Letter to the Editor

Could menopause drug fezolinetant show promise for vasomotor symptoms associated with androgen deprivation therapy?

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Vasomotor symptoms (VMS) affect up to 80% of females during the menopause transition, with hot flashes being one of the most common and troublesome symptoms. Hot flashes are defined as an uncomfortable, sudden feeling of warmth, flushing and diaphoresis that usually involve the upper body and face. Traditionally, the standard treatment for hot flashes has been hormone-based—with a focus on oestrogen replacement as the body's natural production slows down. However, exogenous oestrogen is problematic and not suitable for all patients. This has led to the exploration of alternative therapies for this common and bothersome condition.

Globally, prostate cancer is the second most frequent cancer amongst males. Approximately one-third of males with prostate cancer are likely to receive some form of androgen deprivation therapy (ADT), either surgical (bilateral orchidectomy) or medical [gonadotropin-releasing hormone (GnRH) analogues] (1). Severe VMS are associated with ADT. Up to 80% of men on ADT experience hot flashes and 27% cite this as the most bothersome side-effect (2). VMS also occur in males with hypogonadism where the mechanism is similar. The clinical significance and impact of VMS in men is often overlooked. This is, however, an important consideration for oncological community, as the severity of hot flashes may not only impact quality-of-life but also lead to treatment cessation or treatment 'holiday' (1).

The exact mechanism of hot flashes in men on ADT has not been studied, although treatment evidence suggests that oestrogen depletion remains the primary mediator (3). In males, oestradiol is a GnRH-mediated steroid, produced in small amounts by Sertoli cells but mostly via peripheral aromatisation of androgens. Multiple trials have shown hormonal therapy to be efficacious for VMS of ADT (3). However, exogenous oestrogen administration in males is problematic. Side effects include breast enlargement, tenderness, mood changes and sexual dysfunction, in addition to poor patient uptake. Progesterone formulations have also shown efficacy in ADT-related VMS, but might be associated with prostate cancer progression (4).

Non-hormonal agents with trial evidence in ADT include neuroactive agents venlafaxine and gabapentin. Venlafaxine was significantly less effective than cyproterone and medroxyprogesterone ($P<0.0001$) (5). Gabapentin at 900 mg/day was associated with a moderate improvement in hot flash frequency ($P<0.02$) but not severity ($P=0.1$) (6). Venlafaxine and gabapentin, however, remain off-label for this indication. Despite a limited number of trials in men, the mechanisms for non-hormonal management of VMS of ADT should be similar to those in menopause. This provides the uro-oncologic community an option to investigate the role of a new first-in-class treatment for hot flashes.

Fezolinetant (VEOZAH™, Astellas Pharma Inc.,

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Table 1 Phase III trials of fezolinetant in female menopause

Trial	Setting	Results
Skylight 1 (8)	2019–2021; North America, Europe	Reduced VMS frequency by 51% at 4 weeks, and 61% at 12 weeks from baseline, effect maintained at 52 weeks
Skylight 2 (9)	2019–2021; North America, Europe	Reduced VMS frequency by 55% at 4 weeks, and 64% at 12 weeks from baseline, effect maintained at 52 weeks
Moonlight 3	2020–2023; China	Yet to report
Skylight 4 (10)	2019–2022; North America, Europe	Similar incidence of all treatment-emergent adverse events to placebo at 52 weeks

VMS, vasomotor symptoms.

Tokyo, Japan), at a dose of 45 mg daily, was approved by the U.S. Food and Drug Administration in May 2023 as a non-hormonal treatment for moderate-to-severe VMS of menopause (7). This came after efficacy and safety were shown in multiple phase III trials [SKYLIGHT 1 (8), 2 (9), and 4 (10); see *Table 1*]. Fezolinetant is a neurokinin-3 receptor antagonist, which treats VMS by targeting the neuronal mechanism behind this phenomenon. The thermoregulatory centre in the hypothalamus is innervated by kisspeptin/neurokinin B/dynorphin (KNDy) neurons. These KNDy neurons are stimulated by neuropeptide neurokinin B and inhibited by oestrogen. During menopause (and GnRH suppression by ADT), decline in oestrogen levels disrupts this balance, causing neurokinin-3 receptor-mediated hypertrophy of KNDy neurons, leading to unopposed activation of heat dissipation effectors. These, involuntary, mostly autonomic responses result in cutaneous vasodilatation and sweating, leading to hot flashes. Although the relationship between neurokinin, oestrogen and thermoregulation has yet to be studied in human males, experiments in hypogonadal men demonstrate oestradiol (as opposed to testosterone) deficiency as the primary regulator of VMS in men (11). Furthermore, mouse models have demonstrated KNDy neurons mediating systemic vasodilatation in both male and female mice (12).

Fezolinetant signals a paradigm shift in the treatment of bothersome VMS and represents the first available treatment which directly targets the control mechanism behind thermoregulation. If the VMS of ADT is related to oestrogen depletion, then neurokinin B is also predicted to stimulate heat dissipation in males, and therefore, its blockade may be of clinical benefit. Whilst fezolinetant is currently only approved for menopause, its potential utility in prostate cancer and male hypogonadism is promising. Appropriate trials exploring its safety and efficacy in males will determine its suitability for regulatory approval. We hope that pharmaceutical manufacturers will be willing to explore this market, as it may greatly improve the quality-of-life and quality-of-care in men with advanced prostate cancer.

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Footnote

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