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REVIEW

Quantitative comparison of drug efficacy in treating hot flashes in patients with breast cancer

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Abstract

Objective This study aimed to quantitatively evaluate drug efficacy and identify relevant factors that affect the relief of hot flashes in patients with breast cancer.

Methods A comprehensive literature search was performed using public databases. Randomized clinical studies on drug therapy for the treatment of hot flashes in patients with breast cancer were identified. A time-effect model was established, and crucial pharmacodynamic parameters, such as maximal efficacy (E_{max}) and onset time (ET_{50}), were used to reflect the differences in efficacy among the drugs.

Results Eighteen studies involving 5178 subjects were included. It was found that the baseline of hot flashes was an important factor for the E_{max} value of drugs. After correcting the baseline to the level of eight times per day, the E_{max} values of progesterone, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs), neuroleptic agents, tibolone, phytoestrogen, other types of drugs, and placebo were 8.3(95%CI 6.8, 9.9),5.1(95%CI 4.4, 5.7), 4.4(95%CI 3.6, 5.3), 4.0(95%CI 3.6, 4.3), 3.4(95%CI 2.4, 4.3), 2.5(95%CI 0.8, 4.2), and 2.7(95%CI 2.1, 3.3), respectively. The ET_{50} of all the drugs were approximately 2–2.5 weeks, which was obviously longer than that of the placebo (1.2 weeks). When compared with the previously reported efficacy characteristics in natural menopausal women, no significant difference was found between the two populations.

Conclusions Progesterone showed the highest efficacy, followed by SSRIs/SNRIs, neuroleptic agents, and tibolone, while phytoestrogen and other types of drugs showed no efficacy advantages. There is a significant association between the baseline of hot flashes and drug efficacy, while there was no significant difference between breast cancer patients and natural menopausal women.

Keywords Hot flashes · Breast cancer · Medication guidelines · Model-based meta-analysis

Introduction

Estrogen levels decline rapidly in breast cancer patients, resulting in "menopausal" symptoms similar to those of women before and after menopause after endocrine therapy, ovarian function suppression, or oophorectomy [1–4]. Hot flashes are one of the most typical symptoms. If the symptoms are not treated in time, endocrine therapy may be stopped in some patients, thus affecting the prognosis of breast cancer [5]. Therefore, management for hot flashes in patients with breast cancer has always been an important issue of clinical interest [6].

There are several drugs currently used to relieve hot flashes in patients with breast cancer; these include progesterone, selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors (SSRIs/SNRIs),

Ting Li and Juan Yang contributed equally to this work.

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neuroleptic agents, tibolone, phytoestrogens, and other types of drugs [7]. In the past, there have been widespread concerns about the safety of these drugs, such as increased risk of breast cancer recurrence, drug interactions with tamoxifen, and other adverse reactions [8, 9]. However, there are only a few studies on the drug efficacy characteristics in this specific population; many of the conclusions are directly referenced from the results of natural menopause women [10]. Previous studies have shown that the incidence and the intensity of hot flashes in patients with breast cancer are higher than those in natural menopause women [11–13]; but whether there is a difference in drug efficacy between these two types of patients lack a clear conclusion.

This study quantitatively evaluated the drug efficacy in relieving hot flashes and identified relevant impacting factors in patients with breast cancer. Some important pharmacodynamic parameters such as maximum effect and onset time of each drug were measured. The characteristics of drug efficacy between patients with breast cancer and natural menopause women was also compared. This study provided the necessary quantitative information for medication guidelines for hot flashes in breast cancer patients.

Methods

Search strategy

A comprehensive literature search was conducted in Pubmed, Embase, Cochrane Library, and PsyclNFO databases with a search deadline of May 31, 2018. Terms used in the search were "hot flashes" and "breast cancer," the literature type was limited to clinical trials and the language was limited to English. The detailed search strategies are described in Supplementary search strategy.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) randomized controlled trials, (2) patients with history of breast cancer or at high-risk for breast cancer, (3) studies reporting the frequency of hot flashes at baseline and after treatment, and (4) data from the first period of crossover design studies.

Exclusion criteria were as follows: (1) clinical trials of non-pharmacological treatments, (2) subjects with co- morbidities, and (3) patients with a mean frequency baseline of less than five hot flashes per day [14].

Data extraction and quality assessment

WPS Excel (10.1.0.7400) software was used to categorize the relevant information of the included studies. These included the following categories: literature characteristics (i.e., author, year of publication), trial design (i.e., grouping, dosing regimen, sample size, treatment duration, blinding method), characteristics of patients (i.e., age, weight, region, frequency of hot flashes at baseline), and clinical results (frequency of hot flashes at each observation point). If the data given were in the form of graphics, the values in the chart were extracted using Engauge Digitizer (Version 4.1). Two researchers (Ting Li and Juan Yang) independently extracted all the information above, and a third researcher (LJ Li) determined the inconsistencies. The data extraction error should not exceed 2% when reading the graph. If it exceeds 2%, data extraction should be repeated, and the mean values are considered as the final results.

Two researchers (Ting Li and Juan Yang) independently assessed the quality of the included literature based on Cochrane risk-of-bias criteria, and each quality item was graded as low risk, high risk, or unclear risk. The evaluation items included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. We defined other biases as trials in which baseline characteristics were not comparable between different treatment groups.

Model establishment and evaluation

The frequency change of hot flashes from baseline in patients with breast cancer increased with time and reached the platform; this was in line with the typical E_{max} model (Eq. 1).

$$E_{i,j} = \frac{E_{max.i} \times Time_j}{ET_{50,i} + Time_j} + \frac{\varepsilon_{i,j}}{\sqrt{N_{i,j}}} \quad (1)$$

$$E_{max,i} = E_{max,typical} + \eta_{1,i} \quad (2)$$

$$ET_{50,i} = ET_{50,typical} + \eta_{2,i} \quad (3)$$

In Eq. 1, $E_{i,j}$ is the observed efficacy of the ith drug group at time *j*, $E_{max,i}$ is the theoretical maximum efficacy of the ith drug group, and $ET_{50,i}$ is the time it takes to achieve half the maximal efficacy, which reflects the speed of onset of the drug group. $Time_j$ is the observation time point. $\varepsilon_{i,j}$ is the residual error in the ith drug group at time j, and is weighted by the inverse of the square root of the sample size in the ith group at time point *j* ($N_{i,j}$). $\varepsilon_{i,j}$ is assumed to have normal distribution with a mean of 0 and variance of σ^2. In Eqs. 2 and 3, $E_{max,typical}$ is the typical E_{max} value of the overall drug group, and $ET_{50,typical}$ is the typical ET_{50} value of the overall drug group. $\eta_{1,i}$ and $\eta_{2,i}$ are the inter-group variability of E_{max} and ET_{50}, which are assumed to be normally distributed, with a mean of 0 and variances of ω_1^2 and ω_2^2.

After establishing the pharmacodynamic model, there are factors that may have a potential impact on the

pharmacodynamic parameters, such as age, weight, frequency of hot flashes at baseline, blinding method, and ratio of endocrine therapy. Continuous covariates on the parameters were modeled according to Eqs. 4 and 5. Equation 6 tested the influence of categorical covariates on the parameters.

$$P_{\mathrm{i}} = P_{\mathrm{Typical}} + \left(\mathrm{COV} - \mathrm{COV}_{\mathrm{median}}\right) \times \theta_{\mathrm{cov}} + \eta_{\mathrm{i}} \quad (4)$$

$$P_{\mathrm{i}} = P_{\mathrm{Typical}} \times \left(\mathrm{COV}/\mathrm{COV}_{\mathrm{median}}\right)^{\theta_{\mathrm{cov}}} + \eta_{\mathrm{i}} \quad (5)$$

$$P_{\mathrm{i}} = P_{\mathrm{Typical}} + \mathrm{COV} \times \theta_{\mathrm{cov}} + \eta_{\mathrm{i}} \quad (6)$$

As seen in Eqs. 4 to 6, P_{i} is a pharmacodynamic parameter value of the ith drug group, P_{Typical} is the typical value of a pharmacodynamic parameter of the overall drug group, COV is the covariate value of the ith drug group, $\mathrm{COV}_{\mathrm{median}}$ is the median value of the covariate, and θ_{cov} is the correction coefficient of the covariates on the pharmacodynamic parameter. η_{i} is an inter-group variability of a pharmacodynamic parameter.

During the covariate model building process, a reduction in objective function values (OFV) of 3.84 and 6.63 were considered significant at $P=0.05$ and $P=0.01$, respectively, for a nested model with one degree of freedom difference. All covariates were analyzed in a step-wise manner with a forward selection step ($P=0.05$) and a stricter backward elimination step ($P=0.01$).

The model fit was evaluated by graphic assessment, including goodness of fit and visual predictive check (VPC). The VPC was plotted using a 95% confidence interval based on 1000 times using Monte Carlo simulation of the final model.

Typical efficacy analysis

After the model is constructed, the values of the pharmacodynamic parameters and their standard errors were estimated by the Bayesian feedback method. When a covariate is found to have a significant impact on the pharmacodynamic parameters, the parameters need to be corrected by this covariate to make the parameters comparable at different covariate levels. The covariate correction Equations are as follows:

$$P_{\mathrm{i,corrected}} = P_{\mathrm{i}} - \left(\mathrm{COV} - \mathrm{COV}_{\mathrm{median}}\right) \times \theta_{\mathrm{cov}} \quad (7)$$

$$P_{\mathrm{i,corrected}} = P_{\mathrm{i}} \times \left(\mathrm{COV}/\mathrm{COV}_{\mathrm{median}}\right)^{-\theta_{\mathrm{cov}}} \quad (8)$$

$$P_{i,corrected} = P_i - COV \times \theta_{\mathrm{cov}} \quad (9)$$

In Eqs. 7 to 9, $P_{\mathrm{i,corrected}}$ is the corrected value of a pharmacodynamic parameter of the ith drug group, P_{i} is the value of a pharmacodynamic parameter of the ith drug group, COV is the covariate value of the ith drug group, $\mathrm{COV}_{\mathrm{median}}$ is the median value of the covariate, and θ_{cov} is the correction coefficient of the covariate on the pharmacodynamic parameter.

We performed a single-arm meta-analysis to summarize the pharmacodynamic parameters using a random effects models according to the types of drugs, from which the typical value and the 95% CI of the parameters of each drug were obtained. Based on these parameters, the typical efficacy and the 95% CI of each drug at different points in time were simulated 10,000 times using Monte Carlo simulation.

Software

NONMEM 7.3 (ICON Development Solutions, USA) was used for model estimation, simulation, and Bayesian feedback. Meta analysis was performed using Stata software version 13.1 (2013, StataCorp LP, College Station, TX 77845, USA) implementation. Statistical analysis and mapping were performed using the R 3.3.1 software (The R Foundation of Statistical Computing).

Results

Characteristics of the included studies

Eighteen articles were finally included for analysis (Fig. 1), 11 of the studies were placebo-controlled studies. There were 14 kinds of drugs involved, including Progesterone (medroxyprogesterone acetate and megestrol acetate), tibolone, phytoestrogens (black cohosh and soy phytoestrogens), antidepressants (duloxetine, escitalopram, sertraline, and venlafaxine), neuroleptic agents (gabapentin, clonidine and pregabalin), and other types of drugs (magnesium oxide and vitamin E). The total sample size included from the 18 studies was 5178, 2987 were in the drug group, and 2191 in the placebo group.

The mean age of the patients was 41.7–58.4 years (median 53), and the mean frequency of hot flashes at baseline was 5.5–13 times per day (median 8). The treatment duration was 4–13 weeks (median 8). The sample size of each treatment group is 20–1556 (median 54). The drugs were administered orally except for a group of medroxyprogesterone acetate administered by intramuscular injection. Average daily frequency of hot flashes at baseline was 9.2 for progesterone, 8.7 for neuroleptic agents, 8 for SSRIs/SNRIs, 7.0 for phytoestrogen, 8.0 for other types, 6.3 for tibolone, and 7.4 for placebo (Table 1). The detailed information of the included studies were listed in Supplementary Table S1, and the quality of the 18 studies was shown in Supplementary Figure S1.

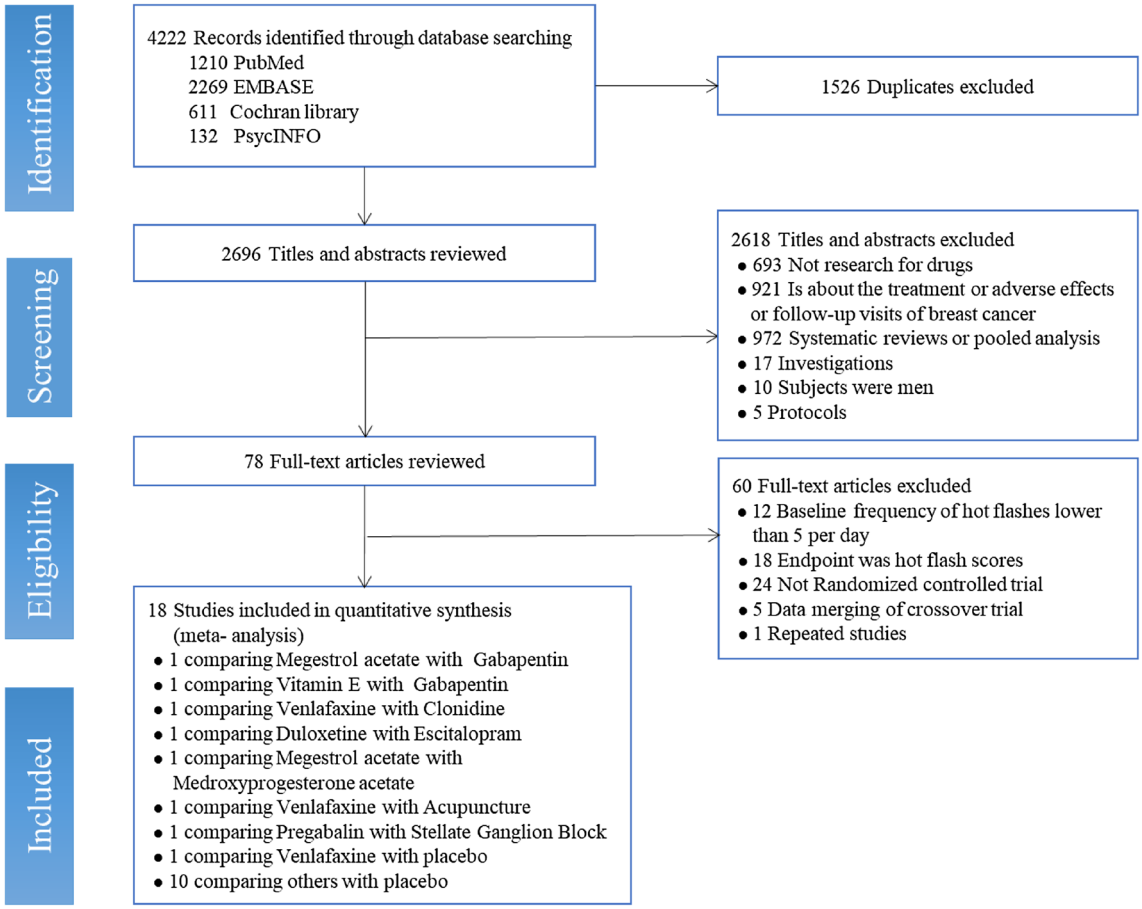

Fig. 1 Flow chart demonstrating the inclusion and exclusion of studies into the analysis

Table 1 Brief characteristics of included studies, median(min–max)

	Overall	Progesterone	SSRIs/SNRIs	Neuroleptic agents	Tibolone	Phytoestrogen	Other types	Placebo
Number of arms	38	4	9	7	1	2	4	11
Total sample size	5178	179	329	536	1556	116	271	2191
Sample size per arm	54 (20–1556)	43 (34–60)	30 (22–56)	60 (20–144)	1556	58 (38–78)	72 (46–81)	57 (22–1542)
Number of efficacy data, per arm	1.5 (1–8)	3.5 (1–6)	1 (1–4)	3 (1–4)	1	1.5 (1–2)	5.5 (1–8)	1 (1–8)
Treatment duration week	8 (4–13)	6 (4–8)	4 (4–12)	8 (4–12)	13	10 (8–12)	8 (4–12)	8 (4–13)
Age, years	53 (41.7–58.4)	50 (42.6–53)	52.2 (45–56.7)	50.5 (41.7–55)	52.5	54.3 (53–55.5)	53	55 (52.3–58.4)
Baseline of hot flashes, per day	8 (5.5–13)	9.2 (8.8–9.9)	8 (6.1–11)	8.7 (6.9–13)	6.3	7.0 (6.9–7.1)	8.0 (6.4–12)	7.4 (5.5–8.9)

Model establishment and assessment

This study aggregated all the efficacy data from the drug groups for modeling. The E_{max} model was used to describe the frequency of hot flash changes from baseline over time. We discovered that the baseline of hot flashes had a significant impact on E_{max} value, and the final model was expressed as follows:

$$E_{\max.i,drug} = 4.92 + (\text{Baseline} - 8) \times 0.738 + N\left(0, 2.3^2\right) \quad (10)$$

$$ET_{50,i,drug} = 2.24 + N(0, 0.7^2) \quad (11)$$

In Eq. 10, $E_{max,i,drug}$ is the E_{max} value of the ith drug group, 4.92 is the typical E_{max} value of the overall drug group, $Baseline_i$ is the baseline of the frequency of hot flashes of the ith drug group. The correction coefficient of the baseline to the E_{max} is 0.738. For every increase in the number of hot flashes in the baseline, the E_{max} value increased by 0.738. N (0, 2.3^2) is the inter-group variation of the E_{max} value, using normal distribution with a mean of 0 and variance of 2.3^2. In Eq. 11, $ET_{50,i,drug}$ is the ET_{50} value of the ith drug group and 2.24 is the typical ET_{50} value of the overall drug group. N (0, 0.7^2) is the inter-group variation of the ET_{50} value, using normal distribution with a mean of 0 and variance of 0.7^2.

Substituting Eqs. 10 and 11 into Eq. 1, the predicted drug efficacy of the ith drug group at the jth observation point can be estimated. To make the predicted data of drug effect closest to the observed data, values from the distribution of the inter-group variations of E_{max} and ET_{50} were taken. This process is estimated by the Bayesian feedback method. The optimal $E_{max,i}$ and $ET_{50,i}$ estimated values and the standard errors for each drug group are shown in Supplementary Table S2.

Similarly, the same method was used to model the placebo data separately. Factors such as age and baseline were not found to have significant effects on parameters of E_{max} or ET_{50} in the placebo group. The pharmacodynamic model of the placebo group was expressed as follows:

$$E_{max,i,placebo} = 2.82 + N(0, 1.05^2) \quad (12)$$

$$ET_{50,i,placebo} = 1.3 + N(0, 0.86^2) \quad (13)$$

In Eq. 12, $E_{max,i,placebo}$ is the E_{max} value of the ith placebo group, 2.82 is the typical E_{max} value of the overall placebo group, N (0, 1.05^2) is the inter-group variation of the E_{max} value, using normal distribution with a mean of 0 and variance of 1.05^2. In Eq. 13, $ET_{50,i,placebo}$ is the ET_{50} value of the ith placebo group, 1.3 is the typical ET_{50} value of the overall placebo group, N (0, 0.86^2) is the inter-group variation of the ET_{50} value, using normal distribution with a mean of 0 and variance of 0.86^2. The optimal $E_{max,i}$ and $ET_{50,i}$ values and the standard errors for each placebo group estimated by Bayesian feedback were shown in Supplementary Table S2.

The diagnostic graphics showed that the model had satisfactory goodness of fit on the data of observed effects from the drug and the placebo groups (Supplementary Figures S2 and S3). The observed data effect of almost all the groups fell within the 95% CI of the predicted value (Fig. 2), indicating that the model has good predictability.

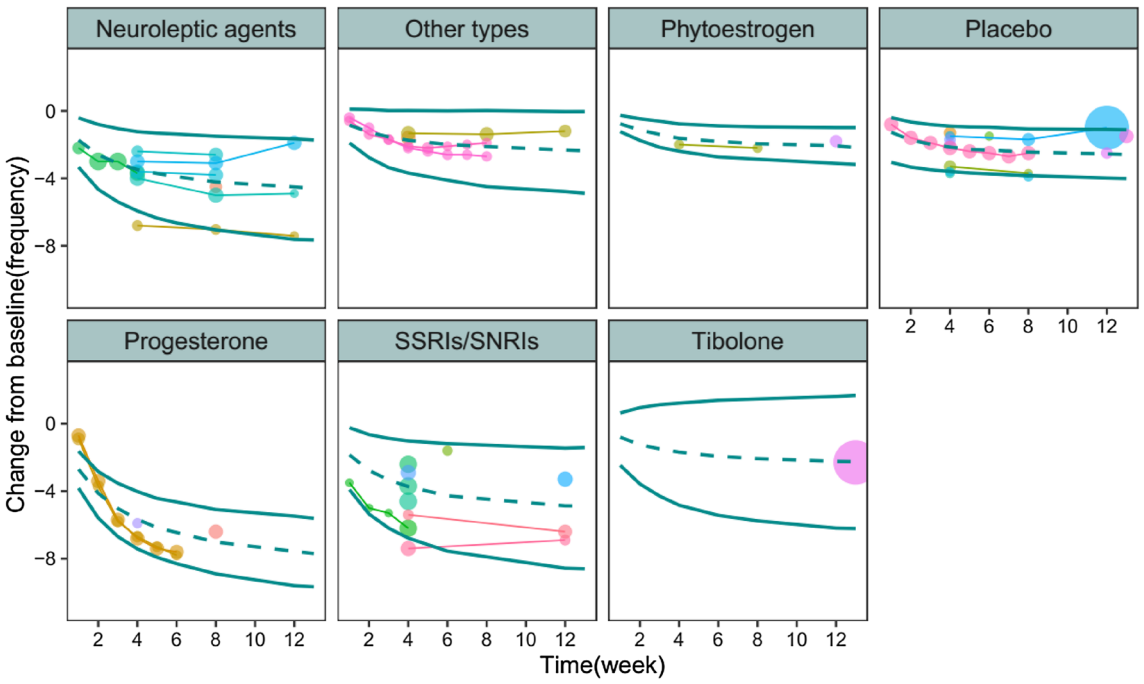

Fig. 2 Prediction-corrected visual predictive check of the final model. Solid points represent observed efficacy data, and symbol size is proportional to sample size. Points linked by a line are from the same arm. Blue lines are the model-predicted 5th, 50th, and 95th percentiles of efficacy

Typical efficacy analysis

It is necessary to perform baseline correction on the E_{max} value for each drug group because the baseline of the frequency of hot flashes had a significant effect on the E_{max} value of the drug group. The correction Equation is as follows:

$$E_{max,i,drug,corrected} = E_{max,i,drug} - (\text{Baseline} - 8) \times 0.738 \quad (14)$$

In Eq. 14, $E_{max,i,drug,corrected}$ is the E_{max} correction value of the ith drug group and the $E_{max,i,drug}$ is the E_{max} value of the ith drug group. This Equation corrects the E_{max} values at different baselines to a level of 8, thereby eliminating the effect of baseline on E_{max} values when comparing the efficacy characteristics of drugs. The results showed that the corrected E_{max} value of progesterone was 8.3 (95% CI 6.8–9.9), which was significantly higher as compared to other drugs. The corrected E_{max} value of tibolone, neuroleptic agents, and SSRIs/SNRIs were 4.0 (95% CI 3.6–4.3), 4.4 (95% CI 3.6–5.3), and 5.1 (95% CI 4.4–5.7), respectively, all of which were significantly higher than the E_{max} value of placebo. The placebo E_{max} value was 2.7 (95% CI 2.1–3.3); the corrected E_{max} value of phytoestrogen and other types of drugs were comparable with that of the placebo. In terms of onset time, the ET_{50} values were approximately 2–2.5 weeks, while the ET_{50} value of placebo was only 1.2 weeks (Table 2).

Based on the corrected pharmacodynamic parameters described above, the distribution of drug efficacy at different time points can be simulated (Fig. 3). One example is the efficacy at week eight; the efficacy of progesterone was 6.4 (95% CI 5.2–7.7). It was followed by SSRIs/SNRIs drugs with an efficacy of 4.0 (95% CI 3.5–4.6). The efficacy of tibolone and neuroleptic agents were similar, with values of 3.1 (95% CI 2.6, 3.6) and 3.5 (95% CI 2.8, 4.2), respectively. The efficacy of phytoestrogen and other types of drugs were 2.6 (95% CI 1.9, 3.4) and 1.9 (95% CI 0.6, 3.3), respectively, and these were comparable with the placebo effect. The placebo efficacy is 2.3 (95% CI 1.8, 2.9). The distribution of drug and placebo efficacy were simulated and shown in Fig. 4.

Among the SSRIs/SNRIs, venlafaxine and duloxetine had the highest efficacy, while sertraline had the lowest efficacy. At week eight, the efficacy of venlafaxine and duloxetine were 1.1 times/day higher than sertraline.

Table 2 Parameter estimations of drugs and placebo

Group	Arms (sample size)	E_{max} (95% CI)	$E_{max,corrected}$ (95% CI)	ET_{50} (95% CI)	Corrected efficacy at week 8 (95% CI)
Progesterone	4 (179)	9.1 (7.8,10.4)	8.3 (6.8,9.9)	2.4 (1.7,3.0)	6.4 (5.2,7.7)
Medroxyprogesterone acetate	1 (37)	10.2 (8.2,12.2)	9.6 (7.7,11.6)	2.7 (1.5,3.9)	7.2 (5.6,8.0[a])
Megestrol acetate	3 (142)	8.7 (7.2,10.2)	7.9 (6.2,9.6)	2.2 (1.5,3.0)	6.2 (4.7,7.6)
Tibolone	1 (1556)	2.7 (2.3,3.1)	4.0 (3.6,4.3)	2.3 (0.9,3.7)	3.1 (2.6,3.6)
Phytoestrogen	2 (116)	2.6 (1.7,3.5)	3.4 (2.4,4.3)	2.3 (1.3,3.3)	2.6 (1.9,3.4)
Black cohosh	1 (38)	3.0 (1.6,4.4)	3.9 (2.6,5.3)	2.3 (0.9,3.7)	3.0 (2.0,4.2)
Soy phytoestrogens	1 (78)	2.3 (1.1,3.5)	2.9 (1.8,4.1)	2.3 (0.9,3.7)	2.3 (1.4,3.3)
Neuroleptic agents	7 (536)	5.4 (4.0,6.8)	4.4 (3.6,5.3)	2.1 (1.6,2.5)	3.5 (2.8,4.2)
Gabapentin	4 (376)	5.8 (3.6,7.9)	4.2 (3.4,5.1)	2.1 (1.4,2.7)	3.4 (2.7,4.1)
Clonidine	2 (130)	4.4 (2.0,6.8)	3.5 (2.7,4.3)	2.0 (1.1,2.9)	2.8 (2.1,3.5)
Pregabalin	1 (20)	5.9 (4.3,7.5)	6.7 (5.1,8.3)	2.1 (0.7,3.5)	5.3 (4.0,6.8)
SSRIs/SNRIs	9 (329)	5.9 (4.3,7.4)	5.1 (4.4,5.7)	2.1 (1.7,2.5)	4.0 (3.5,4.6)
Escitalopram	1 (30)	7.8 (6.0,9.6)	4.9 (3.1,6.6)	2.1 (0.9,3.3)	3.9 (2.4,5.4)
Sertraline	2 (53)	3.4 (1.4,5.5)	4.2 (2.7,5.7)	2.3 (1.3,3.3)	3.2 (2.1,4.5)
Venlafaxine	5 (218)	5.7 (4.0,7.4)	5.4 (4.4,6.5)	2.1 (1.5,2.7)	4.3 (3.5,5.2)
Duloxetine	1 (28)	8.9 (7.1,10.7)	5.2 (3.4,7.0)	1.7 (0.5,2.9)	4.3 (2.8,5.8)
Other types	4 (271)	2.8 (2.2,3.5)	2.5 (0.8,4.2)	2.4 (1.7,3.1)	1.9 (0.6,3.3)
Magnesium oxide	2 (162)	3.2 (2.6,3.8)	3.2 (1.9,4.4)	2.5 (1.5,3.4)	2.4 (1.4,3.4)
Vitamin E	2 (109)	2.2 (1.4,3.0)	1.9 (−1.9,5.6)	2.3 (1.3,3.3)	1.4 (−0.7,3.7)
Placebo	11 (2191)	2.7 (2.1,3.3)	2.7 (2.1,3.3)[b]	1.2 (0.8,1.6)	2.3 (1.8,2.9)

[a]The efficacy value is impossible to exceed 8 when the baseline frequency of hot flashes is 8. If the upper limit of 95% CI exceeded 8, it will be adjusted to 8

[b]Placebo effect was not associated with the baseline frequency of hot flashes, thus the corrected E_{max} values of placebo group was consistent with the original values

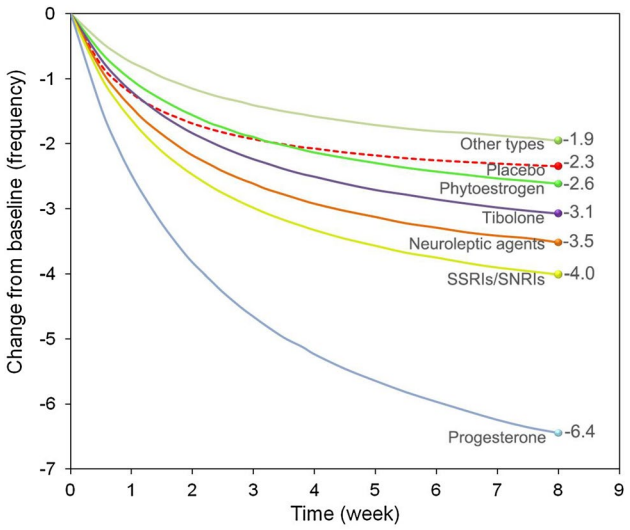

Fig. 3 Predicted typical time course of hot flash reduction of each drug and placebo

Comparison of efficacy in different populations

Based on the pharmacodynamic parameters reported in the literature [15, 16]. we simulated the efficacy distribution of the placebo and SSRIs/SNRIs in natural menopausal women. The results showed that there was no significant difference in the efficacy of placebo and SSRIs/SNRIs drugs between patients with breast cancer and natural menopausal women (Fig. 5).

Discussion

Hot flashes are one of the most troublesome symptoms seen in patients during treatment of breast cancer [17]. Many breast cancer patients stop or change endocrine therapy because of severe symptoms, and less than 50% of patients insist on taking anti-estrogens for five years, resulting in breast cancer mortality of more than 20% [18]. Therefore, the management of hot flashes has always been an important issue for the treatment of breast cancer.

Drug therapy is one of the main means to alleviate hot flashes in patients with breast cancer [19]. There are many drugs currently being used to relieve hot flashes in these patients. However, due to the lack of head-to-head comparison, the difference in efficacy between drugs is not clear. Although several studies have summarized these drugs, they are basically limited to effectiveness judgment and there is a lack of quantitative information [6–8]; hence, these studies cannot be adequately used to guide clinical practice.

In this study, the pharmacodynamics model was established to quantitatively reflect the differences in the efficacy characteristics of different drugs, and to explore related impact factors. We found that the baseline of hot flashes is an important factor affecting drug efficacy. The

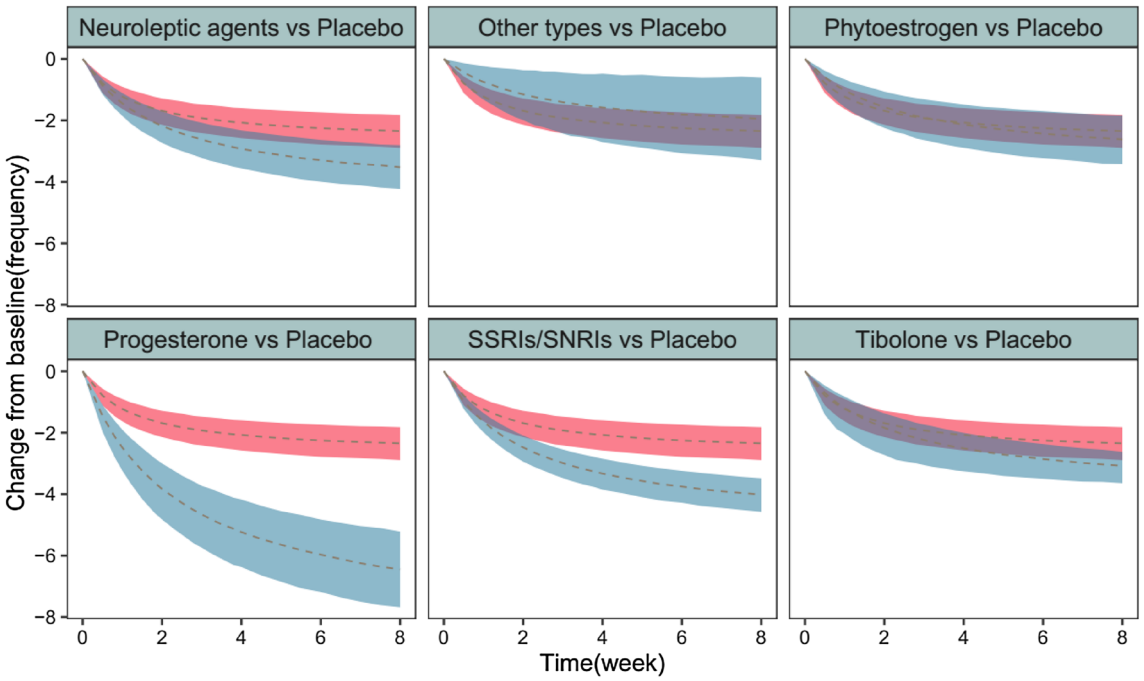

Fig. 4 The predicted typical response of drugs and placebo at the baseline level of 8. The dotted lines represent the typical efficacy, and the shaded areas are their 95% CIs

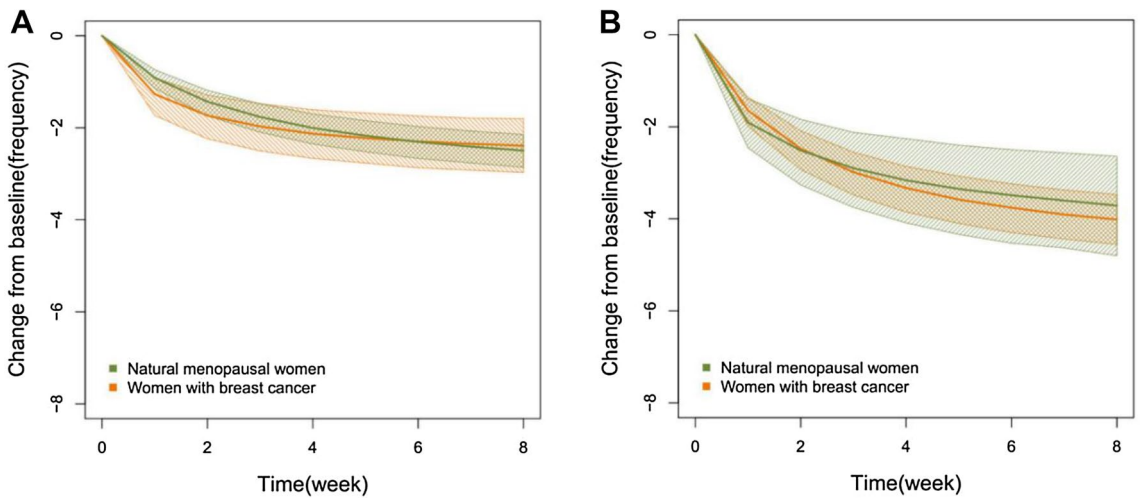

Fig. 5 The predicted typical response of placebo (**a**) and SSRIs/SNRIs (**b**) at the baseline level of 8 in natural menopausal women and breast cancer patients. The dotted lines represent the typical efficacy, and the shaded areas are their 95% CIs

higher the baseline level, the better the drug efficacy. In this study, the baseline of hot flashes was corrected to the level of eight times per day to compare the characteristics of drug efficacy, therefore, reducing the impact of baseline heterogeneity on the results. The results show that, in terms of maximum efficacy (E_{max}), the current drugs can be roughly divided into three categories. Phytoestrogen and other types of drugs have the lowest efficacy, which is comparable to placebo effect. SSRIs/SNRIs, neuroleptic agents, and tibolone have a moderate effect and are significantly superior to that of the placebo. Progesterone are the most effective, about twice as much as neuroleptic agents and tibolone. In terms of onset time (ET_{50}), all the drugs were comparable, and the value was about 2–2.5 weeks, which is 1.1 weeks slower than that of the placebo. The above information provides necessary quantitative supplements for medication guidelines for hot flashes in patients with breast cancer.

When the baseline of hot flashes was eight times/day, the frequency of hot flashes was reduced by 6.4 times/day after 8 weeks of progesterone intervention; hence, hot flashes are close to complete remission. Although the efficacy of progesterone is outstanding, a UK survey showed that only 2% of breast cancer patients use progesterone to relieve hot flashes [17]. The main reason is that people are worried that the use of progesterone may increase the risk of breast cancer recurrence. Although studies have shown that combined estrogen and progesterone increases the risk of breast cancer, whether the use of progesterone alone in breast cancer patients increases the risk of breast cancer recurrence has not yet been confirmed [19]. In view of the excellent advantages of progesterone in efficacy, it is necessary to carry out relevant large-scale clinical trials to make a clear conclusion on the safety of progesterone in breast cancer patients.

SSRIs/SNRIs and neuroleptic agents are neurotransmitter modulators, and they are also widely used in breast cancer patients for relieving hot flashes [17, 20]. We found that these drugs can reduce the frequency of hot flashes by 1.2–1.7 times/day more than the placebo at 8 weeks. However, SSRIs/SNRIs and neuroleptic agents commonly have central nervous system side effects such as insomnia, nausea, dry mouth, dizziness, fatigue, and anxiety [7]. Moreover, some drugs such as paroxetine and fluoxetine are inhibitors of CYP2D6, which prevents tamoxifen from being metabolized into active ingredients in the body, thus reducing its treatment effect on breast cancer [7, 21, 22]. Venlafaxine, duloxetine, and pregabalin have relatively high efficacy when compared to the other SSRIs/SNRIs and neuroleptic agents. The sample size collected for venlafaxine use in this study was large, so the estimated drug effect is relatively accurate. Venlafaxine is a weak inhibitor of CYP2D6 and has less effect on tamoxifen [22, 23]. In addition to this, a survey showed that the highest proportion of patients with breast cancer chose venlafaxine [17]. It suggests that venlafaxine has a better clinical benefit-to-risk ratio; however, it can cause adverse reactions such as nausea and constipation [7].

Tibolone belongs to the group of normethyltestosterone progestogen derivatives and has metabolites that exhibit estrogenic, progestogenic, and androgenic effects. A clinical trial with a large sample size and long treatment duration confirmed the effectiveness of tibolone [24]. Our study found that the efficacy of tibolone was comparable to that of neuroleptic agents, which can reduce the frequency of hot flashes by 1.2 times/day more than the placebo at 8 weeks. However, studies have confirmed that tibolone increases the risk of breast cancer recurrence; the risk ratio compared with placebo is 1.40 (95% CI 1.14–1.70) [24].

Many patients with breast cancer prefer drugs from natural sources, such as black cohosh, soy phytoestrogens, magnesium oxide, and vitamin E because progesterone, SSRIs/SNRIs, neuroleptic agents, and tibolone have more issues on safety [1]. Results showed that there was no significant difference in the efficacy of these drugs when compared with the placebo. Although the sample size of these studies is small, the conclusions of these studies need to be confirmed further. Based on the current efficacy results, it is suggested that the efficacy of these drugs is not outstanding.

Previous studies have shown that the frequency and the intensity of hot flashes in breast cancer patients are higher than that of natural menopausal women. However, there is no clear conclusion whether the drug efficacy in these two types of population is different. A previous study analyzed 20 clinical data from Mayo Clinic/North Central Cancer Treatment Group and it was concluded that the effects of non-estrogenic treatments on hot flashes are similar in women with breast women versus women without a history of breast cancer as well as in women receiving tamoxifen versus women not receiving tamoxifen [25]. In this study, we also found that the efficacies of placebo and SSRIs/SNRIs in patients with breast cancer overlapped with the efficacies reported in natural menopausal women. In addition to this, we discovered that endocrine therapy ratio was not associated with drug efficacy during covariate screening process, which further supported the conclusions of the literature. Therefore, we suggest that future meta-analysis combine the results of these two types of population to increase the accuracy of the estimation of drug efficacy.

The study has the following limitations. First, the number of observation points of some of the drugs was few; hence, the estimation of drug efficacy may contain a certain sampling error. Second, we could not evaluate the pure effects of the drug by removing the corresponding placebo effect because many of the included studies did not have a placebo control group. Third, six of the studies were non-blinded trials, which may have biased results. However, sensitivity analysis showed that the efficacy of each drug was almost consistent with the original results after removing the data from the non-blinded trials (Supplementary Table S3). Finally, the study only included studies published in English, which may result in publication bias.

Conclusions

This study quantitatively analyzed the efficacy of different drugs in relieving hot flashes in breast cancer patients. The results showed that the efficacy of progesterone is much better as compared to other drugs. The efficacy of SSRIs/SNRIs, neuroleptic agents, and tibolone are moderate, while phytoestrogen and other types of drugs have the lowest efficacy. The drug efficacy was significantly associated with the baseline of hot flashes, but there was no significant difference between breast cancer patients and natural menopausal women.

Author Contributions T.L & J.Y selected studies and extracted the data, analyzed and interpreted the data, YH.L & F.Y wrote the manuscript, and revised the manuscript. HX.L and L.X contributed to data extraction and cleaning. LJ.L and QS.Z participated in conception and design of the work and revised the paper critically for important intellectual content. All authors read and approved the final manuscript. All authors have approved the final article.

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Compliance with ethical standards

Conflict of interest All the authors declare no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors.

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