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European Association of Urology

Editorial

Beyond Menopause: Ending the Inequality—Why Men with Prostate Cancer Still Lack Therapies for Hot Flushes

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1. Background

It has been more than 2 yr since the US Food and Drug Administration approved fezolinetant, the first NK3R antagonist, for moderate to severe menopausal hot flushes in women [1]. However, hot flushes are not unique to women or menopause. In men with prostate cancer, androgen deprivation therapy (ADT) induces a hypogonadal state that leads to frequent severe vasomotor symptoms (VMSs) [2,3]. These episodes disrupt sleep, impair cognition and mood, reduce productivity, strain relationships, and may undermine adherence to essential cancer therapies. While NK3R antagonists provide rapid, sustained, and nonhormonal relief in women, an approved treatment is lacking for men, and no sufficiently powered randomised trials have yet been conducted.

In the first part of this Platinum Opinion editorial, we summarise evidence on the epidemiology, mechanisms, and clinical burden of VMS for men on ADT. We then turn to an ethical and policy perspective, arguing that the current lack of trials and approved nonhormonal therapies represents an avoidable inequity rather than an inevitable gap in science.

2. Relevant evidence

Prostate cancer is the second most common cancer diagnosed among men and the fifth leading cause of cancer death worldwide. It is projected that by 2040, the annual case volume will reach 2.4 million, with 712 000 deaths, with millions more men living with the disease or in survivorship. Most patients will receive ADT, often for years, and increasingly in combination with androgen receptor pathway inhibitors. Across studies, hot flushes affect 50–80% of men on ADT, and symptoms frequently persist for 5–8 yr or longer [4,5]. According to recent cohort reports, 30% of men rank hot flushes as the most troubling side effect of therapy, 55% report distress (11% severe), and many experience interruptions or discontinuation of treatment [4,5]. Clinicians recognise this impact: hot flushes disrupt sleep and attention, sap daytime functioning, and erode energy and mood, leading to irritability and social withdrawal. It is clinically and ethically difficult to justify leaving these symptoms undertreated.

Current options for men are insufficient. Off-label use of selective serotonin or serotonin/norepinephrine reuptake inhibitors may offer modest benefits but pose risks of sexual dysfunction, weight gain, sleep issues, and adverse drug interactions. Gabapentin and clonidine have inconsistent efficacy and may cause sedation or hypotension. Oestrogens, megestrol acetate, and cyproterone can suppress flushes but add a risk of thromboembolism, cardiovascular, hepatic, and endocrine complications. Oxybutynin helps some patients, but is associated with mild xerostomia. None of these provides the targeted, nonhormonal, centrally acting mechanism now available to women.

The biological rationale for NK3R antagonism in men is strong [3]. VMSs stem from the hypothalamic circuitry

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https://doi.org/10.1016/j.eururo.2025.12.004

Please cite this article as: M. Pedrani, S. Gillessen, E. Briers et al., Beyond Menopause: Ending the Inequality—Why Men with Prostate Cancer Still Lack Therapies for Hot Flushes, Eur Urol (2025), https://doi.org/10.1016/j.eururo.2025.12.004

involving kisspeptin, neurokinin B, and dynorphin neurons. NK3R antagonists widen the thermoneutral zone by modulating neurokinin B signalling, and thus reduce the frequency and severity of hot flushes without altering sex steroid levels. As ADT-induced hypogonadism in men affects the same circuitry as in menopause, the efficacy observed for women is mechanistically instructive for men. Multiple randomised trials have shown that NK3R antagonists can quickly and meaningfully reduce hot flushes in women and thus improve their sleep and quality of life (QoL), with favourable safety profiles [6]. Effects arise within days and persist for months, which is vital for men on long-term ADT whose sleep and daily function are substantially affected.

Safety in men should be effectively targeted. Early NK3R agents were associated with occasional elevation of liver enzymes, which prompted appropriate regulatory caution [7]. However, evidence for newer dual NK1/NK3 inhibitors indicates that episodes of elevation requiring close monitoring (ALT or AST $\geq 3 \times$ the upper limit of normal [ULN] or alkaline phosphatase $\geq 2 \times$ ULN) were rare, fully reversible, and not causally linked to the drug, with no cases of Hy's law and no meaningful hepatotoxicity signal [8]. These data support structured monitoring of liver enzymes, headache, sleep disturbance, and other mild adverse events rather than continuing the lack of research for men who endure years of distressing VMSs.

3. Addressing inequality for men on ADT

Scientifically, the case is transparent: NK3R antagonists target a shared central mechanism driving VMSs in both women and ADT-treated men, and with predefined algorithms for monitoring liver function, their overall risk-benefit profile appears to be manageable. As nonhormonal agents, NK3R antagonists avoid the risk of thromboembolism and gynaecomastia, and reduce the need for oestrogenic strategies. When biology, safety, and the clinical burden align so clearly, failure to generate evidence for NK3R antagonist use in men perpetuates a two-tier standard of care.

Why are these trials not happening? From here, the question becomes less scientific than organisational. Academic groups such as ANZUP and EORTC have proposed trials to assess NK3R antagonists for men on ADT. Despite strong proposals and initial industry interest, these have not yet been realised.

Market calculation is probably the main reason: the population of menopausal women is larger and more commercially attractive, so female trials have been prioritised over trials in men on ADT. The companies consider this population not commercially tractable, in contrast to successful trials in women with breast cancer on hormonal therapy. But this underestimates the millions of men exposed to ADT for increasingly long periods. Ignoring the severity and persistence of symptoms and the downstream health care burden of unmanaged VMS—sleep issues, mood disturbances, reduced adherence—also overlooks the regulatory and reputational benefits of tackling a clear, high-need group for which a validated therapy already exists. This disparity underscores an avoidable inequity, with major human and clinical implications.

Other barriers also matter. VMSs in prostate cancer sit at the interface of urology, medical oncology, radiation oncology, and primary care, with no clear "owner" of symptom control. Prostate cancer research has long prioritised survival and radiographic endpoints, while supportive care and QoL interventions have been relegated to secondary status. A gendered bias may further contribute: VMSs are culturally coded as a female health issue, making the same symptoms in men less visible and less likely to attract investment. Together, these structural, cultural, and commercial factors sustain an evidence gap in a population that clearly bears a significant burden.

The key question—whether NK3R antagonists can safely and meaningfully reduce VMSs and improve QoL for men on ADT—can be answered with proportionate, pragmatic trials that build directly on the large effect sizes already observed for women. The question is well suited to the N-of-1 trial methodology for enrolment of patients with frequent, bothersome hot flushes [9]. The patients receive multiple-crossover periods with NK3R (or NK1/NK3) antagonists or a placebo. Daily electronic diaries capture VMS frequency and severity at 4 wk and 12 wk as primary outcomes, complemented by validated sleep and QoL measures, and by regular monitoring of liver function and other safety parameters with prespecified thresholds. The N-of-1 approach with multiple-crossover designs is familiar in symptom science, maximises the signal-to-noise ratio for patient-reported outcomes, and allows individual benefit-risk assessment while keeping the overall sample size modest (approximately 120–150 participants) and the total study duration relatively short (~6–9 mo).

Equity in symptom science for men on ADT is a scientific and ethical imperative. The oncology field should pursue evidence in settings in which there is a biological rationale and the symptom burden creates a demand. Industry, cooperative groups, and academic centres should deliver at least one such adequately powered, rigorously monitored study of an NK3R antagonist in men. Regulators should be prepared to consider label expansion on the basis of robust symptom and safety data, as they have for women. Clinicians should normalise VMS screening and trial referral in prostate cancer clinics to signal that these symptoms are legitimate and modifiable targets of care.

4. Conclusions

In conclusion, NK3R antagonists offer rapid and persistent VMS relief, with a mechanistic link directly suited for men on ADT. This therapy could benefit a large, underserved patient group whose QoL is severely compromised. Men deserve the same rigorous approach as women: the clinical burden is substantial, the mechanism is shared, and efficient trials are feasible. Ending the double standard is not about decades or vast cohorts, it is about will, design, and a commitment to equity in supportive oncology.

Conflicts of interest: Silke Gillessen reports personal honoraria for advisory board roles for Sanofi, Orion, Roche, Amgen, and MSD; honoraria

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from RSI (Televisione Svizzera Italiana); invited speaker role for the European Society of Medical Oncology, the Swiss Group for Clinical Cancer Research, the Swiss Academy of Multidisciplinary Oncology, the Orikata Academy Research Group, and the China Anti-Cancer Association Genitourinary Oncology Committee; a speaker bureau role for Janssen Cilag; travel grant from ProteoMEdiX; institutional honoraria for advisory board roles for Bayer, Janssen Cilag, Roche, AAA International; independent data monitoring committee and steering committee roles for Amgen, Menarini Silicon Biosystems, Astellas Pharma, Tolero Pharmaceutcials, MSD, Pfizer, Telix Pharma, BMS and Orion; and a financial interest in patent WO2009138392 for a biomarker research method. Anthony M. Joshua reports institutional research funding from Bayer and Astellas. Pierre Blanchard reports advisory board and speaker roles for Bayer, Astellas, Ipsen, Janssen, AstraZeneca, Boston Scientific, Merck Serono, MSD, and Neolys. Bertrand Tombal reports financial relationships with Amgen Astellas, AstraZeneca, Bayer, Ferring, Janssens, Myovant, Novartis, and MSD. Martino Pedrani reports a travel grant from Bayer. Erik Briers has nothing to disclose.

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