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Quantitative analysis of placebo response and factors associated with menopausal hot flashes

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Abstract

Objective: The aim of the study was to quantitatively analyze the placebo response and the factors associated with menopausal hot flashes.

Methods: The PubMed and Cochrane Library databases were searched for placebo-controlled trials that reported the treatment of menopausal hot flashes, with a retrieval deadline of December 31, 2015. The clinical and demographic characteristics of participants and placebo responses, defined as the percentage of reduction in hot flashes at each observation time point compared with that of baseline values, were extracted from the studies. Model-based meta-analysis was used to describe the time course of placebo response and identify the related factors.

Results: Eighty-five trials in 78 articles, involving 8,302 women, were included in the analysis. Of these, 47 trials were about hormonal drugs, 37 were about nonhormonal drugs, and 1 included both hormonal and nonhormonal drugs. Our results indicated that the placebo responses for hot flashes increased in a time-dependent manner and reached a plateau after week 12. Additionally, the placebo responses were significantly higher in the trials of hormonal drugs than in the trials of nonhormonal drugs at week 24 (−51.2% vs -40.4%; $P < 0.05$), and the difference between them was comparable with the effect of paroxetine.

Conclusions: The placebo response for menopausal hot flashes was related to the active comparator; a higher response rate was observed in trials of hormonal drugs than in trials of nonhormonal drugs. These findings suggest that subjective expectations affect the treatment efficacy of menopausal hot flashes.

Key Words: Hormonal drugs – Hot flashes – Menopause – Model-based meta-analysis – Nonhormonal drugs – Placebo.

Menopause is the phase in a woman's life, which involves loss of the reproductive function of the ovaries, and is generally associated with a wide range of symptoms. Hot flashes are the most common symptoms affecting up to 75% of midlife women undergoing menopause transition.[1] In 10% to 15% of women, the symptoms are more severe, typically lasting for more than 10 years[2] and requiring treatment.[3] Hormone therapy (HT) has been considered the standard treatment regimen for menopausal hot flashes.[4] However, it has been reported to be associated with a higher risk of cardiovascular events and breast cancer in women aged over 60 years.[5] Therefore, many women have opted for alternative, nonhormonal therapies, which include lifestyle changes,[6] mind-body techniques,[7] dietary management and supplements,[8] and other prescription therapies.[9] Nevertheless, few nonhormonal therapies are effective, and, currently, paroxetine is the only nonhormonal drug approved by the US Food and Drug Administration (FDA) for the treatment of menopausal hot flashes.[10] However, in comparison with placebo, this drug induced only a 10% reduction in hot flashes at week 24.[11]

Placebo response (defined as the percentage of reduction in hot flashes at each observation time point compared with that of baseline values) during the treatment of menopausal hot flashes showed a substantial reduction rate of approximately 20% to 60%.[12] Generally, negative conclusions may occur owing to higher placebo response rates due to type II errors, especially in nonhormonal drugs with weaker action. Therefore, investigation into the placebo response would be helpful in aiding trial design and selection criteria.

Currently, several factors have been reported to affect placebo response, such as heterogeneity of trial design,[13] participant characteristics,[14] and subjective expectations.[15] Nevertheless, little is known about the placebo response in the subject area of menopausal hot flashes. To date, a few studies have utilized the post hoc analysis data from individual clinical trials, which evaluated the predictors of placebo response for menopausal hot flashes[16,17]; however,

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no pooled analysis has been performed on this comprehensive data.

Model-based meta-analysis (MBMA) is an efficient method that explicitly incorporates the effects of duration or other covariates using standard pharmacology models and assumptions.[18,19] Compared with conventional meta-analysis methods, MBMA can utilize the data more thoroughly and extract more information.[20-22] Therefore, MBMA was used in this study to determine the time course of placebo response for menopausal hot flashes in a quantitative manner, together with identification of other related factors.

METHODS

Search strategy

The PubMed and Cochrane Library databases were searched for published randomized controlled trials. The retrieval deadline was December 31, 2015, and the search terms used were ''hot flashes'' or ''hot flushes'' and ''placebo.'' The search language was limited to English.

The inclusion criteria for trials were: randomized double-blind and placebo-controlled studies; healthy premenopausal and postmenopausal women; studies reporting the daily frequency of hot flashes or decreased rates of hot flash frequency.

To reduce the heterogeneity and variability in the characteristics of the participants and the study design, the exclusion criteria were: women with breast cancer; placebo group with a sample size of less than 30; a mean frequency of hot flashes at baseline of lower than five per day.

Data extraction and quality assessment

Data were independently extracted by two researchers (JYW and LDD), and checked by a third person (YHL) for any discrepancies. The following data were extracted from the selected studies using a standard Excel spreadsheet: demographics and baseline characteristics of women (ie, age, body mass index [BMI], time since menopause, and region and frequency of hot flashes at baseline), study design (ie, type of test drug, route of administration, sample size of placebo group, and duration of therapy), and outcome measures (ie, reduction rate of hot flashes at each follow-up time point).

To assess the outcome, intention-to-treat (ITT) data were entered when available. In studies only reporting the per-protocol (PP) data, the unreported sample size during the treatment duration was imputed by the sample size at the endpoint. In case of graphically presented efficacy data, the digitizing software Engauge Digitizer (version 4.1, 2002, by Mark Mitchell) was used for data extraction.

The modified Jadad scale evaluation system was used to assess the quality of the identified studies.[23] Two researchers (JYW and LDD) performed independent evaluations, and any disagreement was resolved by discussing with a third investigator (YHL). A study with a modified Jadad score of at least 4 was considered as high quality. For each study, publication bias was assessed by the change of outcomes in hot flash frequency with placebo by constructing a funnel plot.

Model building

The placebo response for hot flashes increased with time and eventually reached a plateau, allowing description in terms of a maximum effect (E_{max}) model. The basic model was described as follows:

$$E_{ij} = -\frac{E_{max} \cdot \exp(\eta_{1,i}) \cdot Time_j}{ET_{50} \cdot \exp(\eta_{2,i}) \cdot Time_j} + \frac{\varepsilon_{i,j}}{\sqrt{No_{i,j}/100}} \quad \text{Formula 1} \tag{1}$$

where E_{ij} is the observed mean change rate of hot flashes frequency from baseline in the ith study at the jth time; E_{max} is the maximum placebo effect; ''time'' is the time of point of observation (week); ET_{50} is the time required to achieve 50% of E_{max} and represents the onset speed of placebo response; $\eta_{1,i}$ and $\eta_{2,i}$ are the interstudy variability of E_{max} and ET_{50}, respectively; No_{ij} is the number of women in the ith study at the jth time; and ε_{ij} is the residual random error of response data in the ith study at the jth time. The value ε_{ij} was weighted by the inverse of the square root of the sample size in the ith study at the jth time, normalized to 100 women. The parameters $\eta_{1,i}$ and $\eta_{2,i}$ were assumed to follow normal distributions with a mean of 0 and estimated variances of ω_1^2 and ω_1^2, respectively. The value ε_{ij} was assumed to be normally distributed with a mean of 0 and a variance of $100 \times \sigma^2/No_{i,j}$.

The covariates tested included the type of test drug, route of administration, age, BMI, time since menopause, region, and frequency of hot flashes at baseline. A difference in the objective function value (OFV) of 6.63 (χ^2, $\alpha = 0.01$, d.f. = 1) was considered to be statistically significant in the covariate model building.

Model validation

During model building, several aspects were used for evaluation of the model, which included plausibility of the parameter estimates, change in OFV, standard goodness-of-fit plots, visual predictive check, and relative standard errors (RSEs) of the parameter estimates. The 95% confidence interval (CI) for the parameter estimation was derived from 1,000 bootstrap replications by successful convergence of both the estimation and covariance steps.

Statistical analysis

The model estimation and simulation were performed using NONMEM 7 software (Level 1.0, ICON Development Solutions). Statistical analysis and plotting were performed using R scripting (version 3.0.1, The R Foundation of Statistical Computing, Open source software). P value less than 0.05 was considered to be statistically significant.

RESULTS

Data

Nine hundred thirty-seven articles were identified from the search of electronic resources; of these, 78 articles including

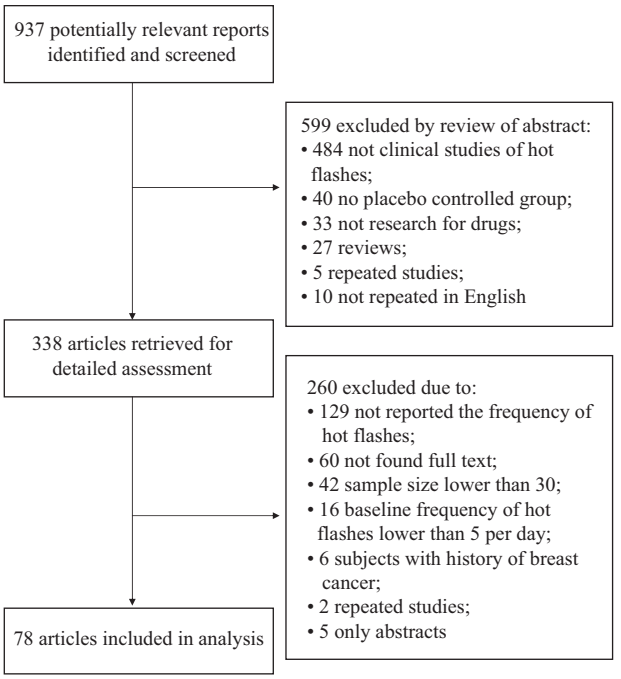

FIG. 1. Flow chart demonstrating the inclusion and exclusion of studies into the analysis.

85 trials met the inclusion criteria for entry into the pooled analysis. The process of search strategy and study selection is depicted in Figure 1. The summary of available information for each randomized clinical trial is provided in the Supplementary Table S1 (http://links.lww.com/MENO/A219). The list of included articles is also provided in the Supplementary Information.

The 85 trials included 8,302 premenopausal and postmenopausal women in the placebo group: 47 trials reported hormonal drug data, 37 reported nonhormonal drug data, and 1 simultaneous trial of hormonal and nonhormonal drugs was included (Table 1). The follow-up duration ranged from 4 to 52 weeks. The mean age of women at enrollment ranged from 48 to 56.5 years. The mean time since menopause before enrollment in the trials ranged from 16.1 to 118.8 months. The mean frequency of hot flashes at baseline ranged from 5 to 14.8 per day. The risk of bias assessment showed no evidence of publication bias in the trials of hormonal and nonhormonal drugs (Fig. S2, http://links.lww.com/MENO/A219).

Model establishment and validation

The final model parameters showed that only the type of test drug was associated with E_{max} (Table 2). Other factors such as age, BMI, time since menopause, mean frequency of hot flashes at baseline, and route of administration were not significantly related to E_{max} and ET_{50} (Fig. S3, http://links.lww.com/MENO/A219). The typical value of E_{max} was higher in hormonal drug trials than in nonhormonal drug trials (56.9% vs 44.8%). The typical value of ET_{50} in all the trials was estimated at 2.63 weeks. From 1,000 bootstrap runs, all runs had successful minimization and covariance steps. The 95% CI of E_{max} in trials of hormonal drugs and E_{max} in trials of nonhormonal drugs did not overlap, which indicated significant differences between these two parameters.

The RSEs of all parameters were less than or near to 30%, which indicated that the estimation of the parameters was robust. The goodness-of-fit plots for the final model indicated a satisfactory fit of the model presented in the Supplementary Figure S1 (http://links.lww.com/MENO/A219). As revealed in Figure 2, the 95% CI of drug efficacy estimated by the model covered almost all of the observed data, which implied a satisfactory accordance between the observed and predicted values.

No statistical difference was observed in the characteristics of participants and study design between the trials of hormonal and nonhormonal drugs ($P > 0.05$). Although the route of administration between the trials of hormonal and nonhormonal drugs was significantly different ($P < 0.05$), placebo responses among the different routes of administration were similar (Fig. 3). This implied that the administration route was

TABLE 1. *Characteristics of included studies*

		Type of test drug		
	Overall	Hormonal drug	Nonhormonal drug	*P*
Number of trials (total sample size)	85 (8302)	47 (4424)	37 (3721)	
Sampel size per arm, median (min-max)	72 (34-589)	75 (37-427)	59 (34-589)	>0.05
Age, y, median (min-max)	53 (48-56.5)	52.2 (48-56.5)	53.9 (48.6-56.5)	>0.05
BMI, kg/m^2, median (min-max)	26.3 (22.1-29.7)	26 (22.3-28.9)	26.4 (22.1-29.7)	>0.05
Time since menopause, mos, median (min-max)	56 (16.1-118.8)	57.2 (25.9-118.8)	55.2 (16.1-90.2)	>0.05
Treatment duration, wks, median (min-max)	12 (4-52)	12 (4-24)	12 (4-52)	>0.05
Mean frequency of hot flashes/d at baseline, median (min-max)	9.9 (5-14.8)	10.3 (5.7-14.3)	9.5 (5-14.8)	>0.05
Region				>0.05
Asian	5 (5.9%)	4 (8.5%)	1 (2.7%)	
Non-Asian	80 (94.1%)	43 (91.5%)	36 (97.3%)	
Route of administration				<0.01
Oral	63 (74.1%)	25 (53.2%)	37 (100.0%)	
Transdermal	17 (20.0%)	17 (36.2%)	0 (0.0%)	
Other	5 (5.9%)	5 (10.6%)	0 (0.0%)	

Comparisons of continuous variables between two subgroups were completed using Student's *t* test or Mann-Whitney *U* test, and the chi-square test was used for categorical variables.
BMI, body mass index.

TABLE 2. *Pharmacodynamic parameters of placebo response*

Parameters	Value	RSE (%)	1,000 Bootstrapped median (95% CI)
E_{max}, trials of hormonal drug, %	56.9	4.9	57.0 (51.8-62.2)
E_{max}, trials of nonhormonal drug, %	44.8	6.5	45.1 (38.7-50.8)
ET_{50}, wks	2.63	12.7	2.62 (2.05-3.40)
η (E_{max}), %	31.3	26.7	30.6 (22.6-39.2)
η (ET_{50}), %	103.4	30.7	102.0 (65.3-133.8)
ε, %	2.52	17.2	2.50 (2.07-2.96)

E_{max} is the maximal effect of placebo response; ET_{50} is the time to achieve 50% of E_{max}; η is the interstudy variability of pharmacodynamic parameter; ε is the residual error.
CI, confidence interval; RSE, relative standard error.

not associated with the difference in placebo response between the trials of hormonal and nonhormonal drugs.

Typical time course of placebo response

Based on the final model, we simulated the typical time course of placebo response and its 95% CI in the trials of hormonal and nonhormonal drugs, respectively. Compared with the trials of nonhormonal drugs, placebo effects in the trials of hormonal drugs were significantly higher at week 24 ($P < 0.05$), their median value and 95% CI were −51.2% (−46.4%, −56.4%) and −40.4% (−35.2%, −45.7%) (Fig. 4A). The difference in placebo response between the trials of nonhormonal and hormonal drugs was similar to the actual efficacy of paroxetine (Fig. 4B).

DISCUSSION

The prevailing view is that placebo response in medical treatment is characterized by a rapid, but transient,

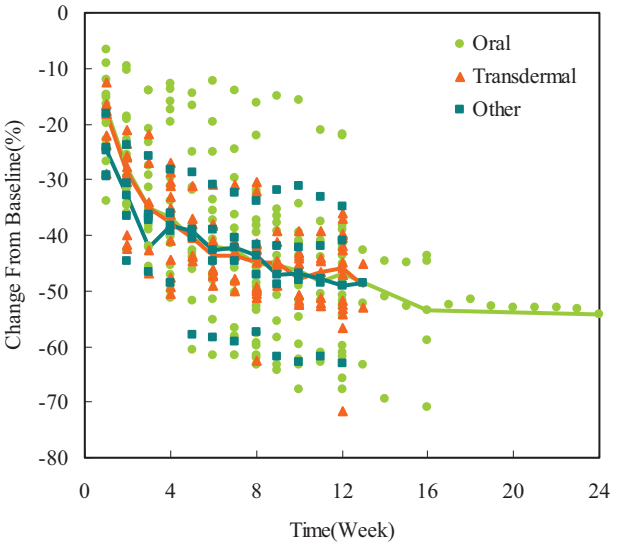

FIG. 3. Observed placebo response in the trials of hormonal drugs, differentiated by routes of administration. The points indicate the observed efficacy data of placebo response. The solid lines are the median values of placebo response in the different administration routes.

improvement.[24] However, our study showed that placebo response for menopausal hot flashes increased with time and reached a plateau after 12 weeks of treatment. Additionally, significant differences were observed in placebo responses in the trials included in this study, which varied from 5.8% to 71.8% at week 12. A high placebo response may lead to difficulty in the discernment of a positive treatment effect, particularly for nonhormonal drugs with a weaker action. Therefore, identification of

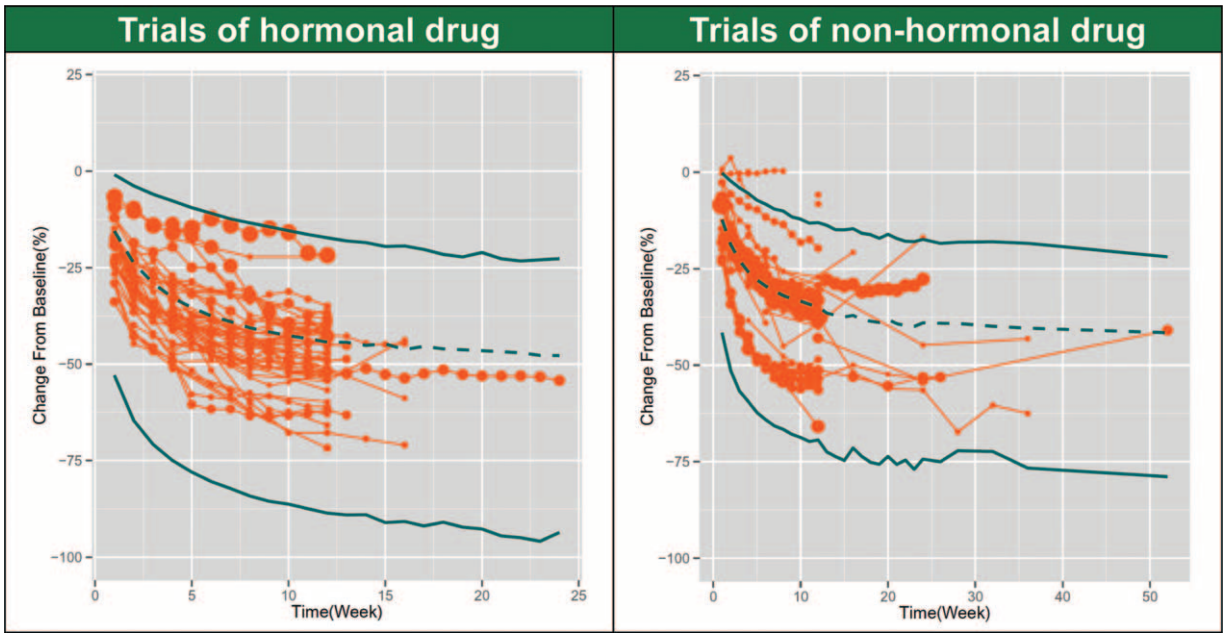

FIG. 2. Prediction-corrected visual predictive check of the final model. The solid points represent the observed efficacy data, and the symbol size is proportional to the sample size. The points linked by the line are from the same arm. The green lines are the model predicted 2.5th, 50th, and 97.5th percentiles of efficacy.

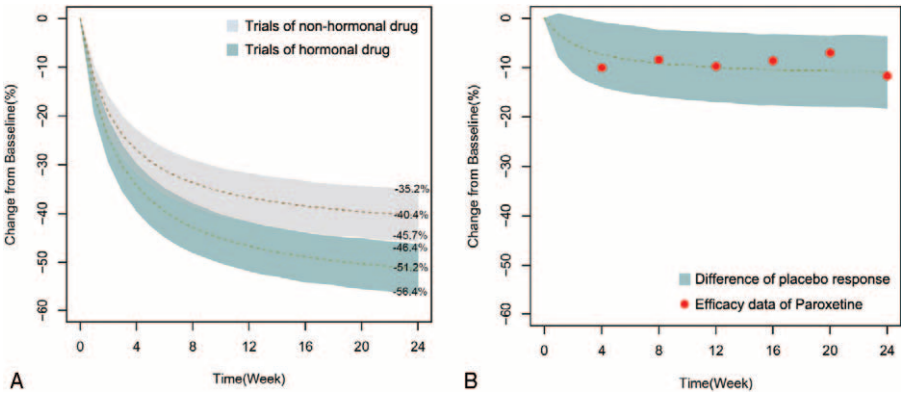

FIG. 4. (**A**) The typical predicted placebo response and its 95% CI in the trials of hormonal and nonhormonal drugs. (**B**) The differences of the typical predicted placebo responses and its 95% CI between the trials of hormonal and nonhormonal drugs. The dashed lines in (**A**) and (**B**) represent the median value of typical efficacy, and the shaded areas are their 95% CIs. The points in (**B**) represent the observed efficacy data of paroxetine after elimination of the corresponding placebo effect. CI, confidence interval.

the possible factors associated with placebo response will be helpful for clinical trial design.

In this study, we tried to identify the predictors of placebo response, including the type of test drug, route of administration, and characteristics of the women. Our results indicated that only the type of test drug was validated as a covariate for the placebo response. The model showed E_{max} of placebo response was significantly higher in trials of hormonal drugs ($P < 0.05$) than in trials of nonhormonal drugs. No significant differences were noticed in the baseline characteristics of women in the trials of hormonal and nonhormonal drugs; therefore, we attributed the differences in placebo response between these two types of trials to the psychological expectations of the women.[25] Previous studies have showed that when information provided to participants was of a positive nature, rather than negative or neutral, a significant increase in the treatment efficiency was observed in those who received placebo or active drug treatment.[25] To date, HT has been considered the most effective treatment for hot flashes.[4] Therefore, a higher expectation of the effects of hormonal drugs may result in higher placebo responses in the trials of hormonal drugs. In the included studies, a run-in period design was used in 17 trials, including 7 trials of hormonal drugs and 10 trials of nonhormonal drugs. After the run-in period, participants with poor compliance and high placebo response were excluded. We found that the intertrial variability of the placebo response was significantly lower in the run-in period trials than in the nonrun-in period trials (Fig. S4, http://links.lww.com/MENO/A219). Therefore, the incorporation of a run-in period into study design is suggested to increase the sensitivity and accuracy of the efficacy measures in the trials.

High placebo response was more likely to result in a ''negative'' outcome of treatment trials[26]; however, employing the response in a clinical treatment may improve treatment efficacy. If participants are confident in the efficacy of a drug, the overall efficacy may be improved compared with higher placebo responses. For women with HT contraindications, non-HT is almost the only choice; however, most of the nonhormonal drugs showed weaker action. Paroxetine was reported to induce a reduction of only approximately 10% in the hot flashes after removal of placebo effects.[11] In this study, the difference in placebo response between hormonal and nonhormonal trials was similar to the actual efficacy of paroxetine. Therefore, placebo responses should definitely be used in clinical contexts to achieve a higher response rate.

The route of administration is another important factor that may influence the placebo response. Previous studies have shown that placebo effects from injections were stronger than those from pills.[15] Transdermal administration was the most common route of application in the clinical trials of hormonal drugs. However, no study has investigated the difference in placebo response between transdermal and oral administration. This study demonstrated no significant association between the placebo response for hot flashes and the route of administration, but they remain comparable. Therefore, it was concluded that transdermal administration does not contribute to the improvement of participants' expectations on drug efficacy.

According to previous studies, the baseline characteristics of participants have also been frequently identified as a predictor of placebo response.[14] In this study, placebo response was defined as the reduction rate in the frequency of hot flashes compared with baseline levels, and this was corrected to the baseline of the frequency of hot flashes. It was reported that weight loss may alleviate hot flashes,[27] but no significant correlation was identified between the reduction of hot flashes and BMI in this study. This might be due to the narrow BMI distribution (22.1-29.7) in the included studies.

Indeed, there are some limitations to this study. First, only published studies and studies in English were included, which may lead to publication or language bias. Because most of the women were in the postmenopausal stage, the difference in placebo response between premenopausal women and postmenopausal women could not be studied. In addition, most studies were from Western countries and a small number from Asian countries, and because differences between races were not investigated, the results cannot be generalized to other populations.

CONCLUSIONS

This study quantified the placebo response for menopausal hot flashes. Our findings indicated the importance of subjective expectation as a factor for placebo response during menopausal hot flashes. Meanwhile, placebo responses for oral and transdermal administration were comparable. These results suggest that placebo response should be strictly controlled in clinical trials to achieve positive results. Additionally, the inclusion of placebo response in clinical treatments may improve efficacy.

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