

REVIEW-SYSTEMATIC

Gabapentin for the treatment of hot flashes in menopause: a meta-analysis

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Abstract

Objective: Gabapentin is used to treat vasomotor symptoms (VMS) in postmenopausal women with contraindications to hormonal therapy or who prefer alternatives. We investigated the efficacy and tolerability of gabapentin for treating menopausal hot flashes via a meta-analysis.

Methods: We searched the PubMed, MEDLINE, EMBASE, and CENTRAL databases for English-language articles published until June, 2018. The following search terms were used: “menopause,” “hot flashes,” “vasomotor symptoms,” “gabapentin,” and “non-hormonal therapy.” Primary outcomes were frequency, duration, and composite score of hot flashes. Secondary outcomes were adverse effects and dropout rate. We estimated the standardized mean difference (SMD) and combined odds ratio (OR) using fixed or random-effects models, depending on study heterogeneity. Subgroup and meta-regression analyses of gabapentin dosage were performed.

Results: We included seven randomized controlled trials that compared single-agent gabapentin with placebo for treating hot flashes in the meta-analysis. Women who received gabapentin reported a significantly greater reduction in the frequency (SMD 2.99 [95% confidence interval 2.01-3.98], $P < 0.001$), duration (0.89 [0.49-1.30], $P < 0.001$), and composite score (2.31 [1.50-3.11], $P < 0.001$) of hot flashes. Adverse events were significantly more frequent among those taking gabapentin than among those taking the placebo (OR 1.58 [0.98-2.18], $P < 0.001$; and 1.19 [0.43-1.95], $P = 0.002$ for dizziness and unsteadiness, respectively).

Conclusions: Gabapentin could be used to treat VMS in postmenopausal women with contraindications to hormonal therapy. Future studies should investigate the lowest effective dose of gabapentin to minimize adverse effects.

Key Words: Gabapentin – Hot flashes – Menopause – Nonhormonal therapy – Vasomotor symptoms.

Video Summary: <http://links.lww.com/MENO/A521>.

Menopause is the permanent cessation of a woman's menstrual cycle. Despite increasing life expectancy worldwide, the average age at the onset of menopause has remained at approximately 51 years.

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Considering that the average life expectancy of women in the United States is 81 years, women may be postmenopausal for more than one-third of their lives. Hot flashes and night sweats are the most common menopausal symptoms, and there is evidence these symptoms may last for 4 to 10 years, peaking in the year around the final menstrual period and with an average duration of 7 years in some studies.^{1,2} Around 25% of women experience problematic vasomotor symptoms (VMS) that reduce quality of life, requiring treatment in severe cases.³

Estrogen has been used as a hormonal supplement in the treatment of menopausal symptoms for over 60 years, and estrogen therapy is the most effective treatment for VMS in postmenopausal women.⁴ However, more recently, randomized trials such as the Women's Health Initiative (WHI),⁵ which included women who were mostly at a stage long after the onset of menopause, have shown no such benefit. Moreover, an increased risk of coronary heart disease (CHD) and breast cancer associated with hormone therapy (HT) has led to an abrupt decrease in the use of this treatment.⁶ Subsequent reanalysis of data from the WHI with age stratification, newer

randomized and observational data, and several meta-analyses now consistently show that CHD and mortality are reduced when HT is initiated soon after menopause.⁷ Although these recent data show that women who are younger (aged <60 years) and generally healthy at the onset of menopause have a very favorable risk-benefit profile when using HT, there is still concern amongst general practitioners and women that the risks of HT far outweigh the benefits. Additionally, estrogen therapy is contraindicated for treatment of VMS in women with a history of breast cancer, CHD, previous venous thromboembolic events, transient ischemic attack, or stroke; unexplained vaginal bleeding; high-risk endometrial cancer; and active liver disease.⁸

For this reason, nonhormonal approaches have been considered to treat VMS in postmenopausal women.

Nonhormonal prescription therapies including selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), gabapentin, and clonidine have been tested in randomized placebo-controlled trials, and shown to be effective.⁹ In 2015, The North American Menopause Society (NAMS) published recommendations based on their review of evidence regarding the nonhormonal management of menopause-associated VMS. They reported that cognitive behavioral therapy and clinical hypnosis may be effective nonprescription therapies for the reduction of VMS, and summarized that there is suggestive evidence for the efficacy of SSRIs, SNRIs, gabapentinoids, and clonidine as nonhormonal therapies for VMS.¹⁰ However, some SSRIs interfere with tamoxifen metabolism by inhibiting the CYP2D6 enzyme that metabolizes tamoxifen to its more potent metabolite, endoxifen.¹¹ While paroxetine has been shown to have a strong interaction, venlafaxine and gabapentin are not known to interact with tamoxifen.¹² Gabapentin could be used for the treatment of VMS in postmenopausal women with contraindications to HT, especially patients with breast cancer who are taking tamoxifen as endocrine therapy or for high-risk women who are taking tamoxifen to reduce their risk of breast cancer. To the best of our knowledge, only one meta-analysis¹³ has been conducted on this topic, which revealed that gabapentin reduced the frequency and severity of VMS.

In the present study, we conducted an updated meta-analysis including the latest evidence to evaluate the efficacy and tolerability of gabapentin for the treatment of menopausal hot flushes. Our investigation included subgroup, sensitivity, and meta-regression analyses.

METHODS

Search strategy

Three of the authors of the present study (S.H.Y., C.M.L., and J.Y.L.) designed the protocol and extraction forms in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines.^{14,15} Reviews and original articles were searched for in MEDLINE, PubMed, and EMBASE databases and in the Cochrane Central Register for Controlled Trials (CENTRAL) in the Cochrane Library up to June 2018. The following search terms were used:

“menopause,” “hot flushes,” “vasomotor symptoms,” “gabapentin,” and “non-hormonal therapy.” All relevant reports were retrieved and reference lists were reviewed manually to identify further studies. A manual search of PubMed was also performed for related articles. No attempt was made to identify unpublished studies unless they had been released as online publications ahead of print. No reports from scientific meetings were included. The above-mentioned searches were performed by an accredited clinical librarian.

Selection criteria

Inclusion criteria for studies were as follows: randomized controlled trials (RCTs); participants of interest were postmenopausal women meeting the following criteria—amenorrhea for more than 12 months or amenorrhea for 6 to 12 months with a serum follicle-stimulating hormone level >40 mIU/mL and estrogen level <30 pg/mL, or postbilateral oophorectomy for 2 months; no estrogen, progestin, leuprolide, or tamoxifen therapy within the past 2 months; interventions of interest were gabapentin and identical-appearance placebo; primary outcomes were percentage reduction or mean difference in frequency, duration, or severity of hot flushes; and secondary outcomes were adverse events and dropout rate. Uncontrolled and open-label studies were reviewed but not included in the meta-analysis. Reviews, abstracts, editorials, letters to the editor, preliminary reports, and studies published in languages other than English were excluded. Study selection was performed independently by three reviewers (S.H.Y., H.J.L., and J.Y.L.). Any disagreement was resolved unanimously by consultation and discussion with a fourth author (S.N.K.).

Data extraction

Three authors (S.H.Y., H.J.L., and J.Y.L.) scored the studies and collected information independently. The following data were recorded for each eligible study: name of the first author, study location, year of publication, study design, sample size, duration of treatment, dosage of gabapentin, hot-flush frequency (number of recorded episodes per day), hot-flush duration (average duration in minutes of all hot flushes experienced per day), hot-flush severity (expressed as a composite score calculated for each study), adverse events (dizziness or somnolence symptoms), and dropout rate. Continuous variables including duration, frequency, and composite score of hot flushes are described in percentage changes or mean difference from baseline to 1, 2, 3, or 6 months for each measure. Primary outcomes are reported as the standardized mean difference (SMD). Secondary outcomes are presented with odds ratios (ORs). Discrepancies in data extraction were jointly reviewed until a consensus was reached.

Quality assessment

The Jadad score was used to assess the quality of RCTs.¹⁶ Studies with a Jadad score of 2 or higher were considered to have high quality. Studies were included regardless of their quality; however, sensitivity analysis was performed based on quality. We assessed the risk of bias of included studies as

low, unclear, or high using the Cochrane Collaboration tool,¹⁷ and considered the method of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Studies considered to have a high risk of bias were those graded as having a high risk for the method of sequence generation, allocation concealment, blinding procedures, or incomplete outcome data. Any disagreement was resolved after discussion and reevaluation with the fourth author (S.N.K.).

Data synthesis and analysis

Heterogeneity across studies was examined using I^2 , which measures the percentage of total variation across studies,¹⁸ and substantial heterogeneity defined as an I^2 value $>50\%$.¹⁹ A random or fixed-effects model was used to estimate the SMD and combined OR for randomized studies depending on whether significant heterogeneity was present or not, respectively. Subgroup analysis was then conducted for the dosage of gabapentin (300, 900, or 1,800 mg). Subgroup analysis was planned a priori before data collection and analysis. Meta-regression analysis was carried out to evaluate the relationship between dosage of gabapentin and the mean difference in these variables.

Sensitivity analysis was performed to evaluate the influence of single studies on the overall estimate. Publication bias was evaluated using the Begg and Mazumdar rank correlation test,²⁰ Egger's test,²¹ and fail-safe N test.²² A funnel plot was constructed to assess this bias using the standard error and

diagnostic OR.^{23,24} Comprehensive Meta-Analysis version 3.3 (Biostat, Englewood, NJ) was used for all statistical tests. We considered $P < 0.05$ to indicate statistical significance. Data are presented according to a checklist created based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).²⁵

RESULTS

Literature search

A total of 347 articles were originally identified after removal of duplicates, including 135 from PubMed, 51 from Cochrane, and 163 from EMBASE. Figure 1 presents the flow diagram for the identification of relevant studies. After applying the selection criteria, 13 articles reporting RCTs were identified as eligible. Of these, six were excluded because they compared gabapentin with estrogen,^{26,27} venlafaxine,²⁸ vitamin E,²⁹ hypnotherapy,³⁰ or pregabalin.³¹ Finally, seven studies were selected, which compared gabapentin with placebo.³²⁻³⁸

Study characteristics

The seven studies were from the United States,^{32-34,37} Canada,³⁵ Iran,³⁶ and India,³⁸ and were published between 2003 and 2014. Table 1 shows the study characteristics in detail. In this meta-analysis, 1,446 menopausal women with VMS were enrolled including 789 individuals who received gabapentin, 637 who received a placebo, and 20 women who received conjugated estrogen in Reddy et al's³⁴ study. In this

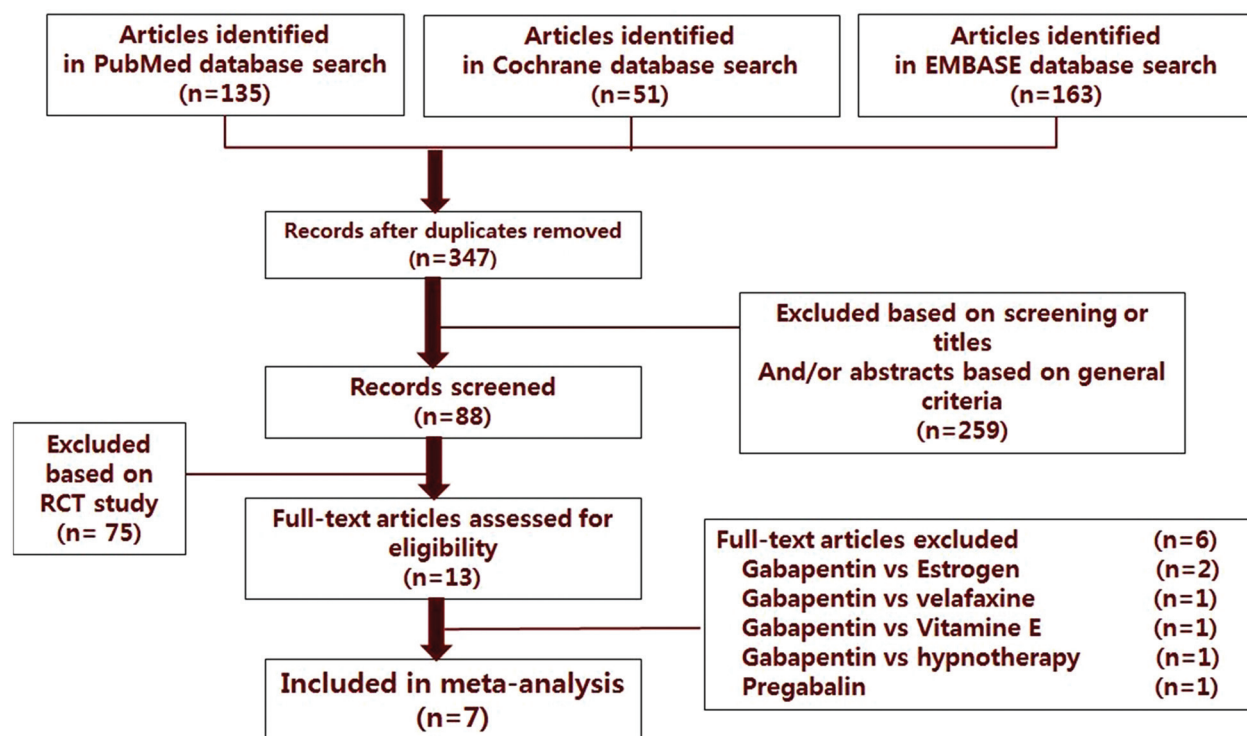


FIG. 1. Flow diagram of the procedure for literature search (PRISMA 2009 flow diagram).

TABLE 1. Characteristics of studies included in the meta-analysis

Author, country, year	Design	Inclusion criteria	Intervention, control, sample size	Outcomes	Quality score (Jadad score)
Guttuso et al, ³² United States, 2003	Randomized, double-blind, placebo-controlled, parallel	Postmenopausal women, amenorrhea >12 month, amenorrhea 6-12 mos with FSH >40 mIU/mL and estrogen <20 pg/mL, BSO >2 mos previously with ≥7 HF/d and sweating	59 Women: 30 GB 900 mg/d for 3 mos; 29 placebo control; 26/28, respectively, completed study	Frequency, composite score, adverse event, PGIC, POMS	5
Pandya et al, ³³ United States, 2005	Randomized, double-blind, placebo-controlled, parallel	Women with history for breast cancer, only endocrine therapies allowed, ≥2 HF/d	420 Women: 139 GB 300 mg/d for 2 mos; 144 GB 900 mg/d for 2 mos; 137 placebo control; 114/ 120/113, respectively, completed study	Frequency, severity, duration, adverse event	4
Reddy et al, ³⁴ United States, 2006	Randomized, double-blind, placebo-controlled, parallel	Menopausal women, ≥50 moderate HF/wk for <2 mos, BSO >12 mos, amenorrhea >6 mos with FSH >30 mIU/mL, no other therapy for HF	60 Women: 20 GB 2,400 mg/d for 3 mos; 20 CE 0.625 mg/d for 3 mos; 20 placebo control; 17/17/19, respectively, completed study	Composite score, adverse event	5
Butt et al, ³⁵ Canada, 2008	Randomized, double-blind, placebo-controlled, parallel	Postmenopausal women, natural cessation of menses ≥1 y, ≥14 HF/wk, no hormone, tamoxifen, SSRI, SNRI, or antiseizure therapy, no BSO	197 Women: 99 GB 900 mg/d for 1 mo; 98 placebo control; 95/98, respectively, complete study	HF score, frequency, MENQoL score, adverse event	4
Saadati et al, ³⁶ Iran, 2013	Randomized controlled, parallel	Postmenopausal women >1 y, natural menopause	60 Women: 30 GB 900 mg/d for 3 mos; 30 placebo control	Frequency, duration, intensity	1
Pinkerton et al, ³⁷ United States, 2014	Randomized controlled, parallel	Postmenopausal women, amenorrhea >12 mos or amenorrhea for 6 to 12 mos with FSH >40 mIU/mL, or 6 wks or more postbilateral oophorectomy	600 Women: 302 GB 1,800 mg/d for 6 mos; 298 placebo control; 299/294, respectively, complete study	Frequency, severity, sleep interference scale, PGIG, CGIG, adverse event	4
Agarwal et al, ³⁸ India, 2014	Pilot study: prospective, randomized, double-blind, placebo-controlled	Natural menopause, >1 y amenorrhea, FSH greater than 40 mIU/mL, no pelvic pathology, normal papanicolaou smear and presence of HF	50 Women: 25 GB 900 mg/d with calcium; 25 placebo with calcium control	Frequency, duration, integrated HF score, HF composite score	3

BSO, bilateral salpingo-oophorectomy; CE, conjugated estrogen; CGIC, clinical global impression of change; FSH, follicle-stimulating hormone; GB, gabapentin; HF, hot flashes; MENQoL, menopause-specific quality of life; PGIC, patients' global impression of change; POMS, profile of mood states; SNRI, serotonin and noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

paper, data of three groups (gabapentin, placebo, and estrogen) were presented separately, so we included this paper in the meta-analysis using the raw data of two groups (gabapentin and placebo).³⁴ One of the seven articles included patients with breast cancer.³³ The dose of gabapentin ranged from 300 to 2,400 mg, and the treatment and follow-up period ranged from 1 to 6 months.

Overall, the reporting of studies was not uniform, and the efficacy of gabapentin was evaluated differently across studies, although the inclusion criteria, recruitment methods, and reporting of baseline characteristics were clearly stated; in general, primary outcomes (hot flush frequency, duration, and composite score) were assessed using different scales such as percent reductions^{32,33,35} and/or mean absolute difference changes.^{33,35-38} Adverse events were described in four articles^{32,34,35,37} and the dropout rate was described in five articles.^{32-35,37}

The Jadad score was 1 to 7 points (Table 1). Saadati et al's³⁶ paper scored 1 point because it mentioned the method of randomization, but did not describe the blinding method and withdrawals. Agarwal et al's³⁸ paper scored 3 points because it described all three items (randomization, blinding, and withdrawals). None of the seven studies were considered to have a high risk of bias (Fig. 2).

Meta-analysis

Meta-analysis of the seven RCTs that compared single-agent gabapentin with placebo for the treatment of menopause hot flashes identified two studies^{32,34} that described the efficacy of gabapentin through percentage reductions. Another two studies^{33,35} described the efficacy using percentage reductions and absolute mean difference. Three recent studies³⁶⁻³⁸ used the absolute mean difference to describe the efficacy of gabapentin. Therefore, we analyzed the efficacy of gabapentin for hot flush frequency, duration, and composite score using the SMD.^{33,35-38}

Five studies reported the frequency of hot flashes and 12 detailed the results according to gabapentin dose and duration of treatment. We used a random-effects model because I^2 (98.62%) suggested heterogeneity. There was a significant difference in frequency when comparing placebo and gabapentin (SMD 3.00 [95% confidence interval⁵ 2.02-3.98], $P < 0.001$; Fig. 3A).

The duration of hot flashes was reported in three studies, and 10 detailed the results according to the dose of gabapentin and duration of treatment. We used a random-effects model because I^2 (90.72%) suggested heterogeneity. There was a significant difference in duration when

Risk of Bias Summary

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Agawal 2014	+	?	?	+	?	?	+
Butt 2008	+	+	+	+	+	+	+
Guttuso 2003	+	+	+	+	+	+	+
Pandya 2005	+	+	+	+	+	+	+
Pinkerton 2013	+	+	+	+	+	+	+
Reddy 2006	+	+	+	+	+	+	+
Saadati 2013	?	?	?	+	?	?	+

FIG. 2. Diagrammatical summary of the risk of bias.

comparing placebo and gabapentin (SMD 0.90 [0.49-1.30], $P < 0.001$; Fig. 3B).

Five studies reported the composite score of hot flushes, and 13 detailed the results according to gabapentin dose and duration of treatment. We used a random-effects model because I^2 (98.39%) suggested heterogeneity. There was a significant difference in the composite score when comparing placebo and gabapentin (SMD 2.31 [1.50-3.12], $P < 0.001$; Fig. 3C).

Two common adverse events—dizziness and somnolence—were analyzed. Dizziness was reported in four studies. A fixed-effects model was used for the dizziness meta-analysis because I^2 (0%) did not suggest heterogeneity. There was a significant difference in dizziness when comparing placebo and gabapentin (OR 1.58 [0.99-2.18], $P < 0.001$; Fig. 4A). Somnolence was reported in three studies, and a fixed-effects model used for the somnolence meta-analysis because I^2 (44.01%) did not suggest heterogeneity. There was a significant difference in somnolence when comparing placebo and gabapentin (OR 1.20 [0.44-1.96], $P = 0.002$; Fig. 4B).

The dropout rate was reported in five studies. A fixed-effects model was used for dropout rate analysis because I^2 (40%) did not suggest heterogeneity. The dropout rate was not

different between the placebo and gabapentin groups (OR 0.97 [0.80-1.18], $P = 0.759$; Fig. 4C).

In sensitivity analysis, results based on omission of one study at a time and calculation of SMD or pooled OR for the remaining studies revealed that no study had a significant effect on SMD or pooled OR (Supplementary Fig. 1, <http://links.lww.com/MENO/A522>).

Subgroup analysis by dosage

Supplementary Fig. 2 (<http://links.lww.com/MENO/A523>) shows the VMS for each study and the SMD for categories of gabapentin dosages of 300, 900, and 1,800 mg/d.

Of the five studies that reported frequency of hot flushes, one reported a gabapentin dose of 300 mg/d, four a dose of 900 mg/d, and one reported a gabapentin dose of 1,800 mg/d (Supplementary Fig. 2A, <http://links.lww.com/MENO/A523>). In the 300 mg/day group, SMD was 1.37 (0.95-1.80, $P < 0.001$, $I^2 = 77.0\%$); in the 900 mg/d group, it was 2.86 (1.56-4.16, $P < 0.001$ and $I^2 = 97.34\%$); and in the 1,800 mg/d group, it was 4.40 (2.66-6.14, $P < 0.001$ and $I^2 = 98.92\%$). There was a significant difference among the three groups ($P = 0.001$).

Among the three studies reporting the duration of hot flushes, one reported a gabapentin dose of 300 mg/d, three a gabapentin dosage of 900 mg/d, and no studies reported a dose of 1,800 mg/d (Supplementary Fig. 2B, <http://links.lww.com/MENO/A523>). In the 300 mg/d group, the SMD was 1.40 (1.19-1.60, $P < 0.001$ and $I^2 = 0\%$), whereas in the 900 mg/d group, it was 0.76 (0.28-1.24, $P = 0.002$ and $I^2 = 89.63\%$). There was a significant difference between the two groups ($P = 0.016$).

Among the five studies reporting hot flush composite score, one reported a gabapentin dose of 300 mg/d, four a dose of 900 mg/d, and one study reported a gabapentin dose of 1,800 mg/d (Supplementary Fig. 2C, <http://links.lww.com/MENO/A523>). In the 300 mg/d group, the SMD was 1.07 (0.31-1.83, $P < 0.001$ and $I^2 = 93.37\%$), in the 900 mg/d group, the SMD was 2.16 (1.06-3.25, $P < 0.001$ and $I^2 = 97.32\%$), and in the 1,800 mg/d group, it was 3.53 (2.18-4.89, $P < 0.001$ and $I^2 = 98.64\%$). There was a significant difference among the three groups ($P = 0.006$).

Meta-regression analysis by dosage

Graphical representation of the relationship between gabapentin dosage and mean difference in hot flush frequency and composite score revealed a significant positive trend (Supplementary Fig. 3A and B, <http://links.lww.com/MENO/A524>), whereas no significant trend was found in hot flush duration (Supplementary Fig. 3C, <http://links.lww.com/MENO/A524>).

Publication bias

The Begg-Mazumdar rank correlation test showed no evidence of publication bias. Funnel plots for publication bias regarding frequency, duration, composite score of hot flushes, adverse events, and dropout rate were symmetric (Supplementary Fig. 4, <http://links.lww.com/MENO/A525>).

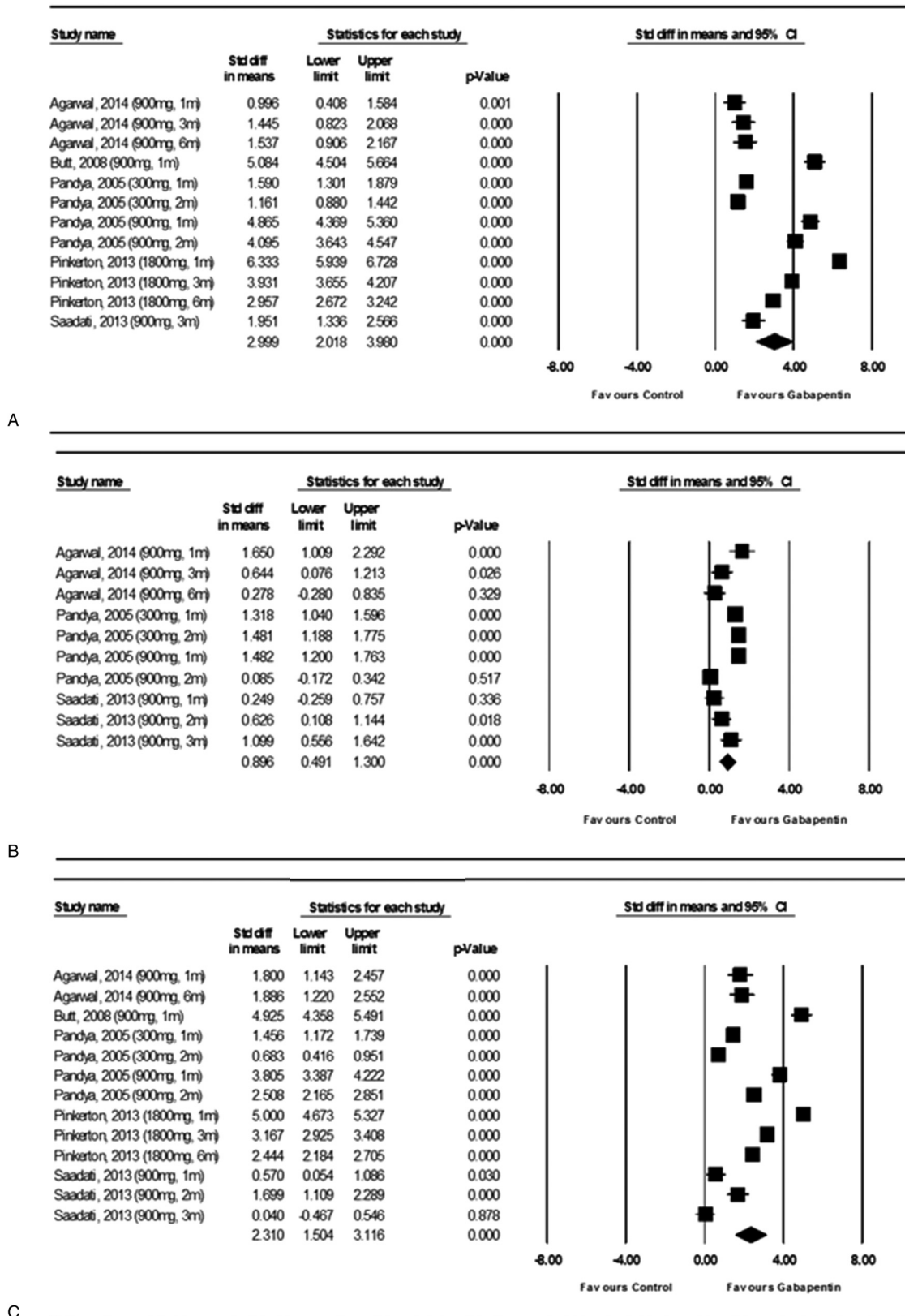


FIG. 3. Forest plot comparing the efficacy of gabapentin and a placebo in terms of (A) frequency, (B) duration, and (C) composite score of hot flashes.

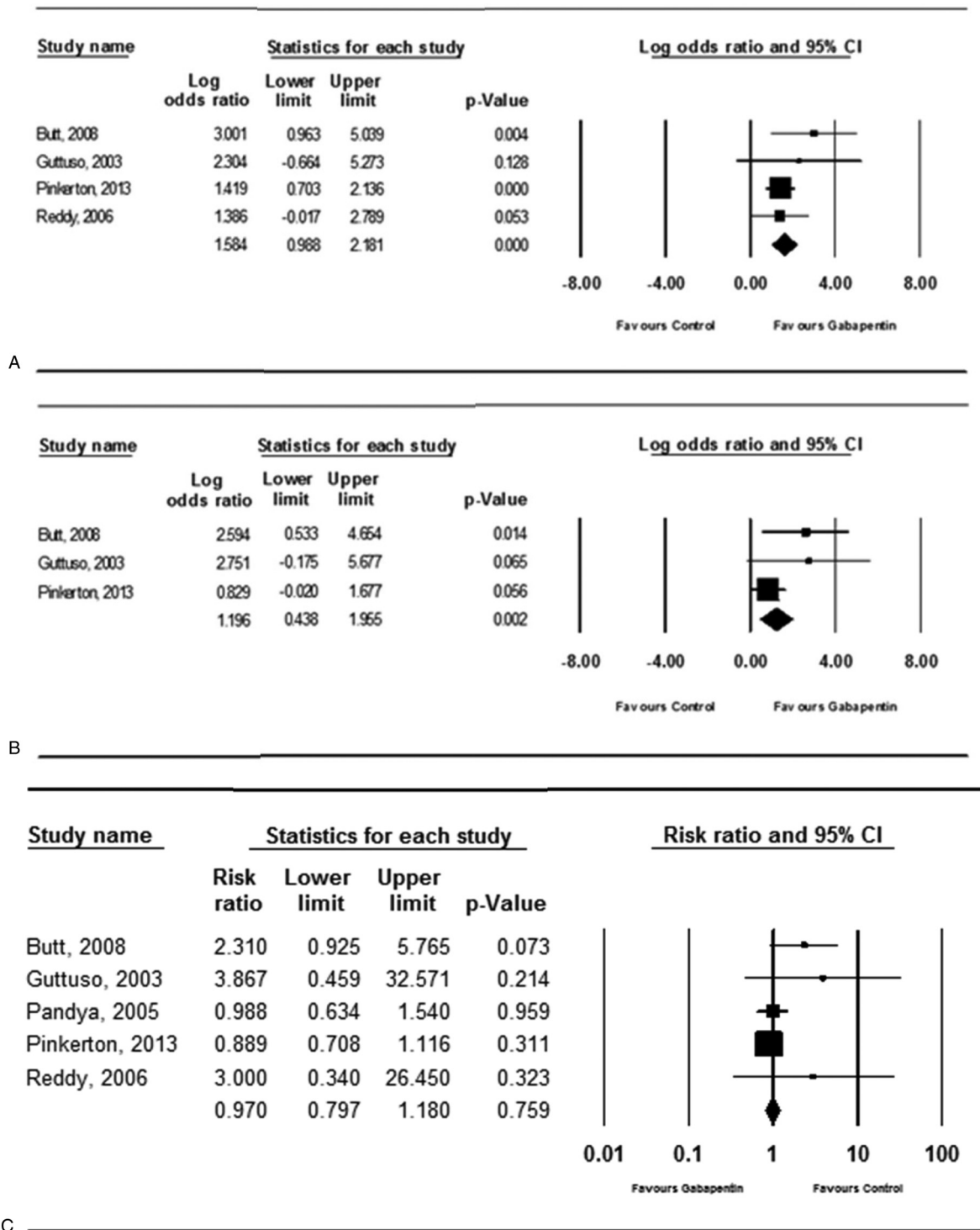


FIG. 4. Forest plot comparing (A) dizziness, (B) somnolence, and (C) dropout rate among women with hot flushes who were administered gabapentin or a placebo.

DISCUSSION

The present meta-analysis demonstrates that gabapentin reduces hot flush frequency, duration, and composite score in postmenopausal women. Subgroup analyses revealed the frequency, duration, and composite score of hot flushes reduced with all doses of gabapentin, and meta-regression

analysis indicated gabapentin dose to be a significant predictor of frequency and composite score, but not duration, of hot flushes.

Although the mechanism underlying menopausal hot flushes is not fully understood, the thermoregulatory zone is narrowed during menopause; therefore, body temperature

changes of as little as 0.1°C can trigger a hot flush.^{39,40} Gabapentin possibly affects the thermoregulatory center in the hypothalamus, and may have nociceptive activities due to its high affinity for binding sites on calcium channels.⁴¹ The drug binds to hypothalamic calcium channels, thereby widening the thermoregulatory zone and potentially decreasing the incidence of hot flushes.^{32,34,42} Although gabapentin is structurally related to γ -aminobutyric acid (GABA), it does not appear to affect GABA synthesis or reuptake.⁴³ Based on the above mechanism and the results of this meta-regression analysis, the dose of gabapentin appears to decrease the frequency of hot flushes, but not the duration. The decrease in frequency of hot flushes was more significant than the decrease in duration.

Regarding adverse events, we found that gabapentin leads to increased incidence of dizziness and somnolence. However, there was no difference in the dropout rate. These results suggest that although gabapentin may be associated with adverse effects, they are not so severe that patients wish to discontinue treatment.

Gabapentin is a structural analog of the neuro-transmitter GABA, which is used in the treatment of epilepsy, neurogenic pain, restless legs syndrome, essential tremor, bipolar disorder, and migraine.⁴⁴ It is used for the treatment of neurogenic pain during chemotherapy and symptoms of persistent numbness after chemotherapy for gynecological cancers (cervical, endometrial, and ovarian cancer). Salpingo-oophorectomy is often employed in the case of ovarian and endometrial cancer for treatment and staging. This procedure can lead to iatrogenic menopause, which can lead to intractable menopausal symptoms. In this situation, gabapentin is preferred over HT for treatment of menopausal symptoms. Survivors of breast cancer—a representative female cancer—are often prescribed tamoxifen and sometimes complain of menopausal symptoms associated with the drug.^{45,46} Tamoxifen and aromatase-inhibitor therapy do not alter efficacy of venlafaxine, citalopram, or paroxetine in terms of hot flush treatment.¹¹ However, some antidepressants may interfere with tamoxifen metabolism by inhibiting CYP2D6 which metabolizes tamoxifen to its more potent metabolite, endoxifen.¹¹ Paroxetine has been shown to interact with tamoxifen, whereas gabapentin has not.¹² A retrospective study of women with breast cancer who were taking tamoxifen and paroxetine showed that combined use of both agents was associated with a significantly increased risk of death from breast cancer.⁴⁷ Gabapentin could be a promising pharmacologic hot flush treatment for survivors of breast cancer who are taking tamoxifen.

The strengths of this study, compared with the meta-analysis published in 2009¹³ which analyzed gabapentin and menopause symptoms, are as follows: first, this meta-analysis included only RCTs, and three new studies have been added since the previous review. Second, an additional variable was added to assess the efficacy of gabapentin. Third, the measurement of efficacy of gabapentin was changed from percentage of reduction to mean difference in hot flush parameters. The reason for this change is that the additional

three new RCT studies described outcomes using the mean difference to present data before and after administration of gabapentin. Fourth, we used various statistical methods to verify whether the heterogeneity could be explained and to investigate the efficacy of gabapentin according to dosage. Specifically, we performed subgroup and meta-regression analyses according to gabapentin dosage, which were not performed in the previous meta-analysis.

Nonetheless, the results of this study should be interpreted with caution because of several limitations. First, our meta-analysis included seven studies, despite attempts to conduct an extensive systematic literature search and identify all relevant articles. Some bias may have been introduced because we only included articles published in English. Attempts to communicate with authors to obtain additional information and missing data were unsuccessful. Second, the small number of RCTs included in the meta-analysis reduces the reliability of the results, along with the significant heterogeneity observed across the studies ($I^2 > 90\%$). In addition, we analyzed different variables to assess the efficacy of gabapentin, and included different doses and treatment durations in our main analysis, which created heterogeneity within the analysis. We used a random-effects meta-analysis to explain heterogeneity and performed a number of sensitivity and subgroup and meta-regression analyses. Third, it was not possible to conduct subgroup analysis of an aggregated population comprising women with either natural or tamoxifen-induced menopause and with a history of breast cancer. Finally, the authors reported conflicts of interest in three of the seven studies included in the meta-analysis.

CONCLUSIONS

Gabapentin represents a potentially beneficial treatment for VMS in postmenopausal women who are contraindicated to HT or who prefer alternatives. Future studies should investigate the lowest effective dose of gabapentin to minimize adverse effects. Management of menopausal symptoms should be individualized and address patients' aims and treatment preferences.

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