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Effect of sulpiride on menopausal hot flashes: a randomized, double-blind, placebo-controlled clinical trial

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ABSTRACT

Low doses of sulpiride have been used off-label to treat menopausal hot flashes in Southern Brazil despite limited scientific evidence. This randomized controlled trial aimed at assessing the effects of sulpiride as compared to placebo on the frequency and severity of hot flashes. Postmenopausal women, aged 47–62, were recruited from the Menopause Clinic at Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil, between March 2016 and January 2017. After a baseline assessment of 4 weeks, women were included if they had at least a mean of five moderate to severe hot flashes per day and then randomized to receive for 8 weeks either placebo (n= 14) or sulpiride 50 mg/d (n= 14). The number and severity of hot flashes were evaluated after the 8-week intervention. A generalized estimating equations (GEE) model with Bonferroni correction was used to simultaneously assess the frequency and severity of hot flashes. Baseline frequency and severity of hot flashes/day were similar in both groups. Sulpiride significantly reduced the total weekly mean of hot flash frequency (GEE, \( p_{interaction}=0.019\)) and the total weekly mean of severity scores (GEE, \( p_{interaction}=0.006, p_{time}<=0.0001\)) after 4 and 8 weeks of treatment. Treatment with sulpiride 50 mg/d significantly reduced the frequency and severity of hot flashes. Further studies are needed to confirm its benefits and related mechanisms of action.

INTRODUCTION

Vasomotor symptoms are part of the spectrum of the menopausal syndrome [1,2] that can lead to a significant reduction in quality of life [3,4]. Up to 80% of postmenopausal women present such manifestations [3–7]. Ethnicity, demographic characteristics, seasonal temperatures, and health status can influence the number and sensation of hot flashes [1,3]. Hormone therapy (HT) is the most effective treatment option for vasomotor symptoms [1,2,8]. However, some women do not want or may not be eligible for HT, such as those at increased risk of venous thrombosis or with a history of hormone-dependent cancers [8,9].

New studies on non-hormonal therapies for moderate-to-severe hot flashes are warranted [5,10]. Despite increased research on non-hormonal alternative-treatments for hot flashes, few clinical studies have shown better results than placebo [10,11,12]. Although it is known that mood disorders may influence hot flashes [2,6], the benefits of selective serotonin reuptake inhibitors (SSRIs) might be linked to the hypothalamic effects of serotoninergic and dopaminergic mediators [10]. Sulpiride is an atypical neuroleptic that blocks postsynaptic and pre-synaptic self-inhibitory dopaminergic receptors; hence increasing the available amount of the dopamine neurotransmitter in the synaptic cleft [13,14]. In addition, in low doses it can act on serotonin receptors [15].

Due to the fact that sulpiride has been used off-label in low doses for hot flashes in Southern Brazil for a number of years, and considering the lack of related research, the main objective of this study was to determine the effect of sulpiride 50 mg/d on hot flash frequency and severity after an eight-week follow-up period.

METHODS

TRIAL DESIGN

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at the Hospital de Clínicas de Porto Alegre (HCPA), Rio Grande do Sul, Brazil. Prior to any data collection, ethical approval was obtained from the Institutional Review Board of the HCPA, Porto Alegre/RS, Brazil (Ref. No. 2014–0038), which was registered online (www.saude.gov.br/plataformabrasil; CAAE Ref. No. 26901714.9.0000.5327). The study was also registered in ClinicalTrials.gov (Ref. No. NCT02749747). The study was conducted according to the CONSORT guidelines and the ethical standards of the Declaration of Helsinki [16].

SAMPLE SELECTION AND RANDOMIZATION

Winpepi\textsuperscript{®} version 11.43 was used to calculate the sample size [17]. It was estimated that a sample of 28 women, 14 in each group, would be needed to detect a difference of 21 hot-flashes per week between means with an 80% power and an \( \alpha = 0.05\),
Participants were recruited from the HCPA Menopause Outpatient Clinic and through online/newspaper advertisement between March 2016 and January 2017 and informed of the research, its aims and requested to provide informed consent. All information about women was kept strictly confidential and the study did not involve physical, moral or psychological harm to them.

The inclusion criteria were healthy postmenopausal women who recorded after a baseline assessment period of 4 weeks a daily mean of at least five moderate to severe hot flashes. Recording was carried out in a daily diary specifically created for this trial. Indeed, participants filled out a log form each day recording the number of hot flashes and categorizing the severity of each hot flash (mild, moderate, or severe), as well as the period in which they occurred (day or night). They were included only after having completed this daily form for four weeks. Those who had used HT or psychiatric medications in the last 3 months prior to recruitment were excluded. Upon enrollment, they also underwent clinical laboratory tests (blood chemistry and hormone levels) and an electrocardiogram, mammogram, and Pap smear.

The exclusion criteria were a history of hypersensitivity to sulpiride, a prolactin-dependent pituitary tumor, current or treated breast cancer, diagnosis or suspicion of pheochromocytoma, concomitant use of levodopa, cardiac problems with electrocardiogram abnormality (QT prolongation, bradycardia less than 55 beats per minute), electrolyte imbalance (mainly hypokalemia), and stroke.

Of 37 postmenopausal women initially assessed for eligibility, 32 met the inclusion criteria. Of these, three were excluded after the baseline 4-week diary period of the study. Thus, a total of 29 women were randomly allocated either to sulpiride 50 mg/d or placebo treatment. The sample selection and randomization diagram are shown in Figure 1. Randomise was used to generate the randomization table, carried out in blocks of one to guarantee the same number of participants in each group. This tool was produced by the Department of Social Statistics, Southampton University, UK. Random number codes were placed in sealed dark envelopes with the participant’s sequential number printed on the outside of the envelope.

Outcome measures and procedures

The main endpoint of this study was to test the effect of sulpiride on mean weekly frequency and severity of hot flashes. After the baseline 4-week diary period, participants with a daily mean of five or more moderate to severe hot flashes were randomized 1:1 to receive sulpiride 50 mg/d or placebo for 8 weeks more, time in which they continued to record the number and severity of daily hot flashes.

In the analysis, the weekly mean of total hot flashes episodes registered in the diaries was computed for all assessed periods (baseline, 4 and 8 weeks of treatments). Additionally, based on Carpenter et al. [19] a weekly hot flash severity score was computed for each woman, attributing the following weights: mild = x1, moderate = x2, and intense = x3.

The researcher who conducted the trail and delivered the structured interviews, as well as the participants enrolled in this study, were kept blind to the group allocation from baseline until the end of the study. Upon assigning numbers, the researchers concealed the names of the participants and their random allocation to the different groups to ensure the blinding of the data entry operator and data analyst.

Sulpiride (Equilid, Sanofi-Aventis Farmacêutica Ltda., Suzano, Brazil) was used as a 50 mg pill. The placebo was a pharmaceutically inert substance (sugar pill) similar to the sulpiride pill. Both the researchers and the participants were double-blinded regarding the groups and substances. The potential adverse effects of sulpiride 50 mg/d were analyzed through a structured questionnaire.

Statistical analyses

SPSS version 18.0 was used for data processing, double database entry, and review (SPSS Inc., Chicago, IL). Normally-distributed quantitative data, according to the Shapiro–Wilks test, were expressed as mean ± standard error of mean (SEM), and non-normally-distributed quantitative data were expressed by median and interquartile range [IQR]. Categorical variables were described as absolute (n) and relative (n %) frequencies.

Student’s t-test for independent samples was used to compare the means between groups. For non-normally distributed data, the Mann–Whitney test was used to perform comparisons. Proportions between categories were compared with the Chi-Square test with standardized adjusted residuals.

A generalized estimating equation (GEE) model with Bonferroni correction was used to simultaneously assess the number (frequency) and severity (severity scores) of hot flashes between and within groups (in different time measurements according to group). Hot flash frequency and severity and GEE scores were assessed through weekly reports for each day and night. Cohen’s d was used to estimate the sulpiride effect size in relation to placebo [20].

Results

Figure 1 shows the participant CONSORT flow chart [21]. Initially, 37 women were screened for eligibility criteria, of whom five were considered ineligible and were excluded, leaving...
32 women. After 4 weeks of recording, the daily frequency and severity of hot flashes, two more were excluded for not having had at least five mean daily hot flashes. The remaining 29 (n = 29) were randomized to the two groups: sulpiride 50 mg/d (n = 15) or placebo (n = 14). Finally, one further participant was excluded due to insufficient information regarding her hot flash diary. Thus, a total of 28 women completed this study, 14 in the sulpiride group and 14 in the placebo group.

The characteristics of both groups were homogeneous at baseline. Table 1 displays body mass index (BMI) of participants, sociodemographic characteristics and severity of hot flashes. Most of the participants were married or living with their partners (75.0%), reported no alcohol consumption (60.8%), and were nonsmokers (82.1%). The median [95% CI] time since menopause onset was 36.0 [27.9–59.6] months.

Sulpiride treatment significantly reduced the total weekly mean of hot flash frequency 4 and 8 weeks after treatment (GEE, \( p_{\text{interaction}} = .019 \)) (weekly mean ± SEM, baseline: 60.3 ± 3.0, 4 weeks: 34.5 ± 3.7, 8 weeks: 27.8 ± 3.0). In the placebo group, a non-significant reduction of the total weekly mean of hot flash frequency was observed (weekly mean ± SEM, baseline: 75.5 ± 3.8, 4 weeks: 65.3 ± 5.3, and 8 weeks: 65.1 ± 5.5) (Figure 2, top).

By means of the Carpenter score, compared to placebo, sulpiride 50 mg/d reduced total weekly mean of hot flash severity scores after 4 and 8 weeks of treatment (GEE, \( p_{\text{interaction}} = .09, p_{\text{group}} = .006, p_{\text{time}} \leq .0001 \)) (weekly mean ± SEM, baseline: 98.8 ± 9.2, 4 weeks: 57.3 ± 12.5, and 8 weeks: 43.8 ± 9.5). In the placebo group, a non-significant reduction of the mean weekly hot flash severity score was observed (weekly mean ± SEM, baseline: 125.5 ± 12.0, 4 weeks: 114.7 ± 18.5, and 8 weeks: 107.1 ± 20.3) (Figure 2, bottom).

Although Cohen’s analysis revealed that sulpiride had a small-to-medium effect size on hot flash frequency/severity (Cohen’s d up to 0.44), clinical improvement in the sulpiride 50 mg/d group could be inferred.

Breast engorgement was reported by two women (7.1%), with no reports of galactorrhea, indicating that the undesired effects of this treatment were minimal (Data not shown).

### Table 1. Baseline characteristics of studied women.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sulpiride (n = 14)</th>
<th>Placebo (n = 14)</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) – mean ± SEM</td>
<td>54.9 ± 1.1</td>
<td>53.2 ± 0.8</td>
<td>.242</td>
</tr>
<tr>
<td>Body mass index (kg/m²) – mean ± SEM</td>
<td>27.4 ± 0.9</td>
<td>27.0 ± 1.2</td>
<td>.800</td>
</tr>
<tr>
<td>Family monthlyincome (minimum wagesa) – median [IQR]</td>
<td>4.5 [3.5 – 8.0]</td>
<td>3.5 [2.5–6.0]</td>
<td>.246</td>
</tr>
<tr>
<td>Marital status – n (%)</td>
<td></td>
<td></td>
<td>.801</td>
</tr>
<tr>
<td>- Single or living without partner</td>
<td>1 (7.1)</td>
<td>6 (42.9)</td>
<td>-</td>
</tr>
<tr>
<td>- Married or living with partner</td>
<td>13 (92.9)</td>
<td>8 (57.1)</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol use (Frequency/week) – n (%)</td>
<td>9 (64.3)</td>
<td>8 (57.1)</td>
<td>-</td>
</tr>
<tr>
<td>- 0</td>
<td></td>
<td></td>
<td>.901</td>
</tr>
<tr>
<td>- 1 – 3</td>
<td>4 (28.6)</td>
<td>5 (35.7)</td>
<td>-</td>
</tr>
<tr>
<td>- 4 – 7</td>
<td>1 (7.1)</td>
<td>1 (7.1)</td>
<td>-</td>
</tr>
<tr>
<td>Smoking habit – n (%)</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>- No</td>
<td>12 (85.7)</td>
<td>11 (78.6)</td>
<td>-</td>
</tr>
<tr>
<td>- Yes</td>
<td>2 (14.3)</td>
<td>3 (21.4)</td>
<td>-</td>
</tr>
<tr>
<td>Time after menopause (months) – median [IQR]</td>
<td>42.0 [18.0–60.0]</td>
<td>30.0 [15.0–48.0]</td>
<td>.306</td>
</tr>
<tr>
<td>Mild hot flashes (Frequency/Week) – mean ± SEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Day</td>
<td>8.5 ± 3.6</td>
<td>8.5 ± 2.1</td>
<td>.993</td>
</tr>
<tr>
<td>- Night</td>
<td>3.30 ± 1.07</td>
<td>1.38 ± 0.60</td>
<td>.172</td>
</tr>
<tr>
<td>Moderate hot flashes/week – mean ± SEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Day</td>
<td>14.0 ± 1.9</td>
<td>16.2 ± 2.2</td>
<td>.459</td>
</tr>
<tr>
<td>- Night</td>
<td>9.4 ± 1.1</td>
<td>11.2 ± 2.2</td>
<td>.496</td>
</tr>
<tr>
<td>Intense hot flashes/week – mean ± SEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Day</td>
<td>12.7 ± 11.6</td>
<td>16.9 ± 3.2</td>
<td>.279</td>
</tr>
<tr>
<td>- Night</td>
<td>12.7 ± 3.1</td>
<td>21.3 ± 3.8</td>
<td>.094</td>
</tr>
<tr>
<td>Hot flash scores – mean ± SEM</td>
<td>98.8 ± 9.5</td>
<td>125.5 ± 12.4</td>
<td>.100</td>
</tr>
</tbody>
</table>

SEM: standard error of the mean; IQR: interquartile range

*aBrazilian household income unit reference/month (2017) in reais (R$, Brazilian currency): R$937.00.

### Discussion

This study found that hot flash frequency and severity and also GEE scores lessened in both groups; however, reduction was greater in the sulpiride group both after 4 and 8 weeks as compared to the placebo group. It is important to emphasize that sulpiride was not developed for the treatment of menopausal symptoms. However, veralipride, a compound related to sulpiride, was reported and marketed as the first non-hormonal treatment to improve vasomotor symptoms in climacteric women as compared to placebo, and the effect was significant despite the remarkable sensitivity of these disorders to placebo administration [22]. Despite this, the benefit and safety of veralipride have been confirmed for the treatment of menopausal vasomotor symptoms [23–25].

After 4 and 8 weeks of sulpiride treatment frequency and severity of hot flashes decreased; effect that may be related to temperature control at the central nervous system (CNS). Indeed, sulpiride may increase endogenous opioid mediators and therefore generate better hypothalamic thermoregulation [26,27]. Another possible explanation for symptom relief would be an increase of intracellular dopamine concentration at the presynaptic cleft, thus generating an anti-depressant effect at this low dosage. Sulpiride belongs to the group of orthopramides, widely prescribed for vertigo [28]. Sulpiride may induce hyperprolactinemia depending on the used dose [29]; therefore, prolonged sulpiride treatment may require a surveillance of circulating prolactin levels.

During the menopause transition, estrogen deficiency causes the loss of the gonadotropin-releasing hormone feedback and a hypertrophied kisspeptin-neurokinin B (NKB)-dynorphin (KNDy) signaling system in the hypothalamus [30,31]. This is where sulpiride may exert its effects on dopaminergic signaling. This effect would restore intracellular dopamine concentrations of dopamine. One should bear in mind that an imbalance in serum dopamine levels and increased dopamine availability in the CNS is also related to the onset of hot flashes [4]. Furthermore, sulpiride interacts with serotonin hypothalamic serotonin receptors in a similar manner as SSRIs and SNRIs do [15].
Regarding the possible adverse effects of sulpiride 50 mg/d, only two women reported breast engorgement, with no records of galactorrhea, which indicates that such events were not clinically relevant. This could be due to the dose selected for this trial, which was safe, making the use of sulpiride in daily clinical practice plausible, although the trial involved a small sample of women and only an 8-week follow-up. The innovative nature and promising results of this study support continued investigation into this treatment with larger samples and longer follow-up periods.

Finally, our study has some limitations. First, the results should be considered preliminary and require replication and further analysis. It is probable that some findings failed to reach statistical significance because the sample size was relatively small for some comparisons (type II error). Additionally, it is possible that one or more significant findings may be due to type I error. Furthermore, the sample was rather homogeneous. Future research should also examine hot flashes in samples that are more socio-demographically heterogeneous and analyze more correlates. Indeed, this trial only reported data at 4 and 8 weeks after sulpiride intervention specifically hot flash frequency and severity. As already mentioned, research with longer follow-up and treatment periods is needed, including biochemical measurements of prolactin to enhance safety monitoring of this alternative treatment.

Second, in clinical trials, treatment may involve monitoring activities that should be controlled for during the analysis. If the usual treatment is minimal, the mere fact of being enrolled in a clinical trial, which involves greater attention from clinicians than drug treatment alone, may affect patient outcomes (also known as the Hawthorne effect) [32]. Some results might be due to the particular methods used in this study (e.g. reporting bias, extra attention rather than treatment per se, or drug dose). Finally, our study did not control for hot flashes after the conclusion of treatment, which makes it impossible to analyze any possible rebound effect. Despite the mentioned limitations, sulpiride presents as an interesting non-hormonal option for the treatment of menopausal hot flashes that deserves more detailed studies with larger populations.

**Conclusion**

Treatment with sulpiride 50 mg/d significantly reduced the frequency and severity of hot flashes, but these preliminary results require confirmation with additional randomized trials.

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**Disclosure statement**

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**Author contribution**

All authors contributing to the protocol/project development, data collection/analysis and interpretation and manuscript writing/editing.

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**References**


