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Proprietary Delivery System of a Novel Supplement Reduced Vasomotor Symptoms in Menopausal Women: Evidence from a 90-Day Double-Blind, Placebo-Controlled Clinical Trial

Todd Dorfman[1]*, Romie Mushtaq[2], Amber Krogsrud[3], Alison Gracom[4], Russell Glenn[5], Justin Hai[6]

[1]Owner and Medical Director of Cedalion Health, Boulder, Co-Chief Medical Officer Rebalance Health, USA

[2]Founder , Brain SHIFT Institute and Co-Chief Medical Officer Rebalance Health, USA

[3]Owner of Ocean Naturopathic Wellness Inc. in Los Angeles with a Focus on BHRT, hormone health and peptide therapy, USA

[4]Owner of Complete Care Medical Group, Inc., Irvine, CA. Expert lecturer on the topics of cortisol, USA

[5]Vice President of Product Development Rebalance Health Inc., Boulder, Colorado, USA

[6]President and CEO Rebalance Health Inc., USA

***Corresponding author:**
Todd Dorfman

rglenn@rebalancehealth.com

Cedalion Health, Boulder, Colorado, USA

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Abstract

Objective: To evaluate the efficacy of the Rebalance Health Hot Flash System, a lozenge-delivered nutraceutical, in reducing Vasomotor Symptoms (VMS) in menopausal women over 90 days, and to build on prior open-label findings by validating results under rigorous double-blind, placebo-controlled conditions.

Background: Vasomotor symptoms (VMS), including hot flashes and night sweats, affect up to 80% of menopausal women and significantly impair quality of life. Although Hormone Replacement Therapy (HRT) remains the most effective treatment, many women decline or cannot use it due to associated health risks. Growing demand for non-hormonal, effective alternatives has led to increased interest in plant-based supplements and innovative delivery systems. A previous open-label study by Dorfman et al. (2023) demonstrated a 76% reduction in hot flash frequency using a proprietary lozenge-delivered formulation. The present study was designed to expand on those findings by evaluating the same formulation in a larger, more rigorous double-blind, placebo-controlled trial.

Methods: In this IRB-approved study, 227 eligible menopausal women (mean age 52.1) with moderate-to-severe VMS were randomized to receive either the active lozenge-based supplement or a matched placebo over 12 weeks. Both products were identical in appearance and taste; however, post-trial analysis revealed the placebo contained trace amounts (up to 15%) of active ingredients. Primary outcome was a change in hot flash frequency. Secondary measures included self-reported changes in sleep quality, mood, and energy. Data were analyzed using t-tests and chi-square tests with significance set at $p<0.05$.

Results: Participants receiving the active supplement demonstrated a 66% mean reduction in hot flash frequency vs. 49% in the placebo group. Despite partial contamination of the placebo, the treatment group's improvement was statistically and clinically significant. Adjusted for expected placebo response (~35-40%), the true estimated treatment effect approached 30%. Improvements were also reported in sleep (77%), mood (72%), and daytime energy (66%). No serious adverse events occurred. Minor side effects were infrequent and self-limiting.

Conclusion: This double-blind trial confirms the therapeutic potential of a novel lozenge-delivered supplement in alleviating vasomotor symptoms and enhancing quality of life in menopausal women. Even with partial placebo contamination, the product significantly outperformed control, underscoring its viability as a non-hormonal, well-tolerated alternative to conventional HRT.

Keywords: Menopause; Hot flashes; Vasomotor symptoms; Sleep

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Introduction

Perimenopause and menopause represent a natural continuum of hormonal transition typically occurring between the ages of 40 and 55. One of the most disruptive symptom categories during this period is Vasomotor Symptoms (VMS), including hot flashes and night sweats, which affect up to 75% of women and significantly impair sleep, mood, and overall quality of life [1,2].

While Hormone Replacement Therapy (HRT) remains the most effective treatment for VMS, it is often contraindicated or declined due to safety concerns, comorbidities, or personal preference [3-5]. This has created a critical need for safe, effective, and non-hormonal alternatives that are suitable across a broader population. An earlier open-label study by Dorfman et al. (2023) evaluated a proprietary lozenge-based supplement and reported a 76% reduction in hot flash frequency, along with improvements in sleep and mood [6]. The present trial was designed to build upon those findings by evaluating the same formulation under double-blind, placebo-controlled conditions, thereby strengthening the evidence base for its clinical utility in the perimenopausal and menopausal population.

Materials and Methods

Study design

This was a 90-day, randomized, double-blind, placebo-controlled clinical trial conducted over a 9-month period from August 2024 to May 2025. The study protocol was reviewed and approved by an Institutional Review Board (IRB), medical screening and written informed consent was obtained from all participants prior to enrollment.

Data collection

A total of 227 women (mean age 52.1 years) experiencing moderate to severe vasomotor symptoms (VMS) were enrolled. At baseline, there were no statistically significant differences between groups in terms of hot flash frequency, sleep disruption, or self-reported energy levels. Participants were recruited from across the United States through social media advertising, without targeting or exclusion based on race, ethnicity, or socioeconomic status. The recruitment approach was designed to reflect a diverse and inclusive population representative of the broader menopausal demographic.

Eligible participants were women in the menopausal transition or postmenopausal phase, 40-65 years old experiencing vasomotor symptoms who had not been on hormone therapy or peptide therapy in the past 12 months and did not have a history of low cortisol levels, autoimmune disease, or abnormalities in the buccal mucosa. Exclusion criteria included the use of antifungal medications within 30 days or any investigational drug or device within 60 days prior to the first dose. Pregnant or breastfeeding women, or those planning pregnancy during the study period, were also excluded.

Intervention and dosing

Participants were randomized to receive either the active supplement or placebo, both administered as lozenges five times daily over 12 weeks. The dosing schedule included two lozenges in the morning, two in the afternoon, and one in the evening. Dosage adjustments were permitted based on participant tolerance and investigator discretion. The active formulation matched the previous study by Dorfman et al. (2023) in terms of ingredient dosing, though the number of daily lozenges differed. Post-trial analysis revealed that placebo lozenges inadvertently contained up to 15% of the active compounds.

Randomization and blinding

Participants were stratified by baseline hot flash frequency (2–4, 5–7, 8–10, or ≥ 11 per day) and randomly assigned in a 1:1 ratio to the active or placebo group. Both participants and study personnel were blinded to group assignments throughout the trial.

Assessments

Daily self-reported diaries were used to track hot flash frequency, sleep quality, adverse events, and general feedback. Additional structured proprietary questionnaires were administered at baseline, day 30, day 60, and day 90 to assess changes in mood, sleep quality, cognitive focus, energy levels, stress/anxiety, digestion, libido, and skin appearance.

Outcome measures

The primary endpoint was the percentage reduction in daily hot flash frequency from baseline to day 90. Secondary endpoints included self-reported improvements in sleep, mood, and daytime energy, as measured by validated symptom questionnaires.

Statistical analysis

An independent third party conducted the statistical analysis. Descriptive statistics summarized baseline characteristics. Between-group comparisons were performed using unpaired t-tests for continuous variables and chi-square tests for categorical variables. Statistical significance was defined as $p < 0.05$.

Results

264 participants were enrolled in the study, and 37 participants withdrew consent within the first 2 weeks of the study due to personal circumstances; therefore, 227 were included in the data analysis. The mean age of the women in the study was 52.1, with ages ranging from 40 to 65.

During the 90 day study the analysis indicated a decrease in the mean number of hot flashes by 66% for the active group and 49% by the placebo group (Figure 1).

Adverse events

No serious adverse events were reported in either the active or placebo groups. Mild side effects, including dry mouth and transient nausea, were observed in both groups, distributed evenly, and resolved spontaneously without medical intervention.

Dose adjustments

A total of 66 participants (29% of the cohort) adjusted their dosing regimen during the study:

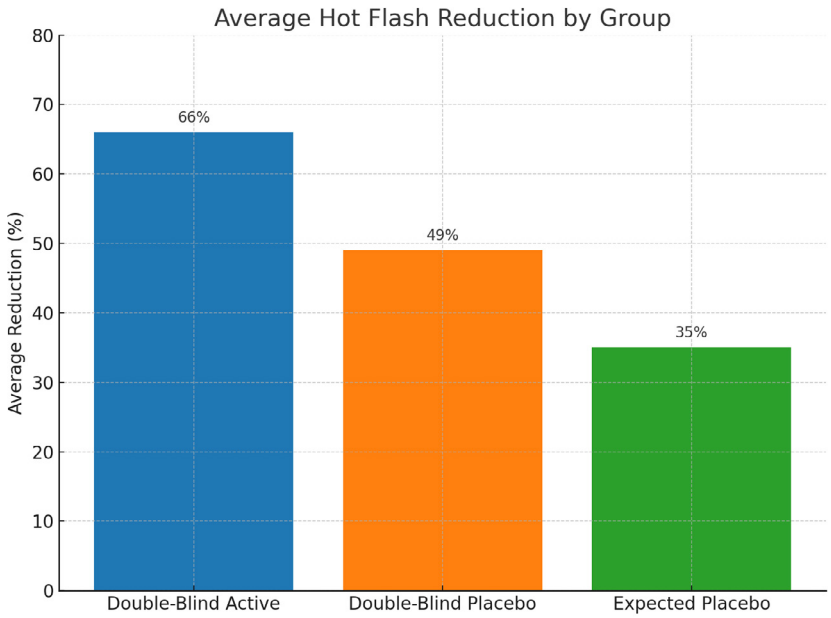

Figure 1 Although the placebo group experienced a greater-than-expected reduction in symptoms.

- **Dose increases (n = 41)** were primarily due to suboptimal efficacy:
  - 5 participants increased both morning and afternoon doses to 3 lozenges
  - 31 participants increased the evening dose
  - 5 participants increased dosing across all time periods (morning, afternoon, evening)
- **Dose decreases (n = 25)** were related to taste aversion or minor adverse effects:
  - 1 participant reduced the morning dose to 1 lozenge
  - 2 participants reduced the afternoon dose to 1 lozenge
  - 4 participants reduced both morning and afternoon doses to 1 lozenge
  - 11 participants reduced the evening dose
  - 7 participants reduced dosing at all three time points

Dose modifications were made at the discretion of the participants and study investigators, in alignment with individual tolerance and symptom response.

Discussion

This study confirms and extends the findings of Dorfman et al. (2023) [6], offering robust evidence that the lozenge-based supplement significantly reduces vasomotor symptoms (VMS) in menopausal women. The proprietary delivery system, Directline®, may enhance mucosal absorption and expedite symptom relief, distinguishing it from conventional oral supplements.

Notably, the placebo group exhibited an unexpectedly high response rate of 49 percent, exceeding the typical 35 to 40 percent benchmark [4,5]. Post-trial analysis suggests this was due to inadvertent contamination, as placebo lozenges contained up to 15 percent of the active ingredients. While this likely compressed the observed treatment effect, the active group still demonstrated superior outcomes in hot flash reduction, sleep quality, mood, and energy levels. When adjusted for an expected placebo response, the estimated true treatment effect approaches 30 percent, surpassing the threshold typically used to define clinical significance in menopausal symptom management [3-5].

Importantly, the data also support real-world efficacy. Over 90 percent of participants receiving the active supplement reported improvement in hot flashes, with 77 percent noting better sleep, 72 percent reporting improved mood, and 66 percent citing increased daytime energy. These gains collectively contribute to quality of life and overall well-being. While hormone therapy is a common treatment for menopause symptoms, it may not address a key underlying factor: elevated cortisol, the body's primary stress hormone. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, our stress response system has been linked to hot flashes, sleep disruption, and mood instability by affecting the brain's temperature regulation and nervous system activity [7,8].

The Rebalance Health lozenges contain adaptogenic botanicals and amino acid derivatives specifically formulated to help restore HPA axis balance and lower cortisol levels [9,10]. By targeting cortisol, this non-hormonal supplement addresses the root cause of menopause symptoms, offering broad relief and an alternative to traditional hormone-based therapies. These results reinforce the growing need for effective, non-hormonal interventions, particularly for women who are unable or unwilling to use hormone therapy. This formulation contributes meaningfully to the evidence base supporting integrative, patient-centered options for managing menopausal transitions [11,12].

Conclusion

This rigorously designed 90-day, double-blind, placebo-controlled trial demonstrates that a novel, lozenge-delivered supplement significantly reduces vasomotor symptoms in menopausal women, even in comparison to a partially active placebo. The supplement also yielded meaningful improvements in mood, sleep quality, and energy—indicating systemic benefits beyond hot flash relief. Importantly, this formulation operates through a distinct, non-hormonal mechanism centered on cortisol modulation, addressing a critical but often overlooked driver of menopausal symptom severity. In a landscape where many women seek effective, hormone-free options, these results highlight the supplement as a safe, well-tolerated, and evidence-based therapeutic alternative.

This trial strengthens the growing body of literature supporting integrative approaches to menopause and positions cortisol regulation as a promising new frontier in symptom management.

Limitations

The primary limitation of this trial was the unintentional inclusion of active compounds in the placebo formulation, which likely inflated the control group's response. Future studies should use a fully inert placebo and consider incorporating objective biomarkers, such as salivary or serum hormone levels, to validate self-reported symptom changes and further elucidate mechanisms of action.

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