence with veralipride and define a measured position without bias in relation to its use.

## Pharmacology

Veralipride is a dopaminergic antagonist of receptor D2, whose formula is N-[allyl-1 pyrrolidiny-2) methyl] dimethoxy-2,3-sulfamoyl-5 benzamide.<sup>36</sup> This drug induces prolactin secretion without any estrogenic or progestagenic effects. Serum levels of follicle stimulating hormone, LH, estradiol, and estrone aren't modified.<sup>37</sup> However, some studies have reported that LH can decrease. Prolactin increase and LH decrease can be explained by a stimulation of endogenous opioid activity.<sup>3,38</sup> This drug is well absorbed when administered orally, achieving maximal concentrations at 2.5 hours. It is poorly metabolized and is eliminated in the urine and feces. After oral administration, the half-life is 4 hours, and 44% is excreted without any changes in urine in the first 120 hours.<sup>3</sup>

## Clinical studies

When evaluating hot flushes, frequency and intensity are taken in account. With veralipride, it has been reported that since the 4th treatment day, hot flushes begin to subside.<sup>3</sup> In other studies in which veralipride has been compared against placebo, it has been reported that there is a statistically significant reduction in frequency as well as in intensity of hot flushes after 20 days of continuous treatment at a dose of 100 mg/day.<sup>3</sup>

When comparing veralipride with HT, a decrease in frequency of hot flushes of 80% versus 100% and of intensity of 71% versus 100%, respectively, has been observed.<sup>7</sup>

Most of the studies agree that the decrease of hot flushes with veralipride use is from 48.0% to 89.9% depending on time of use and method of administration.

Several ways of prescribing veralipride have been reported and not always in accordance with the product directions – many times due to ignorance and others with the idea of decreasing the secondary effects such as hyperprolactinemia as well as those extrapyramidal.

The schedules in use have different rates of effectiveness (Table 2) and secondary effects and are:<sup>7,36,39-41</sup>

- Classic schedule, 100 mg/day for 20 days, with 10 days drug free for no more than 6 months;
- 100 mg/day for 7 days, followed by 100 mg every 48 hours for 1 month, followed by 100 mg/day twice a week for 3–6 months;
- 100 mg/day from Monday to Friday with Saturday and Sunday free of treatment;
- 100 mg/day for 2 days, and 2 days without treatment, and then repeat;
- 100 mg every 48 hours for 3–6 months.

Leo et al indicate that every veralipride prescription schedule must be individualized, and that 6 cycles of treatment are not associated with addiction.<sup>3</sup>

## Secondary effects

One of the main secondary effects of veralipride use is hyperprolactinemia, which may or may not be accompanied by galactorrhea, and can disappear at 48 hours of treatment

**Table 2** Veralipride efficiency with several evaluated schedules

	Schedule	N	Time	Study	Results
David <sup>36</sup>	A	47	2 months	Double blind, placebo controlled, crossover	Hot flush reduction 80% Residual effect 3 months after withdrawal
Wesel <sup>39</sup>	B	40		Double blind, randomized	Similar decrease in hot flushes between groups
Melis <sup>40</sup>	C	40	1 month	Randomized, double blind, placebo controlled	85% reduction
Vercellini <sup>41</sup>	D	36	2 months	Randomized, double blind, placebo controlled	Reduction 78% vs placebo 33%
Carranza-Lira <sup>7</sup>	E	75	3 months	Comparative, randomized, placebo controlled	80% reduction in frequency, 71% in intensity, 82% duration, sweats 66.6%
Morgante <sup>31</sup>	F	29	6 months	Randomized, comparative	Without differences between in number of hot flushes and Kupperman's index Hot flushes decrease in 63% and 66% at 3rd and 6th month respectively
Boukobza <sup>42</sup>	G	166	3 months	Open, multicentric	Hot flush reduction 89.9% In 64.5% residual effect 3 months after withdrawal
Vercellini <sup>43</sup>	H	25	28 days	Open, observational trial	92% of patients have decrease in frequency and intensity of hot flushes
Marais <sup>44</sup>	I	–	1–14 months	Comparative, placebo controlled	48%–72% decrease

**Notes:** A, 100 mg/day for 20 days and 10 days drug free; B, 100 mg/day for 20 days and 10 days drug free versus conjugated estrogens 1.25 mg/day; C, 100 mg/day; D, 100 mg/day; E, 100 mg/day from Monday to Friday; F, Raloxifene plus veralipride in alternate days versus raloxifene and veralipride in alternate months; G, 100 mg/day for 20 days and 10 days drug free; H, 100 mg/day 20 days.

withdrawal,<sup>39</sup> other studies indicate that the normalization of prolactin levels can take 2 or 3 weeks.<sup>45</sup> Reported prolactin levels after 2 cycles have been  $106.2 \pm 41.5$  ng/mL;<sup>39</sup> others have reported levels 10 times higher than those at baseline.<sup>46</sup> A clinical study reported that after veralipride administration at a dose of 100 mg/day for 6 months on alternate days or months, the prolactin levels were not higher than 21 ng/mL.<sup>7</sup> Other reported secondary effects have been galactorrhea, headache, nervousness, insomnia, depression, mastodynia, and weight increase.

The most serious effects that have been reported with veralipride use are those extrapyramidal, such as acute dyskinesia, tardive dyskinesia, Parkinsonism, postural tremor, myoclonia, and dystonia. Many of these have been related to over-dosage and due to the lack of prescription instruction follow-up; however, this it is not always the case.<sup>10,42,46,47</sup> See Table 3.

It's worth mentioning that the Pharmacovigilance committee from the laboratory that produces this drug in Mexico has reported that sales in 5 years have been 2,265,729 pieces. In this time they have been informed of only 35 adverse effects. Of these, 21 have been attributed to incorrect medication use: anxiety (6), depression (6), abnormal movements (2), weight gain (2), lower limb pain (2), neck rigidity (1), galactorrhea (1), and muscular weakness (1). Those which presented after adequate drug intake numbered 14: insomnia (3), nervousness (2), fear (2), fine tremor (1), irritability (1), lack of appetite (1), mastitis (1), galactorrhea (1), pain (1), and head pain (1).<sup>52</sup>

## Contraindications and prescription recommendations

After the review of several non-hormonal options for the treatment of climacteric hot flushes it can be concluded that for a drug to be considered as a good option for the treatment of vasomotor symptoms, an evaluation of the risk-benefit of the chosen therapy is always needed, and this must be well supported by clinical studies that evaluate safety parameters.<sup>53</sup>

Those women than can be candidates for veralipride use must achieve an adequate clinical profile, which means they will lack any history of tardive dyskinesia, Parkinsonism, acute dyskinesia, postural tremor, myoclonia, dystonia, hyperprolactinemia, breast fibrocystic disease, depression, and breast cancer.<sup>37</sup>

## Conclusion

After this review it can be concluded that veralipride is a good option, and a safe drug if recommended doses are

**Table 3** Secondary effects with veralipride use, according to schedule

	Secondary effect	Schedule	N or %
David <sup>36</sup>	Depression+	100 mg/day 20 days and 10 days drug free	19%–47%
Boukozoba <sup>42</sup>	Breast tenderness	100 mg/day 20 days and 10 days drug free for 3 months	1.2%
	Insomnia		0.6%
	Mouth dryness		0.6%
	Somnolence		1.2%
	Digestive problems		0.6%
	Dizziness		0.6%
	Weakness		0.6%
Masmoudi <sup>46</sup>	Parkinsonism	Several schedules	N
	Acute dyskinesia		15
	Parkinsonism plus other in 8 cases		2
	Tardive dyskinesia		6
	Postural tremor		3
	Myoclonia		1
	Dystonia		1
Montemurro <sup>47</sup>	Acute coronary syndrome	100 mg/day	1
Kunhardt <sup>48</sup>	Pyrosis	100 mg/day 20 days and 10 days drug free	1
	Hair fall		1
	Mamary pruritus		1
	Mastodynia		3
	Placebo		
	Headache, joint pain, vaginal discharge mastodynia 1/e		1 each
Raja <sup>49</sup>	Tardive dyskinesia	Not reported	1
Sining <sup>50</sup>	Dystonia	100 mg/day (2 months)	1
	(Hypertension under enalapril treatment)		
Teive <sup>51</sup>	Increase in Parkinsonian symptoms	Not reported	1

respected.<sup>3</sup> Its high effectiveness in the control of vasomotor symptoms allows a high number of patients to be benefited.

The presentation of secondary adverse events is decreased using this medicament at a dose no greater than 100 mg/day, for short time spans, and leaving drug-free intervals between schedules. The drug-free intervals will not decrease drug favorable effects due to the drug's residual effect as shown before.

It's worth investigating safety aspects in the Latin-American population as well as the use of low-dose. Recently, the Mexican Association for the Study of the Climacteric, gave the following recommendations when veralipride is prescribed.

1. An evaluation of medical history must be carried out, following a strict selection profile according to medical history, particularly of neuropsychiatric problems.<sup>37,46</sup>
2. Respect the schedule and dose indicated by producer (20 treatment days with 10 days drug free).<sup>37,46,53</sup>
3. Don't give more than 3 treatment cycles together, and don't repeat more than twice in a year (no more than 6 cycles per year).<sup>3</sup>
4. In those women with chronic use, the drug must be gradually withdrawn to avoid withdrawal symptoms.<sup>3,38,53</sup>

## Disclosure

The author reports no conflicts of interest in this work.

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