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Neurokinin 3 Receptor Antagonists: A Paradigm Shift in Non-Hormonal Management of Menopausal Vasomotor Symptoms

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Mini Review

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Abstract

Vasomotor symptoms (VMS), including hot flashes and night sweats, affect over 80% of menopausal women, significantly impairing sleep, cognitive performance, and quality of life. While hormone replacement therapy (HRT) remains effective, a substantial proportion of women have absolute contraindications (e.g., breast cancer, thromboembolic disease) or prefer non-hormonal alternatives. The discovery of the hypothalamic KNDy (kisspeptin, neurokinin B, dynorphin) neuronal pathway has led to the development of neurokinin 3 (NK3) receptor antagonists, notably fezolinetant and elinzanetant. By selectively blocking neurokinin B signaling on hypertrophied KNDy neurons in the thermoregulatory center, NK3 antagonists rapidly restore homeostatic balance without estrogenic stimulation. Pivotal Phase 3 trials (SKYLIGHT 1, SKYLIGHT 2, and OASIS) demonstrate rapid, statistically significant reductions in VMS frequency and severity within one week, alongside marked improvements in sleep quality. This mini-review synthesizes the clinical pharmacology, efficacy profiles, liver monitoring protocols, and practical positioning of NK3 antagonists in modern gynecological practice.

Keywords: Vasomotor Symptoms; Menopause; Neurokinin 3 Receptor Antagonists; Fezolinetant; Thermoregulation; KNDy Neurons

Abbreviations

VMS: Vasomotor Symptoms; NK3: Neurokinin 3; KNDy: Kisspeptin, Neurokinin B, and Dynorphin; HRT: Hormone Replacement Therapy; MHT: Menopausal Hormone Therapy; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase.

Introduction

Menopausal vasomotor symptoms (VMS) represent an acute manifestation of thermoregulatory dysfunction triggered by ovarian estrogen withdrawal. For decades, menopausal hormone therapy (MHT) has been the gold standard; however, its utilization remains restricted in women with estrogen-sensitive malignancies, cardiovascular risks, or active venous thromboembolism [1,2]. Traditional non-hormonal modalities, such as SSRIs, SNRIs, and gabapentinoids, offer modest efficacy and are frequently burdened by side effects, including sedation and sexual dysfunction [3].

Recent breakthroughs in neuroendocrinology have identified hypertrophied KNDy neurons in the infundibular nucleus of the hypothalamus as the primary thermoregulatory switch [4]. Neurokinin 3 (NK3) receptor

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antagonists represent a first-in-class targeted non-hormonal pharmacotherapy that directly attenuates hyperactive thermoregulatory signaling.

Mechanism of Action & Clinical Efficacy

Under euestrogenic conditions, estrogen provides negative feedback to hypothalamic KNDy neurons. In menopause, loss of estrogenic tone results in hypertrophy of these neurons and excessive release of Neurokinin B (NKB). NKB binds to NK3 receptors in the median preoptic nucleus, inappropriately triggering heat dissipation effectors such as peripheral vasodilation and profuse sweating [5].

Fezolinetant, an oral small-molecule NK3 receptor antagonist, competitively inhibits NKB binding, restoring baseline neuronal firing rates. In the pivotal Phase 3 SKYLIGHT 1 and SKYLIGHT 2 randomized trials, fezolinetant (45 mg daily) achieved statistically significant reductions in moderate-to-severe VMS frequency as early as Day 7, sustained through 52 weeks. Sleep quality interference scores improved markedly, without estrogenic effects on endometrial thickness or mammographic breast density.

Safety Profile and Practical Considerations

Overall, NK3 receptor antagonists exhibit a favorable safety profile. The most commonly reported adverse events include mild headache, fatigue, and transient gastrointestinal discomfort. Asymptomatic elevations in serum transaminases (ALT/AST ≥3× ULN) occurred in approximately 2.3% of trial participants, returning to baseline following treatment cessation. Consequently, regulatory guidelines mandate baseline hepatic enzyme testing, followed by periodic monitoring at 3, 6, and 9 months of therapy.

Dual NK1/NK3 receptor antagonists (such as elinzanetant) are currently undergoing Phase 3 evaluation (OASIS program), demonstrating dual benefits on both hot flashes and sleep architecture.

Conclusion

Neurokinin 3 receptor antagonists have transformed the clinical landscape for menopausal care, bridging a critical therapeutic void for millions of women seeking non-hormonal relief. Future research must delineate their long-term cardiovascular and metabolic safety profiles and evaluate access in low- and middle-income healthcare systems.

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