PLACEBO EFFECT IN VASOMOTOR STUDIES: REFLECTS REDUCTION IN FREQUENCY NOT SEVERITY

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INTRODUCTION

The vasomotor hot flush is the classic symptom of menopause, as well as the major complaint of US women in the peri- and post-menopausal stages of life. The hot flush is a sudden transient sensation ranging from warmth to intense heat that spreads over the body and usually ceases with profuse perspiration[1]. Data suggest that hot flushes occur in up to 75% of menopausal women. The most effective therapy for moderate-to-severe vasomotor symptoms (MSVS: hot flushes and night sweats) is estrogen replacement[2]. The Food and Drug Administration (FDA) guidance requires a placebo-controlled clinical trial to evaluate the efficacy of new estrogen drug products. Since placebo-controlled trials are the onyl objective way of accurately assessing drug response in patients[3], any factor contributing to the placebo response will affect the outcome of the study. In general, the positive placebo response in vasomotor trials has been reported to occur in about 20-50% of patients[4, 5].

A post-hoc analysis, on the data from this study, was undertaken to determine if the placebo effect is a treatment effect (i.e. a reduction in the severity of the vasomotor symptoms over time) or simply a reduction in the frequency of hot flushes.

STUDY DESIGN

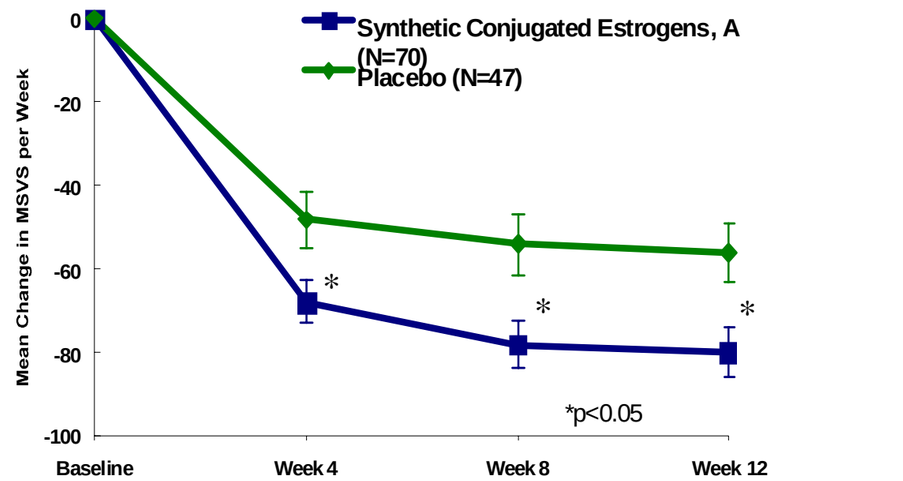
Randomized, placebo controlled, double blind, multicenter investigation of SCE tablets orally administered in doses of 0.3 mg, 0.625 mg or 1.25 mg per day in menopausal women. All women were started on 0.625 mg of SCE daily. Women not achieving sufficient symptomatic relief after 7 days had their estrogen dose increased to 2 x 0.625 mg (a total of 1.25 mg) per day. Women who exhibited any intolerance to the estrogen treatment at any time had their dose decreased (i.e., started at 0.625 mg/day increased to 1.25 mg/day and then decreased back to 0.625 mg/day or started at 0.625 mg/day and decreased to 0.3 mg/day).

The study consisted of: a screening period, a two (2) week baseline period and a 12-week treatment period. The baseline period was defined as the 14-day period that preceded randomization (prior to first dose) where the patient exhibited at least 60 MSVS per week, below which patients were ineligible for enrollment..

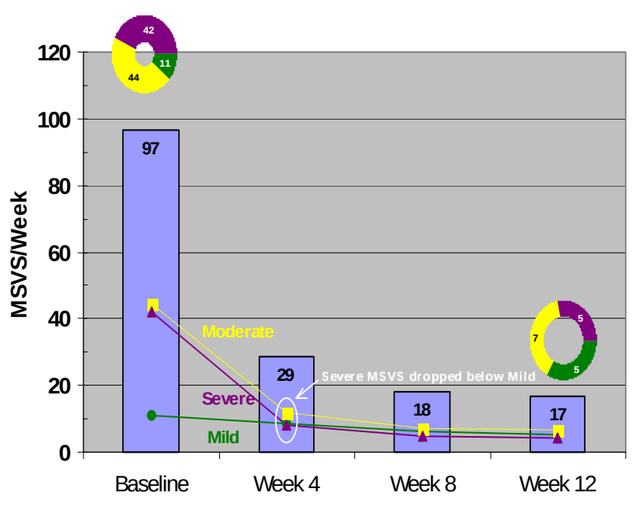
In all, 109 patients (109/120 = 90.8%) completed week 12 of this study. The treatment-allocation population (TAP) totaled 120 patients (48 placebo, 72 active) and was included in all safety analyses. The intent-to-treat population (ITT) was a subset of the TAP population and included all patients with at least one week of data.

RESULTS

Figure 1. Overall Mean (± SEM) Change From Baseline to 4, 8 and 12 Weeks in MSVS During Treatment With Synthetic Conjugated Estrogens, A or Placebo (ITT; n=117).



Active Treatment Patient MSVS Profile (N=70)



Placebo Patient MSVS Profile (N=47)

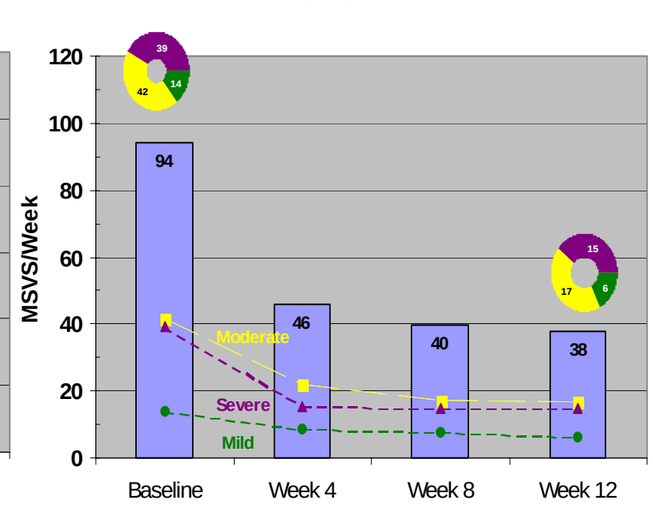


Table 1. Change in Severity by Week 12

	Baseline	Week 12	P value
Active	42	5	0.0001
Placebo	39	15	0.0960

STUDY DESIGN (CONT'D)

The ITT population consisted of 117 patients with 47 in the placebo treatment and 70 in the active treatment groups.

METHODOLOGY

The primary objective was to evaluate the percent change in MSVS from a 2-week baseline to treatment weeks 4, 8 and 12. Severity of symptoms was reported as mild, moderate, or severe.

Post-hoc analyses (ANOVA, PROC GLM procedure) was performed on the change from baseline in MSVS for week 4, week 8 and week 12. A 0.01 level of significance was used for determination of normality. T-tests for significantly different changes from baseline within each treatment group were applied to each weekly reduction in MSVS. A multiple comparison of means was performed by the Tukey multiple comparison procedure.

CONCLUSIONS

1. The response of menopausal women to Cenestin® therapy reflects a reduction in both frequency and severity of symptoms, with a shift in the severity from severe to mild.

2. The placebo effect observed in vasomotor trials is a reduction in frequency, however, the severity of symptoms does not change over time, and hence there is no treatment.

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Acknowledgements: The authors wish to acknowledge Niresh Hariparsad for his valuable contribution to the preparation of this poster.