



# Breaking barriers in migraine care: Advancing gender medicine to bridge the gap for men

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In the realm of medical research, achieving gender parity often focuses on ensuring adequate representation of women, who historically have been underrepresented in medical research. However, within migraine studies, this pursuit takes on a nuanced aspect. Migraine disproportionately affects women, with approximately 80% of participants included in migraine clinical studies being female (1). An issue of significant concern in migraine research is the under representation of men in experimental and clinical studies. This limitation hampers the generalizability of many findings of migraine research to men and in the therapeutic area impedes our understanding of how therapies may affect male subjects with migraine, potentially leading to suboptimal outcomes. Rectifying this gap is essential for advancing our understanding of disease pathophysiology and ensuring equitable access to effective migraine management for all migraine patients independent of sex.

The rationale for exploring sex differences in migraine pathophysiology and therapeutics is abundantly clear. Women and men differ in susceptibility to migraine, as well as in the prevalence and type of comorbid diseases and conditions that may impact migraine course. Sex differences may be either quantitative, reflecting disparities in prevalence, or qualitative where the mechanisms promoting migraine differ between men and women (2). Qualitative sex differences can result from gender-specific factors in the disease and offer the opportunity to improve outcomes by considering patient sex in choice of therapies. Sex hormones, alongside psychosocial factors, are recognized influencers in migraine, exhibiting notable differences between genders (3). Additionally, the neurotransmitter calcitonin gene-related peptide (CGRP), pivotal in migraine pathophysiology in some patients, exhibits gender-specific differences, as do other neurotransmitters relevant to migraine mechanisms (4,5).

Consequently, the mechanisms of the disease and the response to drugs and other interventions for migraine treatment may differ between sexes due to both biological and non-biological factors (6).

Sex constitutes a fundamental biological factor that should be integrated into the design of clinical studies and that can influence conclusions from outcomes of clinical trials. Several initiatives have already been suggested to standardize protocols for conducting such research in both animal and human subjects (7,8). Nevertheless, there is a need to implement measures aimed at improving the gathering and examination of sex-specific data, with a nuanced approach tailored to the complexities of each disease. For example, in migraine, factors specific to females, such as the phase of the ovarian cycle, the phase of the reproductive life, and the use of oral contraceptives or hormone replacement therapy, may impact outcomes. Moreover, achieving gender parity in migraine research necessitates concerted efforts to provide robust data informing on the results of any research also for men. There is also the need for establishing and enforcing research guidelines specific for migraine for the inclusion of males in migraine studies.

Addressing sex differences should be a primary focus of clinical trials, which should be sufficiently powered to provide information on both genders. Conducting scientifically robust trials with adequate statistical power to detect sex differences is challenging

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in terms of both time and cost. While it may not be essential for every large-scale, double-blind, randomized, placebo-controlled clinical trial to incorporate sex as a covariate, appropriate preliminary investigations can address this concern. Conducting routine pharmacokinetic and pharmacodynamic analyses during the early stages of drug development (phases I and II) could prove beneficial in identifying potential sex disparities in dosage recommendations and in mitigating adverse reactions. Small-scale pilot trials can offer insights into the efficacy of drugs or treatments for specific demographic groups, establishing protocols, mitigating undesirable outcomes, and determining the statistically significant sample size required for subgroup analysis. Consequently, standardized protocols remain imperative for determining whether subgroup analysis for sex differences is warranted and whether larger phase III clinical trials should incorporate gender as a covariate. Additionally, post-hoc pooled analyses and real-world studies are additional complementary tools to fill some knowledge gaps more easily regarding effectiveness and safety of migraine treatments in men (9–11). These studies capture treatment outcomes and patient experiences across sexes, offering a comprehensive understanding of effectiveness and impact.

In conclusion, addressing sex disparities in migraine research is essential for advancing our understanding and treatment of the disease. By acknowledging the underrepresentation of men in migraine studies and embracing a sex-inclusive approach, we can bridge critical gaps in knowledge and ensure equitable access to effective migraine management for all patients. *Cephalalgia* is committed to filling this knowledge gap and thus welcomes a Special Topical Collection of papers dedicated to advancing the field of migraine in men. We invite researchers from diverse backgrounds to contribute their insights and findings to this collection, with the aim of fostering collaboration and driving meaningful progress in migraine care.

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