

ORIGINAL RESEARCH ARTICLE

Menopausal symptom management: Fezolinetant's varied doses provide effective relief for vasomotor symptoms in women - A meta-analysis of 3291 participants

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Abstract

Menopause represents the physiological transition when a woman's reproductive period ends associated with a variety of symptoms, including vasomotor symptoms, such as night sweats and hot flashes. This systematic review and meta-analysis aimed to assess the effectiveness and safety of oral Fezolinetant for treating vasomotor symptoms associated with menopause. Five electronic databases were searched from their inception until May 2023. Via the Cochrane risk of bias tool, two reviewers assessed the studies' quality. The primary outcomes were a decrease in VMSs frequency and severity and safety outcomes at 4 and 12 weeks. Data were extracted and then analyzed using RevMan software. This meta-analysis included six trials with a total of 3291 women that compared Fezolinetant to a placebo in the treatment of menopausal VMSs. After 4 and 12 weeks of therapy, fezolinetant at 30 mg QD or 45 mg QD substantially decreased the frequency and severity of VMSs per 24 hours compared to placebo. Fezolinetant at 90 mg BID, 30 mg QD, or 45 mg QD did not show a significant difference in the rate of treatment-emergent adverse events (TEAEs), headache, and TEAEs leading to permanent discontinuation compared to placebo. Fezolinetant proves to be a successful and well-tolerated remedy for menopausal women suffering from VMSs. Notably, the 45 mg daily dosage over 12 weeks exhibited significant efficacy. Nonetheless, extensive future trials are necessary to ascertain its long-term safety, effectiveness, and relative potency compared to alternative VMS treatments like hormone therapy. (*Afr J Reprod Health* 2024; 28 [3]: 99-113)

Keywords: Menopause, vasomotor symptoms, fezolinetant, meta-analysis, safety

Résumé

La ménopause représente la transition physiologique lorsque la période de reproduction d'une femme se termine, associée à divers symptômes, notamment des symptômes vasomoteurs, tels que des sueurs nocturnes et des bouffées de chaleur. Cette revue systématique et méta-analyse visaient à évaluer l'efficacité et l'innocuité du Fezolinetant oral pour traiter les symptômes vasomoteurs associés à la ménopause. Cinq bases de données électroniques ont été consultées depuis leur création jusqu'en mai 2023. Via l'outil Cochrane sur le risque de biais, deux examinateurs ont évalué la qualité des études. Les principaux critères de jugement étaient une diminution de la fréquence et de la gravité des SVM ainsi que des critères de sécurité à 4 et 12 semaines. Les données ont été extraites puis analysées à l'aide du logiciel RevMan. Cette méta-analyse comprenait six essais portant sur un total de 3 291 femmes comparant Fezolinetant à un placebo dans le traitement des SVM ménopausiques. Après 4 et 12 semaines de traitement, le fézolinetant à la dose de 30 mg une fois par jour ou de 45 mg une fois par jour a considérablement réduit la fréquence et la gravité des SMV toutes les 24 heures par rapport au placebo. Le fézolinetant à la dose de 90 mg deux fois par jour, de 30 mg une fois par jour ou de 45 mg une fois par jour n'a pas montré de différence significative dans le taux d'événements indésirables survenus pendant le traitement

(TEAE), de maux de tête et de TEAE conduisant à un arrêt définitif par rapport au placebo. Le fézolinetant s'avère être un remède efficace et bien toléré pour les femmes ménopausées souffrant de VMS. Notamment, la dose quotidienne de 45 mg sur 12 semaines a montré une efficacité significative. Néanmoins, de futurs essais approfondis sont nécessaires pour vérifier son innocuité, son efficacité et sa puissance relative à long terme par rapport aux traitements alternatifs du VMS comme l'hormonothérapie. (*Afr J Reprod Health* 2024; 28 [3]: 99-113).

Mots-clés: Ménopause, symptômes vasomoteurs, fézolinetant, méta-analyse, sécurité

Introduction

Menopause is a physiological transition that occurs when a woman's reproductive years come to an end¹. This phase is characterized by concomitant physiological and hormonal alterations that may give rise to a range of symptoms, including vasomotor symptoms (VMSs), such as night sweats and hot flashes^{2,3}. VMSs are prevalent among women undergoing menopause, with an estimated incidence rate of up to 80%^{4,5}. However, the prevalence of VMSs among menopausal women is well-established, the optimal treatment for these symptoms remains debatable within the scientific community⁶.

For numerous years, hormone therapy (HT) has stood out as the most efficacious treatment for VMSs. Nonetheless, the employment of this intervention has decreased owing to the heightened susceptibility to breast cancer, stroke, and cardiovascular disease linked to its usage^{7,8}. Selective serotonin reuptake inhibitors (SSRIs), gabapentinoids, and serotonin-norepinephrine reuptake inhibitors (SNRIs) are non-hormonal treatment options for VMSs. However, these options may be associated with side effects such as fatigue, queasiness, and vertigo^{9,10}.

Fezolinetant, another newly developed treatment for menopausal VMSs, works as an NK3R antagonist. The hypothalamus, which expresses NK3R, plays a pivotal role in controlling thermoregulatory responses and vasomotor sensitivity during menopause^{11,12}. Fezolinetant reported to reduce the incidence and severity of VMSs by suppressing the function of neurokinin B (NKB)^{13,14}. The hypothalamic NKB/NK3R pathway is theorized to be involved in Fezolinetant's therapeutic efficacy and vital in controlling the body's temperature regulation during menopause¹⁵. Fezolinetant targets the neuroendocrine processes that contribute to the occurrence of VMSs, as opposed to the neurotransmitter activity that SSRIs and SNRIs target^{16,17}.

In a randomized controlled trial (RCT), the frequency of moderate to severe hot flashes decreased more with Fezolinetant than with a placebo¹⁸. In another phase 2b RCT, VMSs were significantly decreased with Fezolinetant compared to placebo¹⁹. Fezolinetant was well-tolerated since no serious side effects were observed in both trials. Hence, multiple trials were published with some side effects and different doses and regimens. Also, they have assessed the drug efficacy through various outcomes measured at different time points. Therefore, our meta-analysis aimed to assess the effectiveness and safety of different oral dosages of Fezolinetant after multiple intervals for the treatment of VMSs associated with menopause, pooling the published RCTs data in order to synthesize stronger evidence.

Methods

Cochrane Handbook for Systematic Reviews and Interventions²⁰ and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards²¹ were adhered to throughout this meta-analysis.

Search strategy

Electronic databases, including Embase, PubMed, Web of Science (WOS), SCOPUS, and Cochrane Library, were searched with the use of keywords and MeSH phrases as follows: ((Fezolinetant OR ESN364) AND ("Postmenopausal Period" OR "Period, Postmenopausal" OR "Post-Menopause" OR "Post Menopause" OR "Post-Menopauses" OR "Post-menopausal Period" OR "Period, Postmenopausal" OR "Post menopausal" OR "Menopausal period" OR "Period after menopause" OR "menopause")). English-language studies published till May 2023 were the only considered articles. Two separate reviewers examined the titles and abstracts of the publications to determine the relevancy. Then, we assessed the full texts of the relevant publications to decide on the final inclusion.

RCTs were included if all of the following criteria were met: (1) patients: postmenopausal women with vasomotor symptoms; (2) Intervention and comparator: Fezolinetant with a placebo; (3) Outcomes: efficacy- and safety-related outcomes. Non-randomized studies were ruled out. If the two reviewers disagreed, it was addressed and resolved by mutual agreement.

Data extraction and study outcomes

Using a preformulated data extraction form, two reviewers extracted data from the included studies independently. The following data were extracted: study design, sample size, patient VMSs details, participant characteristics, doses and follow-up length, conclusion reported, and adverse events. Disagreements between the two reviewers were settled by discussion and consensus. If required, a third reviewer was engaged for arbitration. The study outcomes included changes in the severity and frequency of moderate to severe VMSs per 24 hours and Menopause-Specific Quality of Life (MENQOL) after 4 and 12 weeks of therapy²².

Quality assessment

The Risk of Bias (ROB) tool, version 2, was used to assess the bias of the included studies in this meta-analysis²³. The tool evaluates five domains: bias caused by the following: randomization technique, alterations from planned interventions, missing outcome data, outcome assessment, and the selection of the reported result. For each domain, the risk of bias was rated as low, moderate, or high. Two reviewers independently evaluated each study's bias risk. Any differences were addressed via group discussion.

Data analysis

Review Manager (5.4.1) was used to conduct the meta-analysis. The mean difference (MD) and 95 percent confidence interval (CI) were calculated for continuous outcomes. For binary outcomes, we calculated the risk ratio (RR) and 95% CI. The fixed-effect model was applied. The I2 statistic was used to examine heterogeneity. A subgroup analysis was undertaken to explore the impact of various Fezolinetant dosages.

Results

Study selection and characteristics

Five databases were searched to find 195 records, and 66 duplicates were removed. After looking over titles and abstracts of the rest 129 records, 113 were excluded. Sixteen reports were further looked at to assess if they were eligible. Two were excluded because they were not in English, three were not RCTs, three were meeting papers, and two did not have full texts. Finally, the meta-analysis included 3291 women from 6 articles reporting 5 RCTs^{18,19,24-27}. Figure 1

The average age of the included females in the studies was between 53.3 and 56.8 years. Most women who participated in the studies were White; the percentages ranged from 62.2% to 100%, and the average BMI went from 25.1 to 29.3 kg/m². The number of women who smoke at the time of the studies ranged from 7.0% to 24.4%. *Supplementary Table 1* and *Table 2* provide further data.

Risk of bias assessment

In domains 1-4, all studies were judged as having a low risk of bias (randomization - deviations from intended interventions - missing outcome data - measurement of outcomes). Still, domain 5 (selective reporting) was a concern because all of the study authors worked for Astellas Pharma or got a grant from them. Overall, there was a low chance of bias in the studies. *Figure 2*

Efficacy outcomes

1. Change in efficacy outcomes after 4 weeks

Change in the frequency of VMSs/24 hours.

According to an analysis of three RCTs, including 738 women, Fezolinetant at a dosage of 30 mg QD revealed a reduction in the frequency of VMSs/24 hours compared to placebo after four weeks [MD = -1.89 (-2.45, -1.32), $P < 0.00001$]. Also, Results from 2 RCTs including 331 female participants showed that 45 mg QD of Fezolinetant significantly reduced the frequency of VMSs/24 hours compared to placebo after 4 weeks [MD = -2.29 (-2.89, -1.69), $P < 0.00001$]. The data in both analyses showed homogeneity, with P-values of 0.89 and 0.44 and 0 I2 values, respectively. *Figure 3*

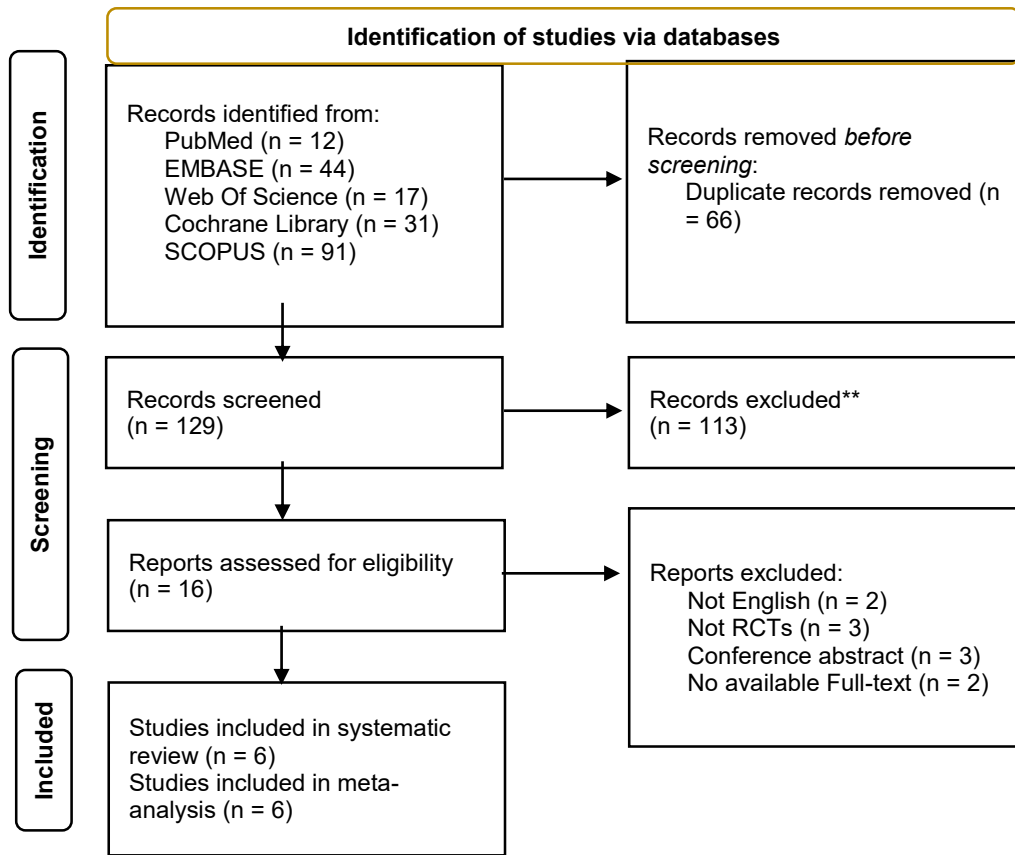


Figure 1: PRISMA flow diagram

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Depypere et al. 2019	+	+	+	+	-	+
	Fraser et al. 2020	+	+	+	+	-	+
	Johnson et al. 2023	+	+	+	+	-	+
	Lederman et al. 2023	+	+	+	+	-	+
	Neal-Perry et al. 2023	+	+	+	+	-	+
	Santoro et al. 2020	+	+	+	+	-	+

Domains:
 D1: Bias arising from the randomization process.
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing outcome data.
 D4: Bias in measurement of the outcome.
 D5: Bias in selection of the reported result.

Judgement
 - Some concerns
 + Low

Figure 2: Risk of bias summary

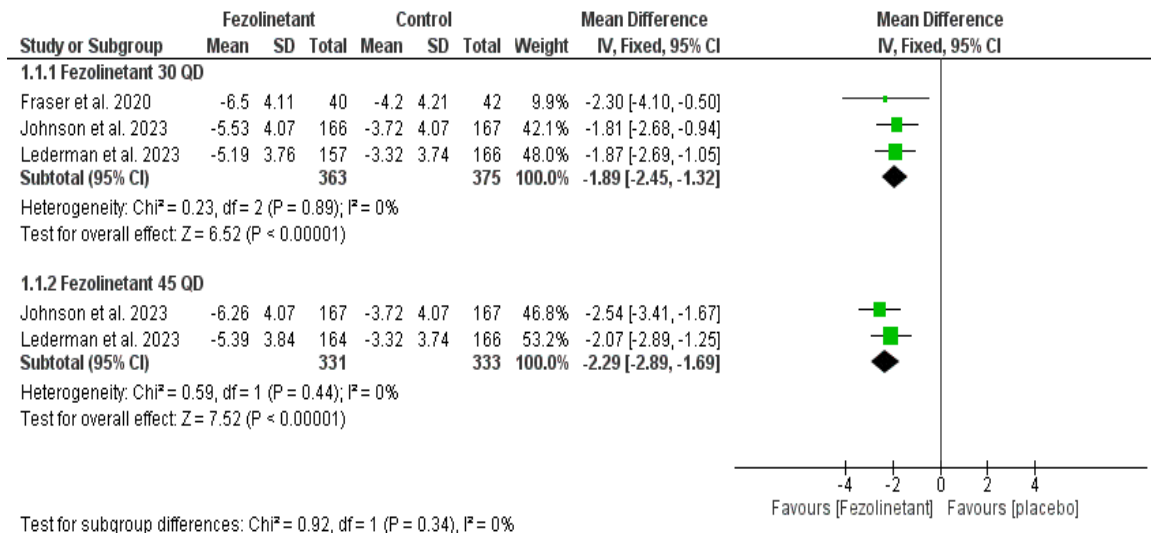
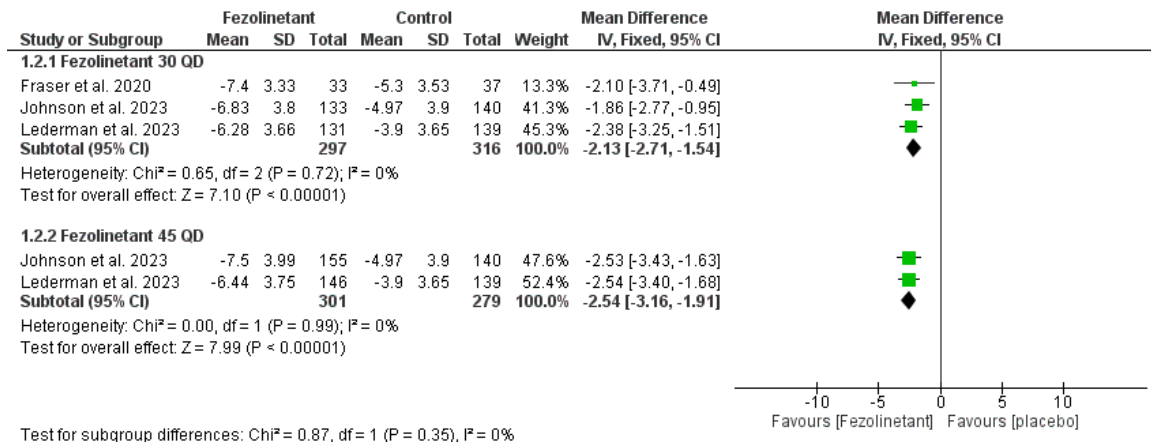


Figure 3: Change from baseline in the frequency of VMSs/24 hours after 4 weeks



Supplementary Figure 1: Change from baseline in the frequency of VMSs/24 hours after 12 weeks

Change in the severity of VMSs/24 hours.

In three RCTs involving 738 women, a daily dose of Fezolinetant at 30 mg significantly reduced the severity of VMSs/24 hours compared to placebo after 4 weeks [MD = -0.16 (-0.25, -0.08), P = 0.0002]. Similarly, in 2 RCTs involving a total of 331 women, daily 45 mg dose of fezolinetant significantly reduced the severity of VMSs/24 hours compared to placebo after 4 weeks [MD = -0.23 (-0.32, -0.14), P < 0.00001]. Both analyses demonstrated homogeneity, with P-values of 0.51 and 0.27, and I² values of 0 and 17%, respectively. *Figure 4*

Change from baseline in MENQOL total score.

Daily 30 mg dose of Fezolinetant was found to significantly reduce the MENQOL total score

compared to placebo in three randomized controlled trials involving 738 women [MD = -0.45 (-0.63, -0.27), P < 0.00001]. A similar effect was observed in two RCTs involving a total of 664 women with Fezolinetant administered at a daily dose of 45 mg [MD = -0.57 (-0.76, -0.39), P < 0.00001]. Both analyses revealed homogeneous data with P-values of 0.69 and 0.87, and 0 I² values, respectively. *Figure 5*

2. Change in efficacy outcomes after 12 weeks.

Change in the frequency of VMSs/24 hours.

After 12 weeks, Fezolinetant at a daily dose of 30 mg QD significantly reduced the frequency of VMSs/24 hours compared to placebo in three RCTs that involved 613 women [MD = -2.13 (-2.71, -

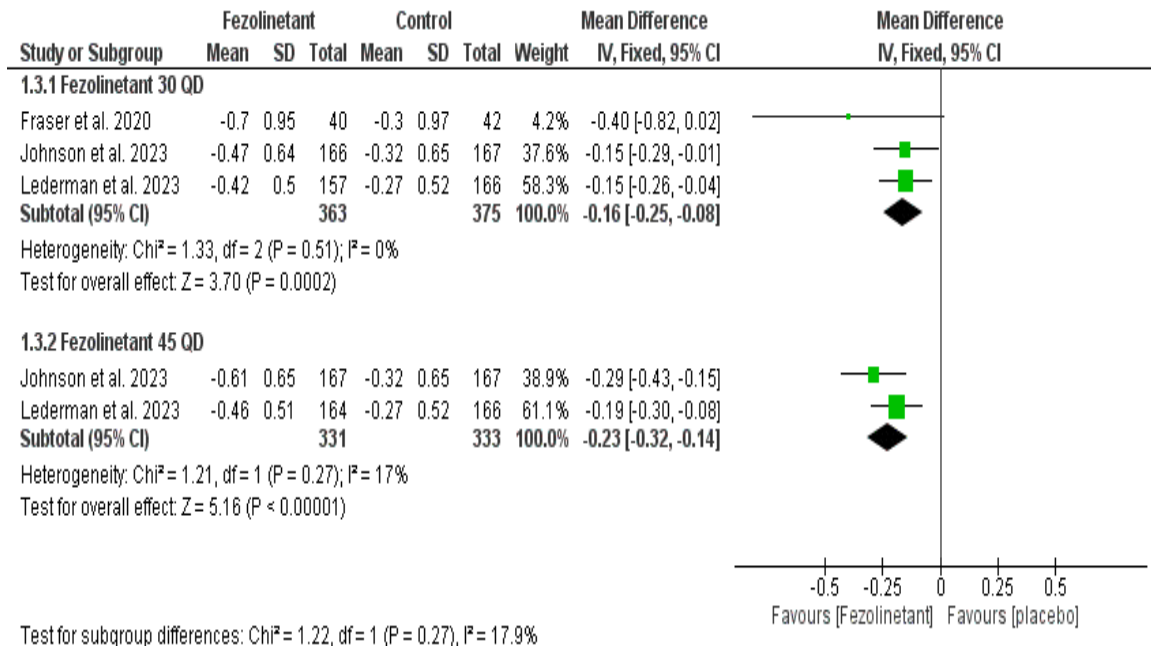


Figure 4: Change from baseline in the severity of VMSs/24 hours after 4 weeks

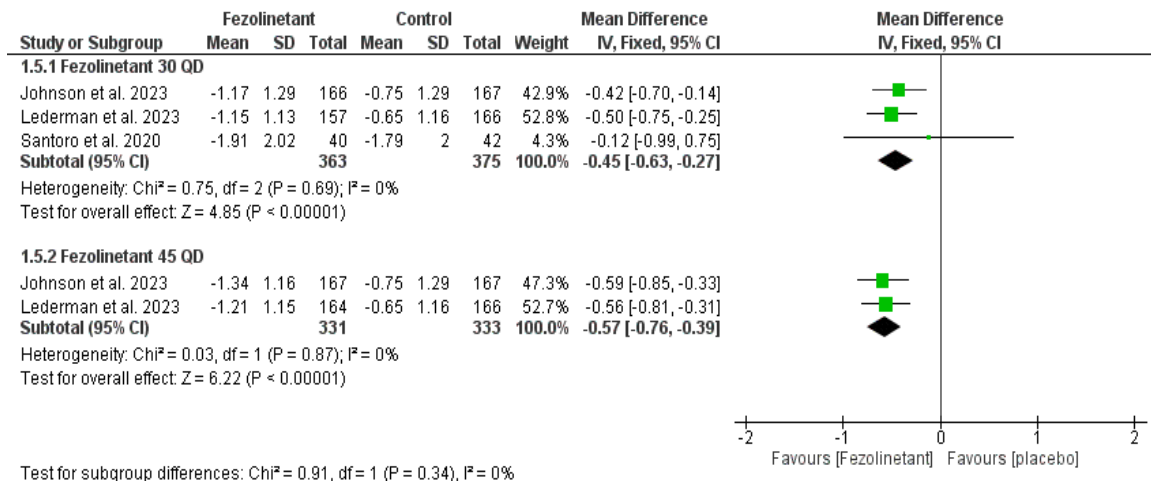
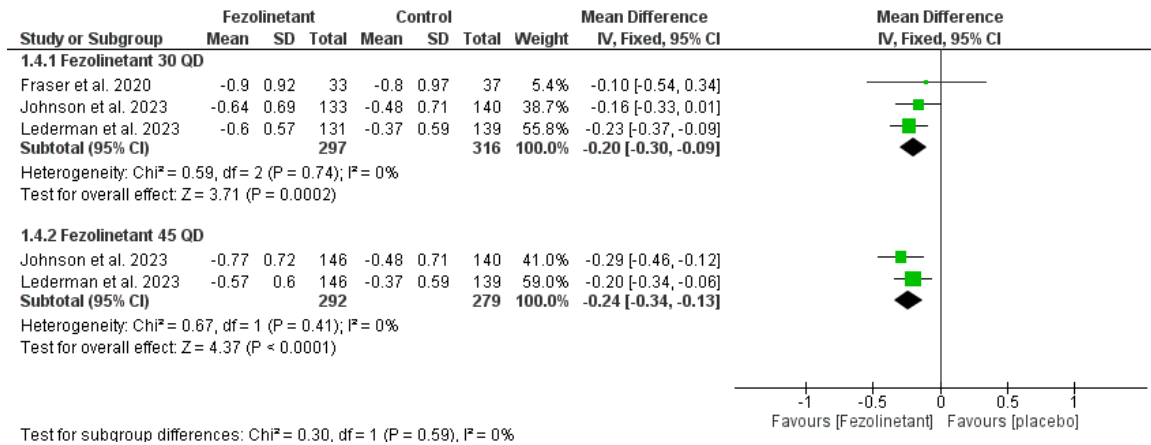


Figure 5: Change from baseline in MENQOL total score after 4 weeks

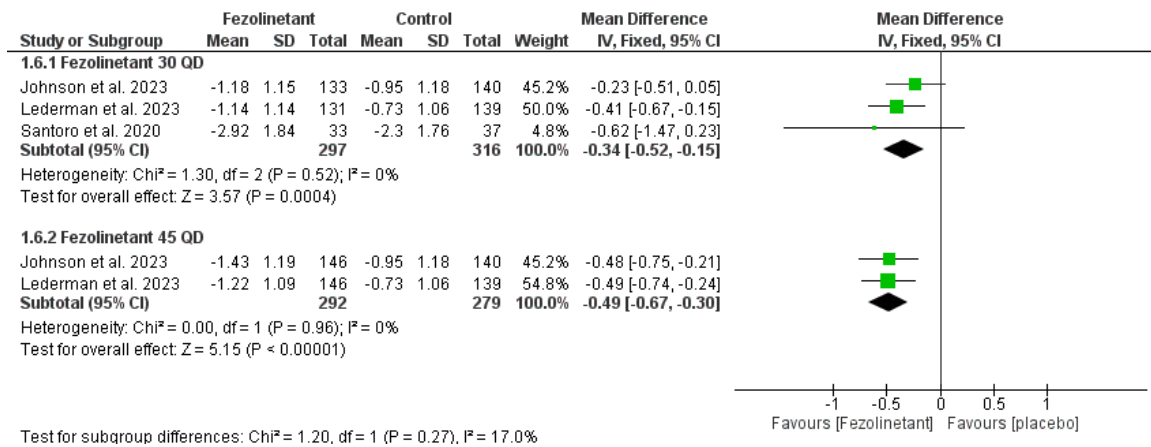
1.54), $P < 0.00001$]. Similarly, in two RCTs that involved a total of 580 women, daily 45 mg dose of Fezolinetant showed a significant reduction in the frequency of VMSs/24 hours compared to placebo after 4 weeks [MD = -2.54 (-3.16, -1.91), $P < 0.00001$]. The data in both analyses exhibited homogeneity, as indicated by the P-values of 0.72 and 0.99, and 0 I² values, respectively. *Supplementary Figure 1*

Change in the severity of VMS/24 hours.

In three RCTs involving 613 women, a daily dose of Fezolinetant at 30 mg significantly reduced the severity of VMSs/24 hours compared to placebo after 4 weeks [MD = -0.2 (-0.3, -0.09), $P = 0.0004$]. Similarly, in two RCTs involving a total of 571 women, daily 45 mg dose of Fezolinetant significantly decreased the severity of VMSs/24 hours compared to placebo after 4 weeks [MD = -



Supplementary Figure 2: Change from baseline in the severity of VMSs/24 hours after 12 weeks



Supplementary Figure 3: Change from baseline in MENQOL total score after 12 weeks

0.24 (-0.34, -0.13), P < 0.00001]. Both analyses demonstrated homogeneity of the data, with P-values of 0.74 and 0.41, and I² values of 0, respectively. **Supplementary Figure 2**

Change from baseline in MENQOL total score.

Fezolinetant, administered at 30 mg daily for 4 weeks, significantly reduced the MENQOL total score compared to placebo in three RCTs involving 613 weeks [MD = -0.34 (-0.52, -0.15), P = 0.0004]. Similarly, in two RCTs involving a total of 571 women, Fezolinetant at a daily dose of 45 mg also significantly decreased MENQOL total score compared to placebo after 4 weeks [MD = -0.49 (-0.67, -0.3), P < 0.00001]. Both analyses indicated homogeneity of the data, with P-values of 0.52 and 0.96, and I² values of 0, respectively. **Supplementary Figure 3**

Safety outcomes

Treatment-emergent adverse events (TEAE).

There was insignificant difference observed in the rate of TEAE between Fezolinetant and placebo at doses of 90 mg BID, 30 QD, or 45 QD, as follows: [RR = 0.86 (0.68, 1.09), P = 0.22], [RR = 1.05 (0.97, 1.13), P = 0.22], and [RR = 1 (0.93, 1.09), P = 0.9], respectively. All three analyses revealed homogeneity of the data, with P-values of 0.87, 0.21, and 0.76, and I² values of 0, 34%, and 0, respectively. **Supplementary Figure 4**

TEAEs leading to permanent discontinuation.

There was insignificant difference in the rate of TEAE leading to permanent drug discontinuation between Fezolinetant and placebo at doses of 90 mg BID, 30 QD, or 45 QD, with the following risk ratios and 95% confidence intervals: [RR = 3.65 (0.62,

Supplementary Table 1: Summary of the included studies

Study ID	Site	Study registration	Definition of menopause	Episodes of moderate/severe VMSs	Fezolinetant Doses	Primary outcomes	Follow-up	Conclusion
Depypere et al. 2019	Belgium	EudraCT (2015-002578-20)	The definition was based on various criteria, including spontaneous amenorrhea for 12 consecutive months, spontaneous amenorrhea for 6 months with biochemical evidence of menopause (FSH levels above 40 IU/L), spontaneous amenorrhea for 3 months with FSH levels above 40 IU/L and estradiol levels below 0.21 nmol/L, or bilateral oophorectomy performed at least 6 weeks before screening.	≥7 episodes of moderate/severe VMSs (per day over a period of 7 consecutive days)	90 mg BID	Change from baseline to week 12 in total VMS	12 weeks	“Fezolinetant had demonstrated a rapid and significant reduction of moderate-to-severe VMS, indicating its potential as an effective nonhormonal treatment option for menopausal women.”
Fraser et al. 2020	US	NCT03192176	Menopause was defined as spontaneous amenorrhea for 12 consecutive months, spontaneous amenorrhea for 6 months with biochemical criteria of menopause (FSH > 40 IU/L), or spontaneous amenorrhea for 3 months with FSH > 40 IU/L and estradiol (E2) < 0.21 nmol/L, or bilateral oophorectomy 6 weeks prior to screening.	≥50 moderate/severe VMS episodes per week based on seven consecutive days of VMS recordings from any point during the 35-day	15, 30, 60, or 90 mg BID, or 30, 60, or 120 mg QD	Reduction in moderate/severe VMS frequency and severity	12 weeks	“Fezolinetant was found to be effective and well-tolerated in reducing moderate-to-severe VMS in a rapid manner.”
Johnson et al. 2023	US, Canada, Czechia, Latvia, Poland, Spain, and the UK	NCT04003142	Menopause was defined as spontaneous amenorrhea for at least 12 consecutive months, spontaneous amenorrhea for at least 6 months with biochemical confirmation of menopause (FSH > 40 IU/L), or bilateral oophorectomy at least 6 weeks prior to the screening visit (with or without hysterectomy).	A minimum average of 7 moderate-to-severe VMS/day	30 or 45 mg QD	Reduction in moderate/severe VMS frequency and severity	12 weeks + 40 weeks extension	“The administration of fezolinetant at daily doses of 30 and 45 mg demonstrated efficacy and safety in alleviating moderate-to-severe VMS in menopausal women.”

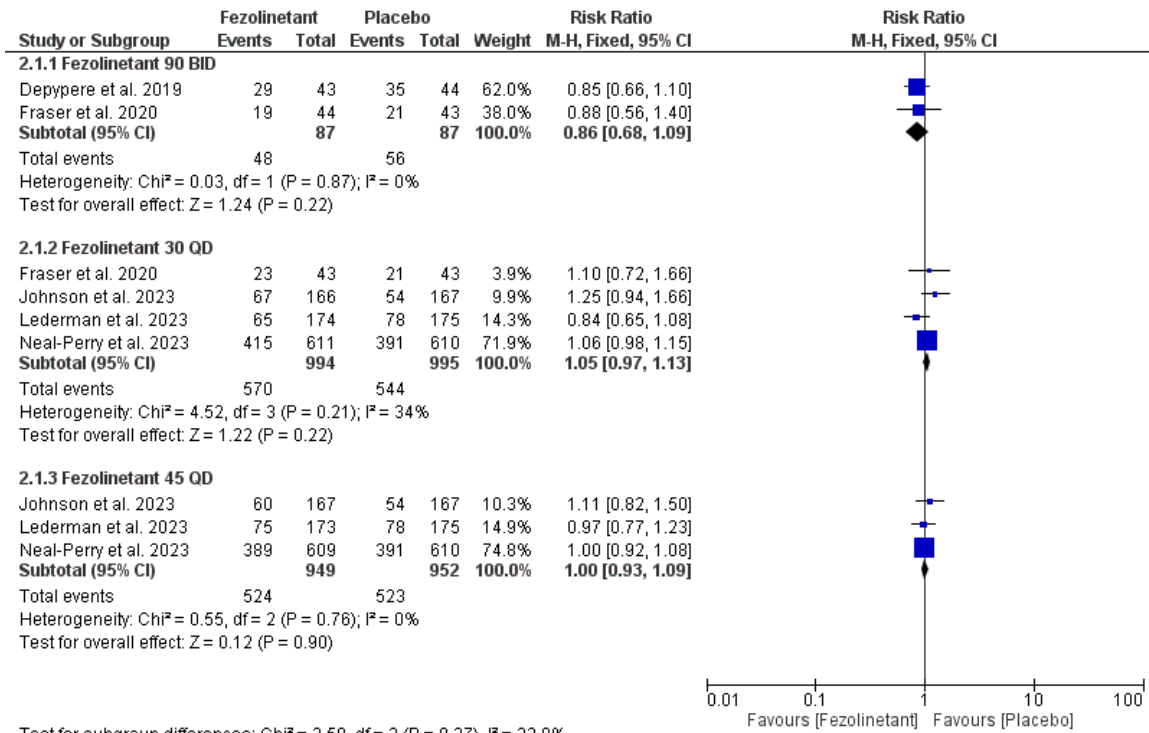
Author	Country	Study ID	Menopause Definition	VMS (per day)	Dose	Outcome	Duration	Conclusion
Lederman et al. 2023	USA, Canada, Czech Republic, Hungary, Poland, Spain, and the UK	NCT04003155	Menopause was defined as (FSH >40 IU/L) or bilateral oophorectomy at least 6 weeks prior to the screening visit, with or without hysterectomy.	≥7 episodes of moderate/severe VMSs	30 or 45 mg QD	Reduction in moderate/severe VMS frequency and severity	12 weeks + 40 weeks extension	“The data suggested that fezolinetant was a viable non-hormonal option for the treatment of vasomotor symptoms in menopausal women.”
Neal-Perry et al. 2023	US, Canada, Czechia, Latvia, Poland, Spain, Ukraine, and the UK	NCT04003389	Menopause was defined as spontaneous amenorrhea lasting 12 or more consecutive months, spontaneous amenorrhea lasting 6 or more months with a FSH level higher than 40 IU/L, or bilateral oophorectomy that occurred 6 or more weeks before the screening visit.	NR	30 or 45 mg QD	Safety outcomes	52 weeks	“The results of this study provided confirmation of the safety and tolerability of fezolinetant over a period of 52 weeks and supported its further development.”
Santoro et al. 2020	US	NCT03192176	Menopause was defined as spontaneous amenorrhea for 12 consecutive months, spontaneous amenorrhea for 6 months with biochemical criteria of menopause (FSH > 40 IU/L), or spontaneous amenorrhea for 3 months with FSH > 40 IU/L and estradiol (E2) < 0.21 nmol/L, or bilateral oophorectomy 6 weeks prior to screening.	≥50 moderate/severe VMS episodes per week based on seven consecutive days of VMS recordings from any point during the 35-day	15, 30, 60, or 90 mg BID, or 30, 60, or 120 mg QD	Quality of life	12 weeks	“Oral fezolinetant resulted in higher responder rates compared to placebo and led to greater improvements in quality of life (QoL) and another patient-reported outcome (PRO) measures.”

Abbreviations: FSH: Follicle-stimulating hormone, VMS: vasomotor symptoms NR: not reported, BID: twice per day, QD: Once per day, US: United States, UK: United Kingdom

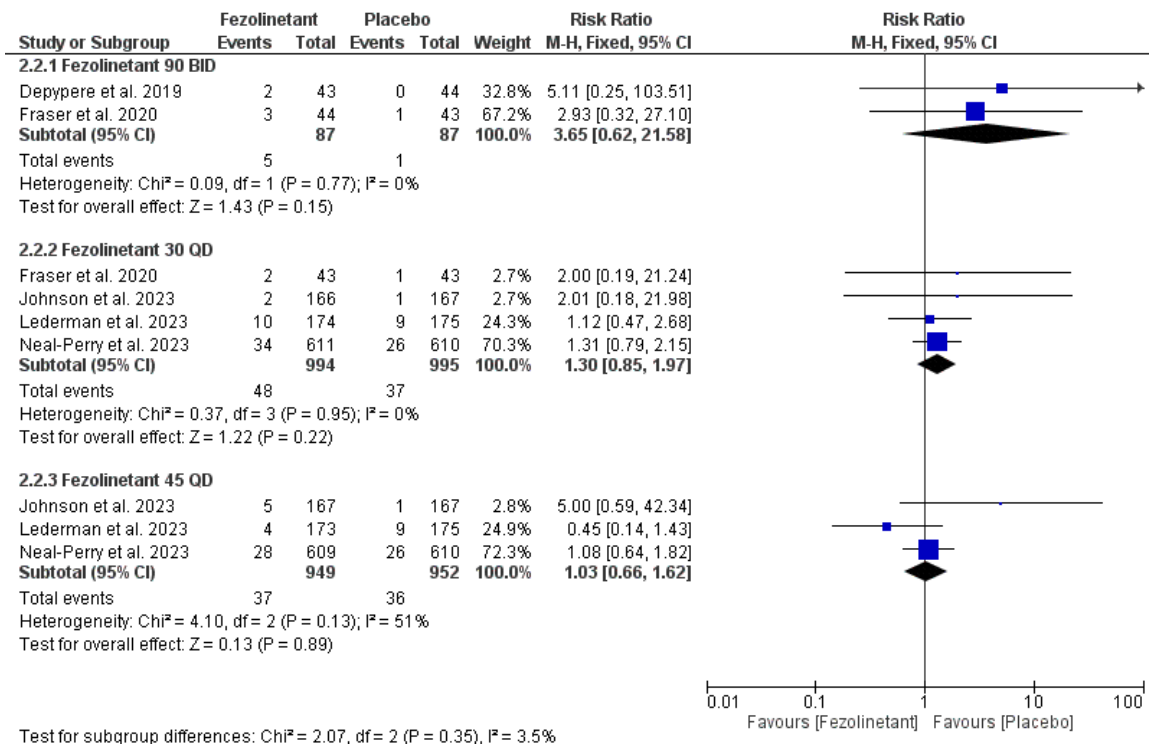
Supplementary Table 2: Baseline characteristics of included studies

Study ID	Study arms	Sample	Age, years, mean (SD)	Race, White, n (%)	BMI, mean kg/m ² , mean (SD)	Current smoker, n (%)	Baseline Frequency/24 h of moderate/severe VMS, mean (SD)	Baseline Severity/24 h of moderate/severe VMS, mean (SD)	Previously used hormone therapy, n (%)
Depypere et al. 2019	90 mg BID	43	53.3 (4.03)	42 (97.7)	25.1 (4.71)*	NR	NR	NR	0
	Placebo	44	53.7 (4.25)	44 (100)	26.5 (6.15)*	NR	NR	NR	0
Fraser et al. 2020 and Santoro et al. 2020	15 mg BID	45	53.7 (5.0)	37 (82.2)	29.3 (4.3)	10 (22.2)	11.1 (7.1)	2.5 (0.3)	1 (2.2)
	30 mg BID	43	53.9 (3.8)	31 (72.1)	28.3 (4.0)	5 (11.6)	9.9 (4.6)	2.4 (0.3)	1 (2.3)
	60 mg BID	45	54.6 (5.0)	28 (62.2)	29.1 (5.2)	8 (17.8)	9.5 (4.0)	2.5 (0.3)	0
	90 mg BID	44	54.9 (4.0)	36 (81.8)	27.3 (4.6)	4 (9.1)	9.3 (3.6)	2.4 (0.3)	3 (6.8)
	30 mg QD	43	52.7 (3.8)	31 (72.1)	28.8 (4.0)	3 (7.0)	11.2 (6.4)	2.4 (0.3)	2 (4.7)
	60 mg QD	45	55.0 (4.9)	34 (75.6)	28.3 (4.4)	11 (24.4)	9.4 (2.7)	2.4 (0.3)	3 (6.7)
	120 mg QD	44	56.8 (4.4)	30 (68.2)	28.8 (4.9)	3 (6.8)	9.7 (3.7)	2.5 (0.3)	1 (2.3)
Johnson et al. 2023	Placebo	43	54.8 (5.5)	30 (69.8)	27.3 (4.8)	3 (7.0)	9.7 (3.5)	2.5 (0.3)	4 (9.3)
	30 mg QD	166	53.9 (4.9)	131 (78.9)	27.94 (18.1-37.6)*	34 (20.5)	11.23 (4.9)	2.4 (0.3)	0
	45 mg QD	167	54.3 (5.4)	132 (79.0)	27.91 (18.0-37.5)*	34 (20.4)	11.79 (8.3)	2.4 (0.3)	0
Lederman et al. 2023	Placebo	167	54.7 (4.6)	134 (80.2)	28.16 (18.6-38.0)*	35 (21.0)	11.59 (5.0)	2.4 (0.3)	0
	30 mg QD	174	54.2 (4.9)	148 (86)	28.1 (4.8)	22 (13)	10.8 (5.1)	2.4 (0.3)	31 (18)
	45 mg QD	173	54.2 (5.1)	141 (82)	28.3 (4.4)	22 (13)	10.6 (4.1)	2.4 (0.4)	30 (18)
Neal-Perry et al. 2023	Placebo	175	54.7 (4.8)	142 (81)	28.2 (4.3)	22 (13)	10.5 (3.4)	2.4 (0.4)	33 (19)
	30 mg QD	611	54.7 (4.7)	479 (78.5)	28.4 (4.5)	116 (19.0)	NR	NR	98 (16.4)
	45 mg QD	609	54.7 (4.8)	479 (78.8)	28.4 (4.7)	116 (19.0)	NR	NR	91 (15.3)
	Placebo	610	54.9 (4.8)	502 (82.3)	28.2 (4.6)	117 (19.2)	NR	NR	115 (19.4)

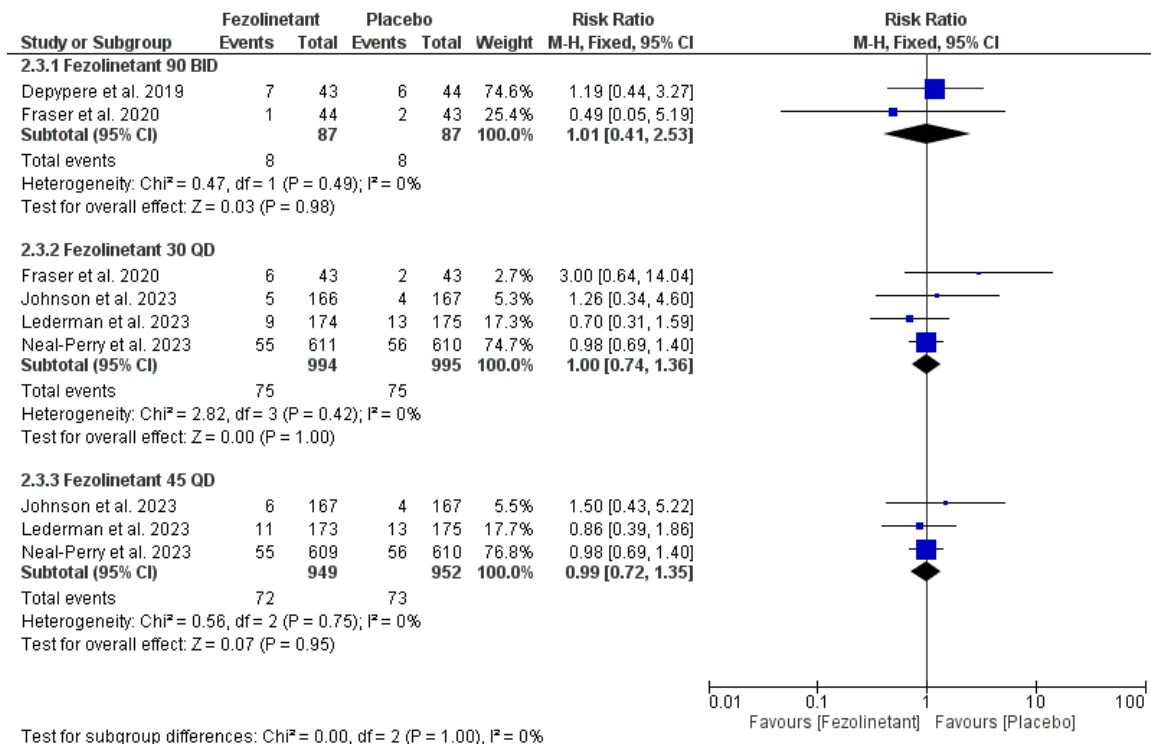
Abbreviations: BMI: body mass index, VMS: vasomotor symptoms NR: not reported, BID: twice per day, QD: Once per day. (*) sign indicates ranges.



Supplementary Figure 4: Incidence of treatment-emergent adverse events (TEAE)



Supplementary Figure 5: Incidence of TEAEs leading to permanent discontinuation



Supplementary Figure 6: Incidence of headache

21.58), $P = 0.15$], [RR = 1.3 (0.85, 1.97), $P = 0.22$], and [RR = 1.03 (0.66, 1.62), $P = 0.89$], respectively. All three analyses demonstrated homogeneity of the data, with P-values of 0.77, 0.95, and 0.13, and I² values of 0, 0, and 51%, respectively. *Supplementary Figure 5*

Headache

There was insignificant difference in the rate of headache between Fezolinetant and placebo at doses of 90 mg BID, 30 QD, or 45 QD, with the following risk ratios and 95% confidence intervals: [RR = 1.01 (0.41, 2.53), $P = 0.98$], [RR = 1 (0.74, 1.36), $P = 1$], and [RR = 0.99 (0.72, 1.35), $P = 0.95$], respectively. All three analyses showed homogeneous data, with P-values of 0.49, 0.42 and 0.75, and I² values of 0. *Supplementary Figure 6*.

Discussion

This is the first systematic review and meta-analysis to our knowledge to evaluate the efficacy of Fezolinetant in reducing the frequency and severity of VMSs and improving MENQOL in women going through menopause. The analysis included six RCTs involving 3291 women. Results indicated that

compared to placebo, Fezolinetant increased MENQOL overall score and decreased frequency of moderate to severe VMSs when taken at a daily dosage of 30 or 45 mg for 4 weeks or 12 weeks. The data were homogeneous in all analyses.

A new family of medications called selective neurokinin 3 receptor (NK3R) antagonists has showed promise in treating menopausal symptoms including hot flashes without using hormones^{28,29}. These drugs target the neurokinin 3 receptor, which is involved in regulating the release of luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) from the pituitary gland³⁰. Inhibiting NK3R, these medications decrease GnRH and LH levels, which in turn decreases ovarian output of estrogen and progesterone, hence alleviating menopausal symptoms like hot flashes³¹. Pavinetant and Fezolinetant have shown efficacy in reducing hot flashes; Fezolinetant appears to have a more favorable safety profile^{32,33}. The most commonly reported side effects were mild to moderate in intensity, including headache, fatigue, and nausea. Other reported side effects were diarrhea, vomiting, dizziness, and abnormal liver function tests. However, no serious adverse events related to

Pavinetant have been reported in the trials conducted so far²⁸.

Fezolinetant may provide an alternative to HT for certain women who would rather not utilize hormones because of personal preference or having medical history such as a history of breast cancer as Fezolinetant is not associated with an increased danger of HT-related health problems such as breast cancer, endometrial cancer, or cardiovascular disease³⁴. Also, SSRIs and SNRIs may have limited effectiveness in treating VMSs and may even be associated with certain adverse effects. A systematic review and meta-analysis of RCTs found that while SSRIs and SNRIs were associated with a modest reduction in VMS frequency, they were not significantly better than placebo in reducing VMS severity or improving the quality of life³⁵. Additionally, these medications may be associated with side effects such as sexual dysfunction, nausea, and weight gain, which may further worsen the quality of life for some women³⁶.

The present study offers several notable strengths. Firstly, this is the first meta-analysis to evaluate Fezolinetant vs placebo for the treatment of VMSs in women beyond menopause. Secondly, the study employed a comprehensive search strategy to identify all relevant studies in multiple databases, thus increasing the likelihood of including all pertinent studies. Thirdly, the inclusion of a large sample size of 3291 women in the meta-analysis provides a substantial sample to produce valid results. Also, our study reports homogeneous data, indicating consistency among the included studies in terms of their results and minimizing the likelihood of heterogeneity bias. Additionally, the data were analyzed after 4 and 12 weeks of treatment and for three different doses of Fezolinetant, with consistent results, thus enhancing the evidence base. Finally, most domains of the included studies were rated as having a low risk of bias, enhancing the findings' validity.

The findings of this meta-analysis should be interpreted with caution as well due to some limitations. Firstly, the limited diversity of participants, with the majority being White, may restrict the generalizability of the findings to other racial/ethnic groups. Secondly, the short duration of treatment in all included studies may not be sufficient to assess the long-term efficacy and safety of Fezolinetant. Finally, there is a risk of bias as most

of the included studies' authors were either employed at Astellas Pharma or received a grant from the company, which may lead to selective reporting bias.

In conclusion, the present study provides evidence that Fezolinetant is an effective and well tolerated treatment option for women with menopause experiencing VMSs. The efficacy of the drug is more prominent with the larger dose (45 mg daily) for the longer follow-up period (12 weeks). These findings may be used to inform clinical practice and improve the quality of life for women with menopause. However, larger future trials with more varied populations are required to assess Fezolinetant's especially long-term safety and effectiveness. Additionally, studies that compare the effectiveness of different doses of Fezolinetant with other treatments for VMSs, such as hormone therapy, would be useful for guiding clinical decision-making.

Conclusions

Fezolinetant is an effective and well tolerated treatment option for women with menopause experiencing VMSs. The efficacy of the drug is more prominent with the larger dose (45 mg daily) for the longer follow-up period (12 weeks). However, larger future trials with longer follow-up periods are required to assess Fezolinetant's long-term safety and effectiveness and to compare between different doses with other treatments available for VMSs, such as hormone therapy.

Conflict of interest

The authors declare no conflicts of interest regarding the publication of this systematic review and meta-analysis.

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Ethical considerations

This systematic review and meta-analysis involved the analysis of previously published studies and did not directly involve human or animal subjects.

Ethical approval was not required for this research. However, the authors followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to ensure the ethical conduct and transparent reporting of this study.

Author contributions

The contributions of each author are as follows: AME, HAF, MH, MMA, IAI, HKM and MAA contributed to the study design, data collection, analysis, and interpretation, and wrote the manuscript. HHA, AAE, AEB, MHA, NHA, IHM, RAM, and AAA assisted with data analysis and interpretation, and critically reviewed and revised the manuscript. FAA, EMA, NIA, ADA, EAA, EAI, SYA, RSA, and PB contributed to the literature search, and data extraction, and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

References

- McCarthy M and Raval AP. The peri-menopause in a woman's life: a systemic inflammatory phase that enables later neurodegenerative disease. Vol. 17, Journal of Neuroinflammation. BioMed Central Ltd; 2020.
- Pachman DR, Jones JM and Loprinzi CL. Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions [Internet]. International Journal of Women's Health. 2010. Available from: <https://www.dovepress.com/>
- Blümel JE, Chedraui P, Barón, G, Belzares E, Bencosme A, Calle A, Danckers L, Espinoza MT, Flores D, Gómez G, Hernández-Bueno JA, Izaguirre H, León-León P, Lima S, Mezones-Holguín E, Monterrosa Á, Mostajo D, Navarro D, Ojeda E, Onatra W, Royer M, Soto E, Tserotas K and Vallejo S. A large multinational study of vasomotor symptom prevalence, duration, and impact on quality of life in middle-aged women. Menopause, 2011a; 18:778–785.
- Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, Powell L, Sternfeld B and Matthews K. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health. 2006 Jul;96(7):1226-35. doi: 10.2105/AJPH.2005.066936. Epub 2006 May 30. PMID: 16735636; PMCID: PMC1483882.
- Woods NF and Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. Am J Med. 2005 Dec;118(12):14–24.
- Umland EM and Falconieri L. Treatment options for vasomotor symptoms in menopause: Focus on desvenlafaxine. Vol. 4, International Journal of Women's Health. Dove Medical Press Ltd; 2012. p. 305–19.
- Mehta J, Kling JM and Manson JAE. Risks, Benefits, and Treatment Modalities of Menopausal Hormone Therapy: Current Concepts. Vol. 12, Frontiers in Endocrinology. Frontiers Media S.A.; 2021.
- Khan SJ, Kapoor E, Faubion SS, Kling JM. Vasomotor Symptoms During Menopause: A Practical Guide on Current Treatments and Future Perspectives. Vol. 15, International Journal of Women's Health. Dove Medical Press Ltd; 2023. p. 273–87.
- Azizi M, Khani S, Kamali M and Elyasi F. The Efficacy and Safety of Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors in the Treatment of Menopausal Hot Flashes: A Systematic Review of Clinical Trials. Vol. 47, Iranian Journal of Medical Sciences. Shiraz University of Medical Sciences; 2022. p. 173–93.
- Stubbs C, Mattingly L, Crawford SA, Wickersham EA, Brockhaus JL and McCarthy LH. Do SSRIs and SNRIs reduce the frequency and/or severity of hot flashes in menopausal women HHS Public Access Summary of the Issues. Vol. 110, J Okla State Med Assoc. 2017.
- Koysombat K, McGown P, Nyunt S, Abbara A and Dhillon WS. New advances in menopause symptom management. Best Pract Res Clin Endocrinol Metab. 2023 Apr;101774.
- Depypere H, Lademacher C, Siddiqui E and Fraser GL. Fezolinetant in the treatment of vasomotor symptoms associated with menopause. Expert Opin Investig Drugs. 2021 Jul 3;30(7):681–94.
- Press Release Astellas Provides Update on Fezolinetant New Drug Application in U.S [Internet]. Available from: <https://www.astellas.com/en>.
- Tahara A, Takamatsu H, Ohtake A, Tanaka-Amino K and Kaku S. Effects of neurokinin 3 receptor antagonist fezolinetant on hot flash-like symptoms in ovariectomized rats. Eur J Pharmacol. 2021 Aug;905:174207.
- Modi M and Dhillon WS. Neurokinin 3 Receptor Antagonism: A Novel Treatment for Menopausal Hot Flashes. Neuroendocrinology. 2019;109(3):242–8.
- Drewe J, Bucher KA and Zahner C. A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. Springerplus. 2015;4(1):1–29.
- Sahni S, Lobo-Romero A and Smith T. Contemporary Non-hormonal Therapies for the Management of Vasomotor Symptoms Associated with Menopause: A Literature Review. Eur Endocrinol. 2021;17(2):133.
- Lederman S, Ottery FD, Cano A, Santoro N, Shapiro M, Stute P, Thurston RC, English M, Franklin C, Lee M and Neal-Perry G. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. Lancet. 2023 Apr 1;401(10382):1091-1102. doi: 10.1016/S0140-6736(23)00085-5. Epub 2023 Mar 13. PMID: 36924778.
- Fraser GL, Lederman S, Waldbaum A, Kroll R, Santoro N, Lee M, Skillern L and Ramael S. A phase 2b,

- randomized, placebo-controlled, double-blind, dose-ranging study of the neurokinin 3 receptor antagonist fezolinetant for vasomotor symptoms associated with menopause. *Menopause*. 2020 Apr;27(4):382-392. doi: 10.1097/GME.0000000000001510. PMID: 32102086; PMCID: PMC7147405.
20. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP and Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019 Oct 3;10(10):ED000142. doi: 10.1002/14651858.ED000142. PMID: 31643080; PMCID: PMC10284251.
 21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009 Oct;62(10):e1-34. doi: 10.1016/j.jclinepi.2009.06.006. Epub 2009 Jul 23. PMID: 19631507.
 22. Radtke J V., Terhorst L and Cohen SM. The Menopause-Specific Quality of Life Questionnaire. *Menopause*. 2011 Mar;18(3):289–95.
 23. Sterne JAC, Savović J, Page MJ and Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF and Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019 Aug 28;366:14898. doi: 10.1136/bmj.14898. PMID: 31462531.
 24. Neal-Perry G, Cano A, Lederman S, Nappi RE, Santoro N, Wolfman W, English M, Franklin C, Valluri U and Ottery FD. Safety of Fezolinetant for Vasomotor Symptoms Associated With Menopause: A Randomized Controlled Trial. *Obstet Gynecol*. 2023 Apr 1;141(4):737-747. doi: 10.1097/AOG.0000000000005114. Epub 2023 Mar 9. PMID: 36897180; PMCID: PMC10026946.
 25. Lederman S, Ottery FD, Cano A, Santoro N, Shapiro M, Stute P, Thurston RC, English M, Franklin C, Lee M and Neal-Perry G. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomized controlled study. *Lancet*. 2023 Apr 1;401(10382):1091-1102. doi: 10.1016/S0140-6736(23)00085-5. Epub 2023 Mar 13. PMID: 36924778.
 26. Johnson KA, Martin N, Nappi RE, Neal-Perry G, Shapiro M, Stute P, Thurston RC, Wolfman W, English M, Franklin C, Lee M and Santoro N. Efficacy and Safety of Fezolinetant in Moderate to Severe Vasomotor Symptoms Associated with Menopause: A Phase 3 RCT. *J Clin Endocrinol Metab*. 2023 Jul 14;108(8):1981-1997. doi: 10.1210/clinem/dgad058. PMID: 36734148; PMCID: PMC10348473.
 27. Depypere H, Timmerman D, Donders G, Sieprath P, Ramael S, Combalbert J, Hoveyda HR and Fraser GL. Treatment of Menopausal Vasomotor Symptoms with Fezolinetant, a Neurokinin 3 Receptor Antagonist: A Phase 2a Trial. *J Clin Endocrinol Metab*. 2019 Dec 1;104(12):5893-5905. doi: 10.1210/jc.2019-00677. PMID: 31415087.
 28. Prague JK, Abbara A, Comminos AN, Jayasena CN, Higham CE, Adaway J, Keevil BG, Veldhuis JD and Dhillon WS. Neurokinin 3 Receptor Antagonists Do Not Increase FSH or Estradiol Secretion in Menopausal Women. *J Endocr Soc*. 2019 Nov 14;4(2):bvz009. doi: 10.1210/jendso/bvz009. PMID: 32318647; PMCID: PMC7159071.
 29. Prague JK, Roberts RE, Comminos AN, Clarke S, Jayasena CN, Nash Z, Doyle C, Papadopoulou DA, Bloom SR, Mohideen P, Panay N, Hunter MS, Veldhuis JD, Webber LC, Huson L and Dhillon WS. Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flashes: a phase 2, randomized, double-blind, placebo-controlled trial. *Lancet*. 2017 May 6;389(10081):1809-1820. doi: 10.1016/S0140-6736(17)30823-1. Epub 2017 Apr 3. PMID: 28385352; PMCID: PMC5439024.
 30. Skorupskaite K and Anderson RA. Hypothalamic neurokinin signalling and its application in reproductive medicine. *Pharmacol Ther*. 2022 Feb;230:107960.
 31. McCarthy MA, Dischino D, Maguire C, Leon S, Talbi R, Cheung E, Schteingart CD, Rivière PJM, Reed SD, Steiner RA and Victor M Navarro. Inhibiting Kiss1 Neurons With Kappa Opioid Receptor Agonists to Treat Polycystic Ovary Syndrome and Vasomotor Symptoms. *J Clin Endocrinol Metab*. 2022 Jan 1;107(1):e328–47.
 32. Menown SJ and Tello JA. Neurokinin 3 Receptor Antagonists Compared With Serotonin Norepinephrine Reuptake Inhibitors for Non-Hormonal Treatment of Menopausal Hot Flashes: A Systematic Qualitative Review. *Adv Ther*. 2021 Oct 12;38(10):5025–45.
 33. Modi M and Dhillon WS. Neurokinin 3 Receptor Antagonism: A Novel Treatment for Menopausal Hot Flashes. *Neuroendocrinology*. 2019;109(3):242–8.
 34. Fournier A, Mesrine S, Dossus L, Boutron-Ruault MC, Clavel-Chapelon F and Chabbert-Buffet N. Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort. *Breast Cancer Res Treat*. 2014 Jun 30;145(2):535–43.
 35. Shams T, Firwana B, Habib F, Alshahrani A, AlNouh B, Murad MH and Ferwana M. "SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials." *Journal of general internal medicine* 29 (2014): 204-213.
 36. Higgins A. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. *Drug Healthc Patient Saf*. 2010 Sep;141.