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EFFICACY AND SAFETY OF NON-HORMONAL NK- 3 RECEPTOR ANTAGONISTS FOR VASOMOTOR SYMPTOMS OF MENOPAUSE: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Vasomotor symptoms (VMS) affect up to 80% of menopausal women. Estrogen withdrawal-induced hyperactivity of hypothalamic KNDy neurons makes NK3 receptor antagonism a targeted non-hormonal therapeutic strategy.
Aim: To evaluate the efficacy, impact on sleep and quality of life, and safety (specifically liver function) of NK3 receptor antagonists for moderate-to-severe menopausal VMS.
Materials and methods: A PRISMA-guided systematic search across PubMed and Scopus (July 15, 2026) yielded 412 records, screened independently by five reviewers via Rayyan. Randomized controlled trials and cohort studies evaluating NK3 antagonists (fezolinetant, elinzanetant, pavinetant, GS1-144) versus placebo in peri-/postmenopausal women were included. Key outcomes were VMS frequency/severity, sleep (PROMIS SD), quality of life (MENQOL), and adverse events.
Results: NK3 antagonists significantly and rapidly reduced VMS frequency and severity versus placebo, with sustained efficacy up to 52 weeks. Subjective sleep quality and MENQOL scores consistently improved, including in breast cancer patients on endocrine therapy. Side effects were predominantly mild (gastrointestinal, neurological) with no endometrial risks. Asymptomatic, transient transaminase elevations (>3×ULN) occurred as the primary adverse event, resolving upon discontinuation.
Conclusion: NK3 receptor antagonists are a highly effective, non-hormonal treatment for moderate-to-severe VMS that substantially improve sleep and quality of life. Periodic liver function monitoring is recommended due to potential transient transaminase elevations.

KEYWORDS

Menopause, Vasomotor Symptoms, Hot Flashes, Neurokinin 3 Receptor Antagonists, Fezolinetant, Elinzanetant, Non-Hormonal Therapy, Quality Of Life, Sleep Quality, Hepatic Safety

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1. Introduction

Menopause is a physiological stage in a woman's life characterized by the permanent cessation of ovarian function and progressive decline in estrogen production. Although it represents a normal biological transition, menopause is frequently accompanied by symptoms that substantially impair physical, psychological, and social well-being. Vasomotor symptoms (VMS), including hot flashes and night sweats, are the hallmark manifestations of menopause and affect approximately 60–80% of women during the menopausal transition. Nearly one third of affected women experience symptoms of moderate or severe intensity that require medical intervention. Importantly, longitudinal studies have demonstrated that VMS often persist for several years after the final menstrual period, making them one of the leading causes of reduced quality of life among postmenopausal women [1–3].

The impact of VMS extends far beyond transient episodes of heat sensation. Frequent hot flashes and night sweats contribute to sleep fragmentation, chronic fatigue, impaired cognitive performance, mood disturbances, anxiety, and reduced health-related quality of life (HRQoL). Consequently, women with moderate to severe VMS frequently report impaired occupational functioning, decreased work productivity, and increased healthcare utilization. Considering that women currently spend nearly one-third of their lives in the postmenopausal period, effective management of menopausal symptoms has become an increasingly important public health priority [1–3].

Menopausal hormone therapy (MHT) remains the most effective treatment for vasomotor symptoms and is recommended as first-line therapy for eligible women. However, its use is limited by contraindications such as hormone-dependentmalignancies, active liver disease, thromboembolic disorders, and certain cardiovascular conditions. Furthermore, many women decline hormonal treatment because of personal preferences or concerns regarding long-term safety. These limitations have stimulated intensive research into novel non-hormonal therapeutic strategies capable of providing clinically meaningful symptom relief without directly influencing systemic estrogen concentrations [2,4].

Recent advances in neuroendocrinology have substantially improved the understanding of the pathophysiology of menopausal vasomotor symptoms. Current evidence indicates that estrogen deficiency leads to hypertrophy and hyperactivity of hypothalamic kisspeptin/neurokinin B/dynorphin (KNDy) neurons located within the arcuate nucleus. Increased neurokinin B release excessively activates neurokinin 3 (NK3) receptors, narrowing the thermoneutral zone and triggering exaggerated heat dissipation responses following even minimal fluctuations in core body temperature. These discoveries have fundamentally changed the understanding of VMS and established NK3 receptor antagonism as the first mechanism-based non-hormonal therapeutic approach targeting the underlying neurobiology of menopausal hot flashes rather than their downstream manifestations [5,6].

The clinical development of NK3 receptor antagonists has rapidly expanded over the past decade. Early proof-of-concept studies with MLE4901 first demonstrated that selective NK3 receptor blockade could rapidly reduce the frequency and severity of hot flashes, providing clinical validation of the KNDy neuron hypothesis. Subsequently, newer compounds with improved pharmacological profiles, including fezolinetant, elinzanetant, GS1-144, and pavinetant, were evaluated in phase II and phase III randomized clinical trials. Among these agents, fezolinetant became the first NK3 receptor antagonist approved for the treatment of moderate-to-severe vasomotor symptoms associated with menopause following the positive results of the SKYLIGHT clinical program. More recently, additional large-scale studies evaluating elinzanetant have further strengthened the evidence supporting neurokinin receptor antagonism as an effective non-hormonal therapeutic strategy for menopausal VMS [7–9].

Although the efficacy of individual NK3 receptor antagonists has been demonstrated across multiple randomized controlled trials, the available evidence remains fragmented owing to differences in study design,

investigated compounds, treatment duration, and reported clinical outcomes. Moreover, careful evaluation of adverse events, particularly hepatic safety, remains essential for determining the overall benefit-risk profile of this emerging therapeutic class. To date, no single synthesis has comprehensively integrated the evidence from all available randomized and observational studies investigating non-hormonal NK3 receptor antagonists while simultaneously evaluating their efficacy, sleep outcomes, quality of life, and safety.

Therefore, the aim of this systematic review was to comprehensively evaluate the efficacy and safety of non-hormonalneurokinin 3 receptor antagonists for the treatment of moderate to severe menopausal vasomotor symptoms. Specifically, we summarized the available evidence regarding reductions in hot flash frequency and severity, improvements in sleep quality and health-related quality of life, and the incidence of adverse events including hepatic safety based on randomized controlled trials and cohort studies.

2. Research materials and methods

To investigate the impact of non-hormonal neurokinin-3 receptor antagonists on the vasomotor symptoms of menopause, a systematic literature search was conducted on July 15, 2026, in the PubMed and Scopus electronic databases.

The following search queries were applied to the PubMed database:

1. *(Fezolinetant[tw] OR Veoza[tw] OR "neurokinin 3 receptor antagonist"[tw] OR NK3R[tw] OR Pavinetant[tw]) AND ("Vasomotor Symptoms"[MeSH Terms] OR "Hot Flashes"[MeSH Terms] OR "hot flashes"[tw] OR "hot flashes"[tw] OR "night sweats"[tw] OR "vasomotor symptoms"[tw]) AND (Menopause[MeSH Terms] OR "Menopause"[tw] OR "postmenopausal"[tw])*

2. *("Receptors, Neurokinin-3"[Mesh] OR "fezolinetant" [Supplementary Concept] OR "elinzanetant" [Supplementary Concept] OR "neurokinin 3 receptor antagonist") AND ("Menopause"[Mesh] OR "Hot Flashes"[Mesh] OR "vasomotor symptoms")*

And Scopus search:

ALL ((fezolinetant OR elinzanetant OR "neurokinin 3") AND (menopause OR "hot flashes" OR vasomotor) AND (sleep OR safety))

As a result of applying the above strategy, 412 records were identified. The results were exported to the Rayyan platform, which is dedicated to literature review management. Using this platform, 284 duplicates were identified by the research team. Finally, 223 unique articles were qualified for the next selection stage.

2.1. Participants

The research inclusion criteria were structured based on the PICOS framework (population, intervention, comparison, outcome, and study design), in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The selected articles aimed to answer the following research question: "What is the clinical efficacy and safety profile of non-hormonal neurokinin 3 receptor antagonists compared with placebo in reducing vasomotor symptoms of menopause?".

The main inclusion criteria were as follows: (1) clinical, cohort, and case-control studies; (2) peri- or postmenopausal women (natural, iatrogenic, or surgical menopause); (3) experiencing moderate to severe vasomotor symptoms; (4) inclusion of a control group consisting of peri- or postmenopausal women receiving placebo or other non-hormonal therapies (e.g., SSRI, SNRI, gabapentin); (5) use of non-hormonal neurokinin 3 receptor antagonists (e.g., fezolinetant, elinzanetant, pavinetant); (6) reporting of changes in the frequency and severity of hot flashes at specified time points (primary outcome) and/or sleep quality (PROMIS SD instrument) and quality of life (MENQOL questionnaire) of the participants (secondary outcome); (7) reporting of adverse event rates (with a particular focus on liver function parameters).

The exclusion criteria were as follows: (1) literature reviews, meta-analyses, and case reports; (2) preclinical studies conducted on animal models, as well as works covering premenopausal women; and (3) studies evaluating hormonal or combined therapies within study cohorts.

2.2. Data collection and analysis

The literature selection process was carried out in multiple stages, strictly following the PRISMA guidelines. Initially, a five-person team of independent reviewers assessed the titles and abstracts of 223 articles, examining their compliance with the main objective of the study. To ensure maximum objectivity and minimize systematic error, this stage was conducted independently on the Rayyan platform. Works failing to meet the basic assumptions of the PICOS protocol were excluded. The next step involved an independent, full-text assessment of the remaining publications by all five authors based on detailed inclusion and exclusion criteria. Potential disagreements and conflicting assessments were subjected to joint analysis and discussed until a final consensus was reached.

2.3. Data Extraction

The following data were extracted from the qualified publications: DOI number, first author's name, year of publication, follow-up period, number of participants in the study and control groups, mean age of participants, menopausal status and etiology, baseline vs. post-intervention frequency and severity of the hot flashes, changes in the sleep quality and quality of life measurements, dosage and administration protocol of the drug, type of placebo used within the control cohort, adverse events rates (with special regard to liver enzyme elevation), and number of withdrawals due to adverse events.

3. Research results

3.1. Changes in the frequency and severity of the hot flashes

Almost all analyzed studies demonstrated an improvement in both the frequency and severity of hot flashes. The majority of the enrolled women were postmenopausal (either natural or post-oophorectomy with or without hysterectomy) aged 40–65 years, who reported at least seven hot flash episodes per day. Elinzanetant served as the therapeutic agent in eight articles [9, 15, 26, 27, 32, 36, 38, 39], pavinetant (MLE4901) in two [42, 43], the GS1-144 molecule in one [9], and fezolinetant in the remainder. Additionally, several studies presented pooled analyses of previously conducted randomized clinical trials (RCT) [14, 16, 19].

Fezolinetant exhibited high efficacy in reducing vasomotor symptoms across multiple time points. A reduction in hot flash frequency at week 12 was reported in the SKYLIGHT 1 RCT [8] and the effect persisted throughout the subsequent 40-week follow-up period. SKYLIGHT 2 study [10] further revealed that fezolinetant contributes to symptom reduction over a 52-week treatment course, a finding confirmed in the SKYLIGHT 4 RCT [11] involving cohorts exceeding 600 participants. Notably, both the 30 mg and 45 mg doses proved effective across these trials. Symptom reduction at week 12 was also reported in other clinical trials [14, 21, 23, 28, 33, 35, 37]. Furthermore, Depypere et al. [23] observed improvements as early as the first day of therapy.

Efficacy at week 24 was documented in the Phase IIIb DAYLIGHT RCT [12, 34], while week 52 efficacy was demonstrated by Yu et al. [20].

Conversely, the lack of a statistically significant superiority of fezolinetant over placebo at weeks 4 and 12 was the outcome of the MOONLIGHT 1 trial conducted by Ruan et al. [25] in an East Asian population of > 300 postmenopausal women.

Elinzanetant reduced vasomotor symptoms at both weeks 4 and 12 of therapy, as established in several studies [9, 15, 26, 36, 38].

A matching-adjusted indirect comparison study by Stute et al. [18] compared the efficacy of fezolinetant (SKYLIGHT 1 and 2 trials) and elinzanetant (OASIS 1 and 2 trials), showing that the frequency and severity of hot flashes did not differ significantly between the two drugs at weeks 1, 4, and 12.

Randomized crossover trial regarding MLE4901 (pavinetant) [42, 43] showed a reduction in the weekly number of hot flashes by 45 percentage points compared to placebo. Improvement was persistent throughout the 4-week follow-up.

The RCT investigating the GS1-144 molecule [17] demonstrated its efficacy at both weeks 4 and 12 for the 30 mg twice-daily dose, as well as for the 60 mg and 30 mg once-daily regimens.

3.2. Effects on sleep quality

Sleep quality was evaluated in many of the included studies and represented one of the most frequently reported secondary efficacy outcomes. Across the included trials, sleep was assessed primarily using validated patient reported outcome measures, most commonly the Patient Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b (PROMIS SD SF-8b). Earlier phase II studies additionally employed the Greene Climacteric Scale, the Hot Flash Related Daily Interference Scale (HF-DIS) and patient global impression scales to evaluate sleep disturbances associated with menopausal vasomotor symptoms [13, 35, 36].

The earliest phase II studies consistently demonstrated that NK3 receptor antagonists improved sleep quality in women experiencing moderate to severe vasomotor symptoms. Significant reductions in sleep disturbances measured using the Greene Climacteric Scale and HF-DIS were accompanied by marked decreases in hot flash frequency and severity, indicating that relief of nocturnal vasomotor symptoms translated into clinically meaningful improvements in subjective sleep quality. These beneficial effects appeared to be dose dependent, with the greatest improvements observed at doses of ≥30 mg twice daily or ≥60 mg once daily, and were maintained during extension studies, suggesting sustained efficacy over time [13, 35, 36].

Among the phase III placebo controlled trials evaluating fezolinetant, improvements in sleep quality were generally observed, although the magnitude of benefit varied between studies. One trial found no statistically significant difference in PROMIS SD SF-8b scores despite significant reductions in vasomotor symptoms [8]. In contrast, another study demonstrated a significant improvement with fezolinetant 45 mg after 12 weeks of treatment (least squares mean difference −2.0 [SE 0.7]; 95% CI −3.5 to −0.6; $P = 0.007$), whereas the 30 mg dose did not significantly differ from placebo [10]. Similar improvements in PROMIS SD SF-8b scores were also reported after 24 weeks of treatment in women for whom menopausal hormone therapy was unsuitable or contraindicated [12, 22].

Additional evidence from long-term and pooled clinical analyses further supported these findings. Significant improvements in PROMIS SD SF-8b scores were consistently observed with fezolinetant 45 mg compared with placebo after 12 weeks of treatment, whereas improvements with the 30 mg dose were smaller and less consistent [15, 16, 29].

Beneficial effects on sleep quality were also consistently demonstrated with elinzanetant. Significant improvements in PROMIS SD SF-8b scores were observed in dose-finding studies, particularly with the 120 mg and 160 mg doses [9]. These findings were subsequently confirmed in phase III clinical trials, in which statistically significant improvements in sleep quality compared with placebo were reported after 12 weeks of treatment [32–34]. Furthermore, an indirect comparative study suggested that elinzanetant may provide greater improvements in sleep quality than fezolinetant, although these findings should be interpreted with caution because they were based on indirect comparisons [18].

Overall, the available evidence indicates that NK3 receptor antagonists are associated with clinically meaningful improvements in sleep quality among women with moderate to severe menopausal vasomotor symptoms. Clinically meaningful improvements in sleep quality were consistently demonstrated across phase II and phase III clinical trials evaluating both fezolinetant and elinzanetant [10, 12, 13, 22, 9, 32–36]. Secondary and pooled analyses further corroborated the durability and clinical relevance of these improvements over longer treatment periods [15, 16, 29].

3.3. Effects on quality of life

Menopause-related quality of life was assessed primarily using the Menopause-Specific Quality of Life questionnaire (MENQOL), which evaluates vasomotor, psychosocial, physical, and sexual domains. The validity and reliability of MENQOL in women experiencing menopausal vasomotor symptoms have been established in psychometric evaluations [26, 41]. Selected studies additionally evaluated daily functioning, activity impairment, and work productivity using standardized patient-reported instruments such as the Work Productivity and Activity Impairment questionnaire (WPAI-VMS) [22].

In the phase IIIb DAYLIGHT trial, fezolinetant 45 mg improved menopause-related quality of life in women considered unsuitable for menopausal hormone therapy [22]. At week 24, the improvement in MENQOL total score was greater with fezolinetant than with placebo, with a least-squares mean difference of −0.44 points (95% CI −0.69 to −0.18; $P < 0.001$). Reductions were also observed in activity impairment ($P < 0.001$), overall work productivity loss ($P = 0.036$), and presenteeism ($P = 0.002$). A greater proportion of

participants receiving fezolinetant reported an overall subjective improvement in vasomotor symptoms. These MENQOL and work-productivity endpoints were exploratory in nature and were not adjusted for multiplicity.

In the 52-week OASIS 3 trial, MENQOL total scores improved in both the elinzanetant and placebo treatment arms [15]. Mean changes from baseline to week 52 were − 1.3 points (95% CI −1.5 to − 1 .1) with elinzanetant and − 1.1 points (95% CI −1.3 to −0.9) with placebo. While the results numerically favored elinzanetant, no confirmatory statistical hypothesis testing was specified for this secondary endpoint, and the study was not formally powered to detect between-group differences in quality of life.

Elinzanetant also improved menopause-related quality of life in women experiencing vasomotor symptoms during endocrine therapy for hormone receptor-positive breast cancer [32]. In this clinical population, improvements in MENQOL scores accompanied statistically significant reductions in hot flash frequency and severity as well as reductions in sleep disturbance. Collectively, these findings indicate that beneficial effects on menopause-related quality of life are observed both in women with natural or surgical menopausal vasomotor symptoms and in those experiencing severe symptoms induced by oncological endocrine therapy [15, 22, 32].

3.4. Side effects of NK-3 receptor antagonists

Across the evaluated clinical trials, neurokinin-3 (NK-3) receptor antagonists, such as fezolinetant, demonstrated a generally favorable safety and tolerability profile. The mechanistic rationale for this favorable profile lies in their highly targeted site of action: by selectively blocking NK-3 receptors expressed on Kisspeptin/Neurokinin B/Dynorphin (KNDy) neurons in the arcuate nucleus of the hypothalamus, these agents normalize central thermoregulatory signaling without modulating peripheral estrogenic pathways. Consequently, NK-3 receptor antagonists circumvent the classic class-related risks of systemic hormone replacement therapy, such as venous thromboembolism and estrogen-driven oncogenesis.

The most frequently reported treatment-emergent adverse events (TEAEs) across clinical phases were predominantly mild to moderate in severity, self-limiting, and rarely led to treatment discontinuation. Neurological, gastrointestinal, and systemic complaints represented the most common manifestations. Specifically, patients most frequently reported headache, nausea, diarrhea, fatigue (characterized predominantly as general lethargy rather than meeting clinical criteria for chronic fatigue syndrome), and upper respiratory tract infections [9, 15, 17, 20, 23, 31–41]. These transient central nervous system and gastrointestinal symptoms are hypothesized to result from off-target or localized NK-3 receptor engagement within peripheral enteric neurons and extra-hypothalamic brain structures. Additionally, routine urinalyses revealed fewer laboratory abnormalities compared to baseline or placebo arms, with low incidences of hematuria, proteinuria, and bilirubinuria [40].

Data collected from Phase 2 trials, such as STARLIGHT, and Phase 3 studies, including SKYLIGHT 1, 2, and 4, documented several secondary and sporadic clinical events [8, 10, 12, 14, 21]. Central nervous system and psychiatric observations included depressive symptoms and sleep disturbances, such as transient insomnia or altered wakefulness patterns. Other documented physical and hematologic events included bone fractures, thrombocytopenia, uterine bleeding, and postmenopausal vaginal or uterine hemorrhages.

Evaluating long-term endometrial safety is paramount when administering non-hormonal therapies to postmenopausal populations. In the 52-week SKYLIGHT 4 safety trial, which specifically evaluated gynecological safety via transvaginal ultrasonography (TVUS) and serial endometrial biopsies, isolated cases of endometrial pathology were recorded. These included endometrial hyperplasia in the 45 mg fezolinetant cohort and endometrial malignancy in the 30 mg cohort [11, 27]. However, subsequent pooled analyses confirmed that these isolated events occurred at rates consistent with baseline background risks in untreated postmenopausal populations (<1%). Crucially, histopathological evaluations demonstrated no evidence of endometrial proliferation, confirming that long-term NK-3 receptor inhibition operates independently of estrogen receptor activation.

3.4.1. Liver elevation

The primary conclusion drawn from the aggregated clinical trial data is that the overall incidence of adverse events between the active NK-3 receptor antagonist groups and placebo control arms showed no statistically significant difference ($p>0.05$), as most reported non-hepatic symptoms occurred at nearly identical baseline frequencies across both cohorts [8, 9, 10–15, 17, 20, 21, 27, 28, 31–41]. Nevertheless, the single distinct drug-related safety signal identified across the study population was asymptomatic elevation of serum transaminases (ALT/AST) exceeding three times the upper limit of normal (>3×ULN) [8, 9, 10–15, 20, 21, 27, 28, 31–36, 38, 41]. Interestingly, this hepatic enzyme elevation showed no linear dose dependence; in the Phase 3 SKYLIGHT trial, the 30 mg dose group paradoxically exhibited a higher incidence of transaminase elevations than the 45 mg dose group. This non-linear pattern suggests that transaminase spikes are driven by individual metabolic variability, such as variations in CYP1A2 pathways rather than direct dose-dependent cytotoxicity. Ultimately, these hepatic events affected isolated patients within the active treatment group, occurred significantly less frequently in placebo controls, and were fully reversible upon drug cessation without progressing to liver failure.

4. Discussion

The findings of this systematic review support neurokinin receptor antagonism as an effective non-hormonal approach to the treatment of moderate-to-severe vasomotor symptoms associated with menopause. Most randomized controlled trials demonstrated reductions in hot flash frequency and severity with fezolinetant, elinzanetant, pavinetant, or GS1-144 compared with placebo [7–10, 12, 13, 15, 17, 23]. These findings are consistent with the role of increased hypothalamic KNDy neuron activity and neurokinin B signaling in menopausal thermoregulatory dysfunction [5, 6].

The evidence was most extensive for fezolinetant. The SKYLIGHT 1 and SKYLIGHT 2 trials demonstrated significant reductions in vasomotor symptom frequency and severity with the 30 mg and 45 mg doses [8, 10], while subsequent analyses supported an early onset and maintenance of the treatment effect [19, 34]. DAYLIGHT confirmed the efficacy of fezolinetant 45 mg over 24 weeks in women considered unsuitable for menopausal hormone therapy [12, 16]. However, MOONLIGHT 1 did not demonstrate statistically significant superiority over placebo in East Asian women [25]. This finding, together with positive results from studies conducted in Japan and China [17, 20, 21], indicates that further research is required to determine whether differences between studies reflect population characteristics, study design, or the magnitude of the placebo response.

Elinzanetant, a dual NK1/NK3 receptor antagonist, reduced vasomotor symptom frequency and severity in the SWITCH-1 and OASIS 3 trials [9, 15] and was also effective in women experiencing vasomotor symptoms during endocrine therapy for breast cancer [32]. An indirect comparison did not identify significant differences between fezolinetant and elinzanetant in vasomotor symptom frequency or severity during the first 12 weeks of treatment [18]. However, this finding cannot establish equivalence because it was not derived from a randomized head-to-head trial. Pavinetant and GS1-144 provided additional proof of the therapeutic relevance of NK3 receptor blockade, although evidence for these compounds was limited by small samples, short follow-up, or the absence of confirmatory phase III trials [7, 17].

Improvements in vasomotor symptoms were frequently accompanied by better patient-reported sleep outcomes [9, 12, 15, 22, 29]. For fezolinetant, the effect on sleep was more consistent with the 45 mg dose, whereas results for the 30 mg dose varied between trials [8, 10, 29]. Elinzanetant also improved subjective sleep disturbance [9, 15], and an indirect comparison suggested a potentially greater effect than fezolinetant [18]. This result should be interpreted cautiously because sleep was assessed mainly with patient-reported instruments and no direct comparison between the drugs was performed. Although these instruments are validated in women with menopausal vasomotor symptoms [26], they do not provide objective information about sleep architecture.

Fezolinetant and elinzanetant were also associated with improvements in menopause-related quality of life. In DAYLIGHT, fezolinetant improved MENQOL scores, activity impairment, and selected measures of work productivity [22]. Elinzanetant showed a numerical advantage in MENQOL scores during the 52-week OASIS 3 trial, although this secondary outcome was analyzed descriptively [15]. Improvements in quality of life were also reported among women receiving endocrine therapy for breast cancer [32]. These results suggest

that treatment benefits may extend beyond reductions in hot flash frequency, but their interpretation should account for the exploratory nature of several analyses and the subjective character of patient-reported outcomes [27, 41].

The overall tolerability of fezolinetant and elinzanetant was generally favorable, and most adverse events were mild or moderate [8–15]. Commonly reported events included headache, nausea, diarrhea, fatigue, somnolence, and upper respiratory tract infections. No consistent signal of endometrial stimulation was identified. In SKYLIGHT 4, isolated cases of endometrial hyperplasia and malignancy remained within the predefined safety thresholds [11], which is consistent with the absence of increased estradiol secretion during selective NK3 receptor antagonism [30]. Nevertheless, follow-up limited to approximately one year does not permit definitive conclusions regarding rare or delayed endometrial outcomes.

Hepatic safety remains the principal concern associated with this therapeutic approach. Elevations of ALT or AST exceeding three times the upper limit of normal were uncommon in fezolinetant trials, generally reversible, and were not accompanied by Hy's law cases in SKYLIGHT 4 [11, 14]. However, transaminase elevations were also observed during pavinetant treatment [7]. Their occurrence with more than one NK3 receptor antagonist supports continued attention to hepatic outcomes when assessing the safety of this therapeutic group.

The available evidence is limited by heterogeneity in investigated agents, doses, populations, follow-up periods, and outcome measures. Several publications were secondary, pooled, subgroup, or responder analyses of the same clinical trial programs and therefore did not represent independent patient populations [14, 16, 19, 22, 28, 29, 34]. Real-world evidence remained limited [24], and follow-up generally did not exceed 52 weeks. Furthermore, the absence of direct comparative trials prevents reliable conclusions regarding differences between individual agents. Longer studies involving more diverse clinical populations are needed to establish long-term hepatic and gynecological safety and determine the comparative effectiveness of neurokinin receptor antagonists.

5. Conclusions

Neurokinin receptor antagonists, notably fezolinetant and elinzanetant, demonstrate high efficacy as mechanism-based, non-hormonal agents for reducing the frequency and severity of moderate-to-severe menopausal vasomotor symptoms. While therapeutic benefits appear rapidly and persist over follow-up, outcomes from East Asian cohorts (MOONLIGHT 1) highlight that the magnitude of clinical response can vary across populations.

Dual NK1/NK3 receptor blockade with elinzanetant and selective NK3 antagonism with fezolinetant show comparable symptom control in short-term indirect comparisons, while proof-of-concept evidence for earlier compounds like pavinetant and GS1-144 requires validation in larger trials. Direct head-to-head randomized studies remain essential to establish relative clinical efficacy.

Reductions in vasomotor symptoms are consistently accompanied by improvements in subjective sleep quality. These sleep benefits appear more robust with higher dosing regimens, such as fezolinetant 45 mg compared to 30 mg, though evidence relies primarily on patient-reported questionnaires rather than objective assessments of sleep architecture.

Treatment with fezolinetant and elinzanetant significantly improves menopause-related quality of life, daily functioning, and work productivity, extending benefits to challenging clinical cohorts such as women receiving endocrine therapy for breast cancer. However, the exploratory nature of these secondary outcomes warrants balanced interpretation.

The overall short-term tolerability of both agents is favorable, with predominantly mild-to-moderate adverse events. Crucially, up to 52 weeks of clinical data indicate no evidence of estrogenic endometrial proliferation, aligning with their non-hormonal mechanism, although follow-up duration remains insufficient to exclude rare or delayed outcomes.

Transient, asymptomatic serum transaminase elevations represent the primary safety signal for this class. Given these hepatic observations, routine baseline and periodic liver function monitoring is recommended, while long-term observational studies are necessary to evaluate multi-year safety and real-world utility.

Author Contributions:

Conceptualization, W.Ż, K.Ś.; methodology, K.Ś,, J.T, J.S, W.Ż and M.L; validation, K.Ś and W.Ż.; formal analysis, K.Ś, W.Ż; resources, K.Ś, J.T, J.S, W.Ż and M.L.; data curation,K.Ś, J.T, J.S, W.Ż, M.L; writing—original draft preparation, K.Ś, J.T, J.S, W.Ż. and M.L.; writing—review and editing, K.Ś; visualization, K.Ś, J.T, J.S, W.Ż and M.L.; supervision, K.Ś and W.Ż.; project administration, K.Ś and W.Ż .; funding acquisition, K.Ś, W.Ż. , J.T., J.S, M.L. All authors have read and agreed to the published version of the manuscript.

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