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Assessing Sex-Based Treatment Responses to Gepants In Migraine Management

You're listening to *On the Frontlines of Mirgraine* on ReachMD. On this episode, we will be assessing sex-based treatment responses to gepants in migraine management.

Migraines affect over a billion people globally and remain a leading cause of disability, with females and males experiencing migraines at a prevalence of 17 and 8.6 percent, respectively. However, gaps persist in our understanding of how newer migraine therapies perform in men, who in some cases represent just 10 to 14 percent of clinical trial participants. This underrepresentation complicates efforts to determine whether treatment responses differ meaningfully between men and women.

To begin addressing this question, Goadsby et al. conducted a secondary analysis, published in *Cephalalgia* in early 2025, focused on sex-based efficacy of two calcitonin gene–related peptide, or CGRP, receptor antagonists: ubrogepant and atogepant. The review drew on data from eight randomized, double-blind, placebo-controlled trials, with four evaluating ubrogepant for acute migraine treatment and four assessing atogepant for prevention.

For the evaluation of acute treatment trials, data were analyzed from two phase 3 single-attack studies, a phase 2b single-attack study, and a phase 3 crossover trial targeting the prodrome phase. As for the analysis of preventive trials, the secondary analysis incorporated two episodic migraine studies, a chronic migraine study, and a trial enrolling patients who had failed two to four preventive treatments.

In the two phase 3 single-attack trials, the efficacy of ubrogepant for acute migraine treatment was evaluated using two co-primary endpoints: freedom from pain and the absence of the most bothersome symptom, both at two hours post-dose. Pooled analyses of these data revealed that two-hour pain freedom was achieved in about 19 percent of males and 21 percent of females, while absence of the most bothersome symptom was reported in about 35 percent of males and 39 percent of females.

However, no statistically significant differences in two-hour pain freedom were observed between sexes, with p-values of approximately 0.15 for pain freedom and 0.1 for the absence of the most bothersome symptom, indicating that treatment effects were consistent across males and females. Response trajectories for both co-primary endpoints also remained similar between sexes throughout the 48-hour post-dose window, reinforcing the conclusion of a comparable treatment response.

Notably, an exception occurred in one of the phase 3 single-attack trials. In the UBR-MD-01 trial, the two-hour pain freedom rate in the male placebo group of 20.4 percent exceeded that of the ubrogepant-treated male group at 14 percent. However, the response rate among males receiving ubrogepant was similar to that of females. This finding likely reflects the greater variability associated with smaller male subgroups.

Further support came from a phase 3 crossover trial evaluating ubrogepant administered during the prodrome phase. At 24 hours post-dose, males treated with ubrogepant had nearly 1.8 times the odds of avoiding moderate-to-severe headache compared to those receiving placebo, although this did not reach statistical significance. In contrast, the odds of this outcome in females were significantly higher, nearly 2.2 times greater than placebo. By 48 hours, the treatment effect became statistically significant in both sexes: males had more than double the odds of avoiding moderate-to-severe headache with an odds ratio of 2.24, closely mirroring the effect in females with an odds ratio of 2.15.

Building on these findings on ubrogepant for acute treatment, the analysis also evaluated whether atogepant would demonstrate similarly consistent treatment responses between sexes in the preventive setting. Pooled analyses of the two episodic migraine trials demonstrated that treatment with atogepant 60 milligrams once daily led to similar reductions in monthly migraine days in males and

females of 1.95 and 1.13 days, respectively, compared to placebo. In a separate trial with participants who had failed two to four prior preventive migraine treatments, atogepant also produced comparable benefits, with reductions of 2.78 days in males and 2.43 days in females.

Results from a chronic migraine trial followed the same trend. Atogepant 60 milligrams once daily reduced monthly migraine days by 1.23 days in males and 1.95 days in females, while the 30 milligrams twice-daily regimen yielded slightly greater reductions in both groups. Taken together, across all 12-week treatment periods with atogepant, reductions in migraine frequency were generally consistent between sexes.

These findings were also supported by pharmacokinetic and exposure-response analyses. In the pooled phase 3 single-attack trials, two-hour pain freedom was achieved in approximately 25 percent of both males and females in the highest quartile of ubrogepant plasma concentrations. For atogepant, exposure–response modeling showed a similar relationship between average plasma concentration and reductions in monthly migraine days in both sexes. Although pharmacokinetic parameters for both agents trended slightly lower in males, all values remained within accepted bioequivalence limits, reinforcing the absence of clinically meaningful sex-based differences in treatment response.

In terms of safety, the most commonly reported treatment-emergent adverse events were nausea and constipation. In some cases, these occurred more frequently in females, while in others, rates were similar between sexes. Overall, treatment-emergent adverse event rates were low.

While these findings are encouraging, the study's limitations must be acknowledged. The low representation of male participants constrains the statistical power to detect treatment effects within or between sexes. Moreover, single-attack acute trials may be more susceptible to variability than longer-duration preventive trials that assess average changes across multiple migraine episodes.

That said, across the broader dataset of the eight analyzed trials, male participants experienced improvements in migraine symptoms. Ubrogepant demonstrated efficacy in males for the acute treatment of migraine when administered during both the headache and prodrome phases, and atogepant significantly reduced monthly migraine days in preventive treatment trials. Also, no differences in pharmacokinetics or safety profiles were observed that would necessitate sex-specific dose adjustments.

Altogether, while these individual trials were not powered to detect treatment differences between sexes, the consistency of treatment responses across male and female participants supports the broader clinical utility of these small-molecule CGRP receptor antagonists. Further studies with more balanced enrollment are needed to confirm these observations, but current evidence suggests that ubrogepant and atogepant offer effective options for both acute and preventive migraine management regardless of sex.

This has been an episode of *On the Frontlines of Migraine* on ReachMD. To learn more or listen to other podcasts, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!