Sex Differences in Response to Triptans

A Systematic Review and Meta-analysis

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Abstract

Objective

To examine the effect of sex on clinical response to triptans in migraine and to determine whether these differences are related to pharmacokinetics of triptans in men and women, we performed a systematic review and meta-analysis.

Methods

We searched clinical trials distinguishing clinical response to or pharmacokinetic parameters of triptans between sexes in PubMed, MEDLINE, Cochrane Library, Embase, and Web of Science up to Dec 12, 2019. Analysis was based on data extracted from published reports. Male-to-female pooled risk ratios (RR) were calculated for clinical outcomes and pooled ratio of means (RoM) for pharmacokinetic outcomes using random-effects models.

Results

Of 1,188 publications on clinical trials with triptans, 244 were identified with sex-related search terms. Only 19 publications presented sex-specific results, comprising n = 2,280 men and n = 13,899 women. No sex differences were revealed for 2-hour headache and pain-free responses, but men had a lower risk for headache recurrence (male-to-female RR 0.64, 95% confidence interval [CI]: 0.55–0.76, Q = 0.81) and adverse events (RR 0.82, 95% CI: 0.72–0.93, Q = 4.93). Men had lower drug exposure with lower area under the curve (RoM 0.69, 95% CI: 0.60–0.81, Q = 18.06) and peak drug concentration (RoM 0.72, 95% CI: 0.64–0.82, Q = 8.24) than women.

Conclusions

Remarkably few publications about sex differences in triptan response are available. The limited number of eligible studies show sex differences in adverse event frequency, which may be partly because of drug exposure differences. This higher drug exposure in women is not reflected in different response rates. Despite higher exposure, women have higher headache recurrence rates possibly because of longer attack duration related to sex hormonal changes.

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Glossary

CI = confidence interval; **RR** = risk ratio; **RoM** = ratio of mean.

Migraine is a common disabling episodic brain disorder, affecting 3 times more women than men.[1] In both sexes, triptans (serotonin 5-$HT_{1B/1D}$ receptor agonists) are the most widely prescribed acute migraine-specific treatments. In contrast to clinical trials in general, where most men are included,[2,3] most trials investigating effectiveness of triptans are performed with approximately 80% women. Because low numbers of men are included, the statistical power to study sex differences in triptan response is limited in individual studies.

Differences between men and women in pharmacokinetics, drug safety, and efficacy may be affected by biological components but also behavioral, social, environmental, and cultural factors. Because most studies only use a dichotomous variable to distinguish men from women without further distinguishing gender role identity, we use "sex" to describe differences between men and women.

Researchers in other neurologic fields, for example, stroke, multiple sclerosis, and Alzheimer's disease, have also noticed that many clinical trials were not designed to detect sex differences.[4–7] Because sex differences in migraine prevalence are even more striking, there is a clinical need to explore effects of sex on response to antimigraine treatments, starting with the most widely used triptans.

With this systematic review and meta-analysis, we investigated whether sex and sex-related differences in pharmacokinetics are determinants in triptan response. It has been debated whether sex differences in triptan exposure are important for efficacy, although subcutaneous sumatriptan showed highest peak concentrations and bioavailability combined with the most effective response.[8] Taken together, clarity on potential important sex differences in triptan response and its possible association to sex-specific pharmacokinetics is needed.

Methods

Search Strategy and Selection Criteria

Procedures used in this systematic review and meta-analysis were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[9] A research protocol was written before the start of the study (ZonMw nr. 849100004).

We performed an electronic search for published studies with a last update on December 12, 2019, in PubMed, MEDLINE, EMBASE, Web of Science, and the Cochrane Library on clinical trials distinguishing clinical response to triptans for sex or pharmacokinetic parameters of triptans for sex. The search was set up with the assistance of research librarians at the Leiden University Medical Center. The strategy for PubMed is available in figure e-1, doi:10.5061/dryad.6djh9w0zb. In addition, we performed a broad search on clinical trials with triptans in PubMed to demonstrate the attention that has been paid to triptans in general.

Study selection was independently performed by 2 investigators (D.S.v.C. and G.M.T.). Disagreement was resolved by dialogue. We included double-blind randomized controlled trials, randomized crossover trials, open-label trials, and prospective observational studies. Case reports, meeting abstracts, editorials, commentaries, articles with a pediatric population (age <18 years), and articles with incomplete information were not eligible. There were no language or date restrictions. Reference lists of included articles were examined to identify studies that might have been missed by the initial database search.

Data Extraction and Risk of Bias Assessment

Data were extracted from all eligible studies using a standardized form. Information was extracted on the following: (1) study design, (2) study population characteristics (sample size, sex, and migraine subtype), (3) type and dose of triptan(s), (4) reported estimates on clinical response outcomes of interest—headache response after 2 hours, pain free response after 2 hours, headache recurrence within 24 or 48 hours, and adverse event frequency—and (5) reported estimates on pharmacokinetic parameters of interest—peak drug concentration (C_{max}), area under the curve from zero to infinite time ($AUC_{0-\infty}$), bioavailability (F), time to reach peak plasma concentration (T_{max}), plasma half-life time ($T_{½}$), and renal clearance (CL_r). The risk of bias of each included study was assessed using the critical appraisal tool—Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument for (pseudo) randomized controlled trials. For all studies, each domain was assigned a score of high, low, or unclear risk of bias. The risk of publication bias was assessed by visual inspection of funnel plots representing effect estimates on the X-axis and standard errors of the effect estimates on the Y-axis.

Data Analysis

For each clinical response outcome male-to-female pooled risk ratios (RRs) with a 95% confidence interval (CI) were used as the main estimated effect measure. For quantitative syntheses, the Mantel-Haenszel method was applied. For the investigation of sex differences in pharmacokinetic outcomes pooled ratio of means (RoMs) were calculated. A formula described by Friedrich et al.[10] was used to calculate corresponding 95% CIs. For quantitative syntheses of pooled RoMs, the inverse variance method was used. We would have

preferred to perform pooled analyses for the different outcome measures separately per triptan. However, because of a limited number of eligible studies per individual triptan, we chose to combine data on different triptans. Especially, sex differences on $T_{½}$ would preferably be calculated separately for different triptans to take relevant differences in drug metabolism into account. As only data of $T_{½}$ on frovatriptan and zolmitriptan were available separated by sex, which are both mainly metabolized by CYP1A2,[11,12] we also chose to perform pooled analyses for these 2 drugs. Furthermore, study arms closest to therapeutic doses were selected from cross-sectional studies to avoid pooling across the same participants. Random-effects models were used to anticipate on clinical between-study heterogeneity. Statistical heterogeneity of the effect between studies was assessed using the χ^2 test of Q. Analyses were conducted using Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A 2-sided p value of ≤0.05 was considered statistically significant.

Data Availability

Additional data (table e-1, table e-2, figure e-1, and figure e-2, doi:10.5061/dryad.6djh9w0zb) are available from Dryad. Data not published within the article will be shared by request from an investigator.

Results

A search for publications on clinical trials with triptans resulted in 1,188 publications, of which 244 remained after adding sex- and gender-related search terms (see flowchart figure 1). Most of these studies were excluded because of the lack of distinguished results for men and women. Sex-specific results were presented in 19 publications, and these were considered eligible for inclusion in the meta-analysis—10 publications with 2,187 men and 13,805 women concerning clinical response outcome measurements and 9 publications with 93 men and 94 women on pharmacokinetic outcomes.

Six of the included publications on clinical response outcome measurements presented data obtained from multiple trials. In 3 publications, the results on clinical response outcomes were pooled across treatments with different triptans (eletriptan 40/80 mg, sumatriptan 100 mg, rizatriptan 10 mg, zolmitriptan 2.5 mg, almotriptan 12.5 mg). Numbers of participants ranged from 280 to 3,714 for women and from 33 to 591 for men, with an 80% female participation frequency. The age of included participants ranged from 18 to 78 years, with a mean age of approximately 40 years. Follow-up duration varied from a single attack treatment to a follow-up of 12 months. From one study, a subgroup was excluded to prevent heterogeneity because it investigated the effect of previous opioid use on response.[13] Sex division in the studies on pharmacokinetic parameters of triptans was nearly equal, with numbers ranging from 6 to 17 per group. The age of included participants in the pharmacokinetic studies also ranged from 18 to 78 years, with a mean age of approximately 35 years. In one study, hypertensive participants received antihypertensive treatment.[14] Table 1 shows characteristics of included studies (for full description see table e-1, doi:10.5061/dryad.6djh9w0zb). The risk of bias of individual publications on clinical response outcomes was mixed with an overall high risk of bias of open-label studies. Blinding of participants, allocators, and outcome assessors was considered to have less influence on the overall risk of bias of studies on pharmacokinetic outcomes (for overview of risk of bias assessments see figure e-2).

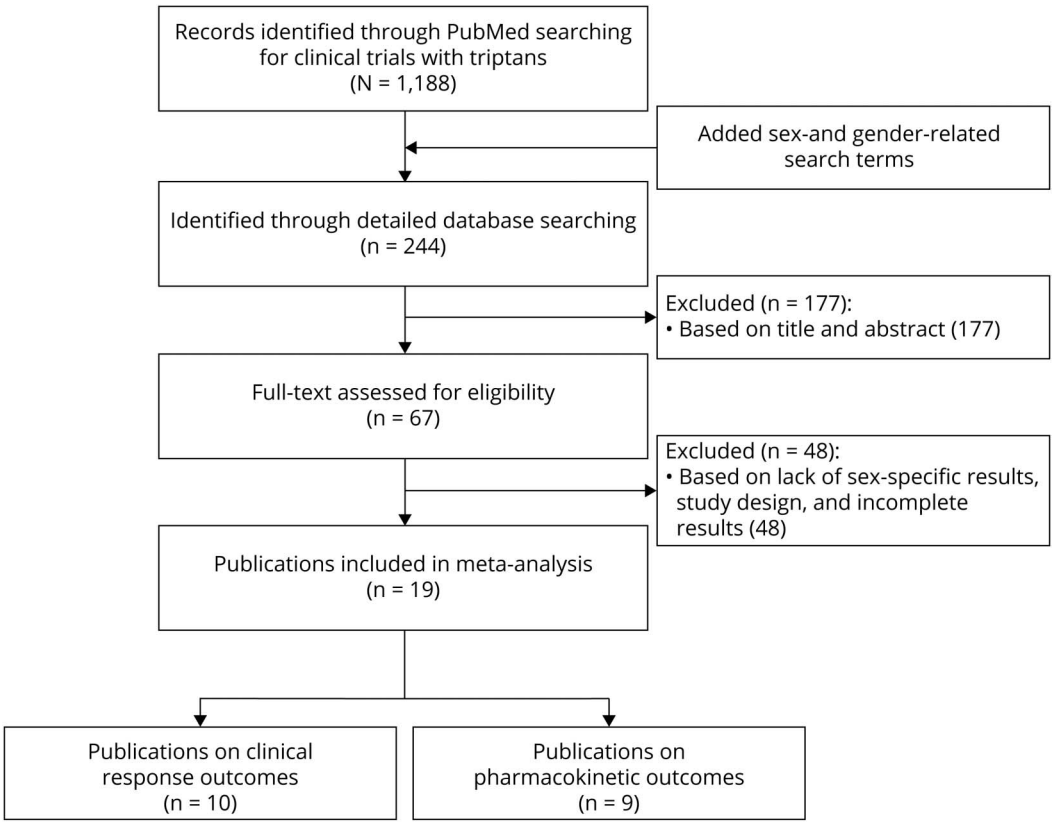
Clinical Response Outcome Measurements

The corresponding forest plots and references are shown in figure 2. Sex-specific information on headache response 2 hours after triptan intake (defined as reduction in headache intensity from moderate/severe before treatment to mild/no pain 2 hours after treatment) was reported in 6 studies. No sex differences were revealed for the 2-hour headache response (male-to-female RR 1.04, 95% CI: 0.98–1.11, p = 0.19, Q = 12.16). Four studies reported sex-specific information on pain-free response 2 hours after the intake of a triptan (defined as a headache reduction of any intensity before treatment to no pain 2 hours after treatment). Men and women had an equal pain-free 2-hour response (male-to-female RR 1.01, 95% CI: 0.96–1.07, p = 0.68, Q = 0.95). Men had a lower risk for headache recurrence (defined as the return or worsening of headache within 24–48 hours after an initial 2-hour headache response) (3 studies, male-to-female RR 0.64, 95% CI: 0.55–0.76, p < 0.001, Q = 0.81). No sex-specific results were available on sustained pain-free response (defined as freedom from pain with no recurrence or use of rescue medication 2–24 hours post dose). Four studies presented distinguished data on the frequency of adverse events for men and women. Men had a lower adverse event frequency after the intake of triptans compared with women (male-to-female RR 0.82, 95% CI: 0.72–0.93, p = 0.002, Q = 4.93). Most frequently reported adverse events were asthenia, nausea, somnolence, dizziness, paraesthesia, dry mouth, and warm sensations. A χ^2 test of Q for statistical heterogeneity of the effect between studies was only statistically significant for the 2-hour headache response (p = 0.03) (figure 2). Except for the 2-hour headache response, corresponding funnel plots showed an equal distribution of number of studies on both sides of the pooled RR.

Pharmacokinetic Outcomes

The corresponding forest plots and references are shown in figure 3. Men had a lower C_{max} (8 studies, RoM 0.72, 95%CI: 0.64–0.82, p < 0.001, Q = 8.24) and $AUC_{0-\infty}$ (9 studies, RoM 0.69, 95%CI:0.60–0.81, p < 0.001, Q = 18.06) than women for frovatriptan, zolmitriptan, and rizatriptan. A pooled analysis on $T_{½}$ for frovatriptan and zolmitriptan showed no sex difference (5 studies, RoM 0.93, 95% CI: 0.80–1.08, p = 0.34, Q = 5.59). A χ^2 test of Q was only statistically significant for $AUC_{0-\infty}$ (p = 0.02) (figure 3). All corresponding funnel plots showed an equal distribution of number of studies on both sides of the pooled RoMs.

Figure 1 Flowchart of the Publication Selection Process



Discussion

This systematic review and meta-analysis show that remarkably few publications about sex differences in triptan response are available. Based on the available data, sex differences in adverse event frequency were shown, with men less prone for adverse events, which may be partly because of drug exposure differences. This higher drug exposure in women is not reflected in differences in response rates. Despite higher triptan exposure, women have higher headache recurrence rates possibly because of a longer attack duration related to sex hormonal changes.

In contrast to clinical trials that investigate the effectiveness of triptans, where most women are included, sexes were equally distributed in trials regarding pharmacokinetics of triptans. We observed no sex differences in headache and pain-free response after 2 hours for triptans, which is in line with a prospective open-label study in which no difference in the time to reach pain freedom were found between men and women for acute medication in general.[15] By contrast, women had a higher adverse event frequency compared with men. Using the GRADE criteria (table e-2, doi:10.5061/dryad.6djh9w0zb), we assessed the certainty of this evidence to be moderate. Women generally tend to report adverse drug reactions more frequently than men, which may be related to both biological and social/cultural differences.[16,17] In our study, the sex difference in adverse event frequency may be partly explained by a higher exposure to the drug in women, which seemed from higher C_{max} and $AUC_{0-\infty}$ values for frovatriptan, zolmitriptan, and rizatriptan. The higher drug exposure seems to exist independent of sex differences in body weight because C_{max} and $AUC_{0-\infty}$ for frovatriptan 2.5 mg are shown to be higher in women when assessing results normalized to body weight.[12] This also applies to various other drugs, such as levodopa and sertraline, of which a higher drug exposure in women may only be partially explained by their lower body weight.[18,19] Therefore, researchers and clinicians should be aware of additional factors leading to a higher drug exposure, and potentially more adverse events, in women. The higher triptan exposure in women might probably be explained by a higher bioavailability because of lower first-pass metabolism or because of alterations in receptor number or receptor binding.[12,20–22] In addition, renal clearance of rizatriptan and zolmitriptan seems to be higher in men than in women.[23–25]

We expected $T_{½}$ for frovatriptan and zolmitriptan to be higher in women because both triptans are mainly metabolized by CYP1A2, which has a higher activity in men.[11,12,26] Surprisingly, no sex differences were revealed on $T_{½}$ for frovatriptan and zolmitriptan. In addition, 2 independent studies did not find sex differences for $T_{½}$ for N-desmethylzolmitriptan, the most active metabolite of zolmitriptan.[14,22] A possible

Table 1 Summary Characteristics of Included Studies

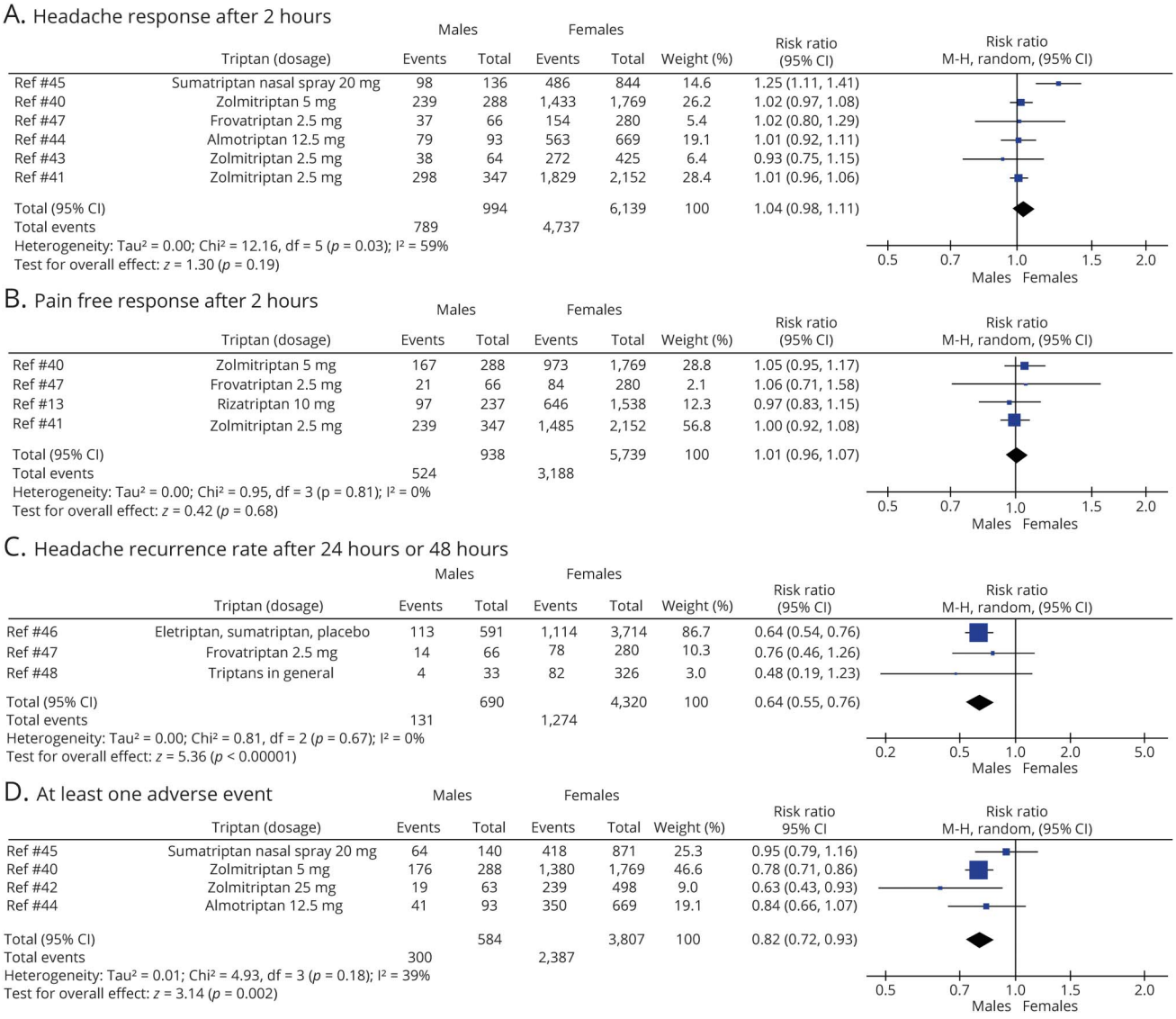
Studies on clinical response outcomes	Publications (n = 10)	Studies on pharmacokinetic outcomes	Publications (n = 9)
Publication year		**Publication year**	
≤2000	5 (50%)	**≤2000**	6 (67%)
2001–2010	4 (40%)	**2001–2010**	3 (33%)
2011–2018	1 (10%)	**2011–2018**	0 (0%)
Study design		**Study design**	
Randomized double-blind placebo-controlled study	5 (50%)	**Randomized double-blind placebo-controlled study**	2 (22%)
Randomized double-blind controlled crossover study	1 (10%)	**Randomized double-blind placebo-controlled crossover study**	2 (22%)
Nonrandomized open-label crossover study	1 (10%)	**Randomized open-label crossover study**	4 (44%)
Uncontrolled open-label study	2 (20%)	**Uncontrolled open-label study**	1 (11%)
Prospective observational study	1 (10%)		
Participants		**Participants**	
Percentage women included >80%	10 (100%)	**Percentage women included 50%**	8 (89%)
Migraine without aura + migraine with aura	10 (100%)	**Percentage women included 50%–55%**	1 (11%)
		Healthy volunteers	9 (100%)
Intervention		**Intervention**	
Almotriptan (12.5 mg)	1 (10%)	**Frovatriptan (2.5 and 40 mg)**	1 (11%)
Rizatriptan (10 mg)	1 (10%)	**Rizatriptan (2.5, 5, 10, and 15 mg)**	3 (33%)
Sumatriptan nasal spray (10 and 20 mg)	1 (10%)	**Zolmitriptan (2.5, 5, 10, 15, and 20 mg)**	5 (56%)
Zolmitriptan (2.5 and 5 mg)	4 (40%)		
Combination of triptans	3 (30%)		

explanation for this finding is the fact that a substantial proportion of female participants in the studies used an oral contraceptive pill. As ethinyl steroid-containing oral contraceptive pills are inhibitors of CYP1A2,[27] this usage might have decreased the clearance of frovatriptan and zolmitriptan in these female participants.

Contrary to what was to be expected based on the higher drug exposure, women did not have higher response rates to triptans and experienced even higher headache recurrence rates compared with men (evidence estimated as moderate based on GRADE, see table e-2, doi:10.5061/dryad.6djh9w0zb). In the included studies, headache recurrence is consistently defined based on a previous definition as the return or worsening of headache within 24 or 48 hours after an initial response (instead of an initial pain-free response). In general, headache recurrence occurs several hours after the half-life time point of triptans. Although frovatriptan has demonstrated lower headache recurrence rates compared with most other triptans, probably because of its long half-life time of 26 hours, recurrence rates are not negligible ranging from 11% to 15% at 24–48 hours.[28] Hence, we conclude that headache recurrence is not directly related to triptan plasma levels because we even showed that women have higher total drug exposure than men and both sexes have similar plasma half-life times. The higher headache recurrence in women despite their higher drug exposure may be explained by the longer attack duration related to sex hormonal changes, such as menstrually related migraine attacks or perimenopausal attacks. Previous studies showed that menstrually related migraine attacks have a longer duration, are less responsive to acute therapy, and are more prone to headache recurrence after treatment with triptans compared with migraine attacks occurring outside the menstrual period.[29–31] In addition, major fluctuations in estrogen levels during perimenopausal transition are associated with an increased prevalence of migraine and an increased risk of high frequency headache.[32–34] Although data regarding attack duration and the risk of headache recurrence specifically in perimenopausal women are lacking, we hypothesize that sex hormonal changes during perimenopause may be of influence on these outcomes.

Our study also has some limitations. Important methodological differences were found across clinical trials, including

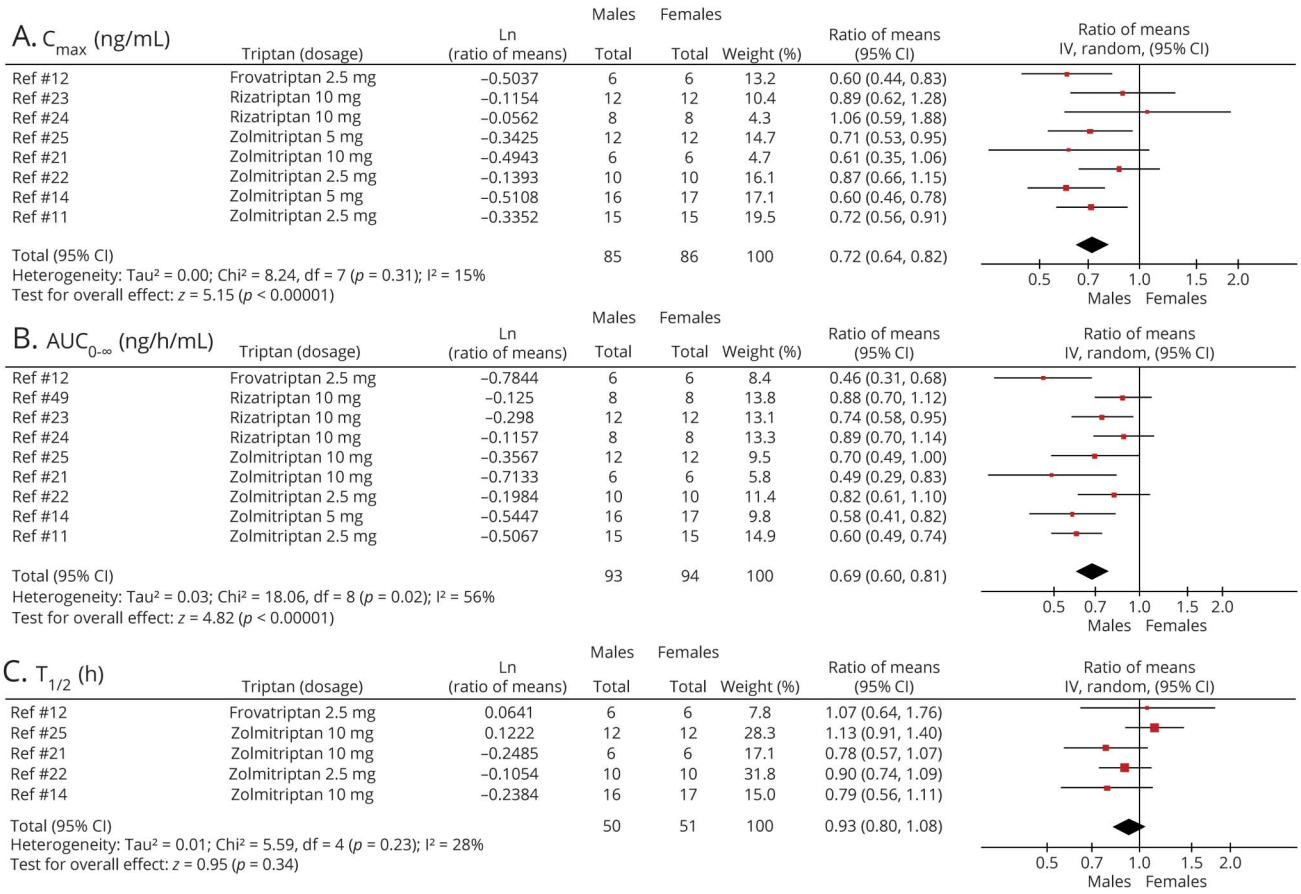
Figure 2 Forest Plots of the Clinical Response Outcomes



Headache response after 2 hours (A), pain-free response after 2 hours (B), headache recurrence rate after 24 hours or 48 hours (C), and the incidence of at least one adverse event after the intake of a triptan in male and female migraine patients (D). M-H = Mantel-Haenszel method; random = random effects model. The squares represent effect sizes of the individual studies (size reflects the weight of the study) and the horizontal lines indicate the 95% confidence intervals (CI). The filled diamonds represent the overall effect size (horizontal width indicates the 95% CI).

the approach of blinding, type and dose of treatment, follow-up duration, and the use of headache recurrence after 24 and/or 48 hours as outcome parameter. Based on the χ^2 test of Q, statistical heterogeneity of the effect between studies was observed for headache response after 2 hours and $AUC_{0-\infty}$, so results of these analyses should be interpreted with caution. Although no significant statistical heterogeneity arose from methodological diversity between studies in the other outcome measures, this limitation of our study should be kept in mind when interpreting the results. We chose to pool all triptans because separated meta-analyses per triptan could not be performed. Although triptans roughly have the same mechanism of action, it must be stressed that there are pharmacodynamic and pharmacokinetic differences between triptans. Pharmacodynamic differences between triptans may include variation in lipophilicity, the ability to cross the blood-brain barrier, and differences in 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptor affinities.[35] Pharmacokinetic differences between oral triptans are $T_{½}$ differences ranging from 2 to 26 hours (exceptionally long for frovatriptan with 26 hours) and T_{max} ranging from 1 to 4 hours, main excretion route through hepatic drug metabolism (by cytochrome P450 and monoamine oxidase enzymes) except for naratriptan, which is partly metabolized by renal excretion.[12,36–38] We have tried to take these limitations into account by using random-effects models for our analyses. Furthermore, in modern meta-analytical approaches, it is unusual to conduct pooled analyses across few studies. Nevertheless, in some analyses, we chose to pool

Figure 3 Forest Plots of Pharmacokinetic Outcomes



Peak drug concentration (C_{max}, ng/mL) (A), area under the curve from time zero to infinite time ($AUC_{0-\infty}$, ng/h/mL) (B), and plasma half-life times ($T_{1/2}$) (C). IV = inverse variance method; random = random effects model. The squares represent effect sizes of the individual studies (size reflects the weight of the study) and the horizontal lines indicate the 95% confidence intervals (CI). The filled diamonds represent the overall effect size (horizontal width indicates the 95% CI). There are a few minor discrepancies with the original studies, at the most two hundredths of decimals, in the calculation of the ratio of means and upper/lower limit of the 95% CIs because of differences in the rounding of decimals.

across only a few studies because limited data were available, and one of our aims was to address that results are currently rarely presented separately for men and women. Although we have performed random-effects meta-analyses, which weight the studies relatively more equally than fixed-effect analyses, most weight was given to one study in pooled analyses on adverse event rates and headache recurrence rates. However, it is reassuring that also smaller, medium-sized clinical trials presenting results on these outcomes point in the same direction as the larger studies. The included studies on sex differences in pharmacokinetic outcomes of triptans are performed in healthy volunteers. However, migraine attacks may be of influence on drug absorption because of delayed gastric emptying and thereby may cause additional variability in pharmacokinetic parameters.[39] Gender differences could not be specifically addressed because corresponding information was not presented in the included studies. Finally, publication bias might be an issue in the reporting of clinical trials because negative findings are less likely to get published. However, it concerned mainly large clinical trials investigating the efficacy and tolerability of triptans, which are less likely to be unpublished. Indeed, visual inspection of funnel plots was unsuspected for publication bias; however, it cannot be excluded. Tests for funnel plot asymmetry were not used because test power is usually too low to distinguish chance from real asymmetry when less than 10 studies are included in the meta-analysis.

We encourage physicians treating patients with migraine to be aware that their female migraine patients will likely report more adverse events after the intake of triptans and more headache recurrences compared with male migraine patients. Physicians should be aware that dose reduction to reduce adverse events seems undesirable because this might further increase the risk for headache recurrence in women and might also affect initial efficacy. Instead, menstrually related attacks and nonmenstrually related attacks should be assessed separately. We also want to underline the importance of prescribing preventive treatments in migraine patients to diminish frequency, duration, and severity of attacks. As we hypothesize that the longer attack duration in women relates to sex hormonal changes, there is an urgent need for clear evidence whether preventive hormonal treatments are

effective (ClinicalTrials.gov NCT04007874). In addition, dedicated studies on gender-related differences in migraine are needed. Finally, we would like to call on headache researchers to present data by sex and, if information is collected, also by gender when performing clinical trials on the efficacy and tolerability of acute and preventive migraine treatments. So far, this has only occasionally been performed for today's important clinical trials on migraine prevention with monoclonal antibodies acting on calcitonin gene-related peptide or on its receptor.

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Tobias Kurth, PhD	Charité–Universitätsmedizin Berlin	Revision of the manuscript for content including medical writing for content, study concept and design, and interpretation of data.
AH Jan Danser, PhD	Erasmus Medical Center, Rotterdam	Revision of the manuscript for content including medical writing for content and interpretation of data.
Gisela M. Terwindt, MD, PhD	Leiden University Medical Center, Leiden	Revision of the manuscript for content including medical writing for content, major role in the acquisition of data, study concept and design, and interpretation of data.
Antoinette MaassenVanDenBrink, PhD	Erasmus Medical Center, Rotterdam	Revision of the manuscript for content including medical writing for content, study concept and design, and interpretation of data.

References

1. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999;53:537–542.
2. Pinn VW. Sex and gender factors in medical studies: implications for health and clinical practice. JAMA 2003;289:397–400.
3. Liu KA, Mager NA. Women's involvement in clinical trials: historical perspective and future implications. Pharm Pract 2016;14:708.
4. Canevelli M, Quarata F, Remiddi F, et al. Sex and gender differences in the treatment of Alzheimer's disease: a systematic review of randomized controlled trials. Pharmacol Res 2017;115:218–223.
5. Kent DM, Price LL, Ringleb P, Hill MD, Selker HP. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. Stroke 2005;36:62–65.
6. Augustine EF, Perez A, Dhall R, et al. Sex differences in clinical features of early, treated Parkinson's disease. PloS one 2015;10:e0133002.
7. Li R, Sun X, Shu Y, et al. Sex differences in outcomes of disease-modifying treatments for multiple sclerosis: a systematic review. Mult Scler Relat Disord 2017;12:23–28.
8. Bigal ME, Bordini CA, Antoniazzi AL, Speciali JG. The triptan formulations: a critical evaluation. Arq Neuropsiquiatr 2003;61:313–320.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
10. Friedrich JO, Adhikari NK, Beyene J. Ratio of means for analyzing continuous outcomes in meta-analysis performed as well as mean difference methods. J Clin Epidemiol 2011;64:556–564.
11. Yates RA, Tateno M, Nairn K, Ikegami A, Dane A, Kemp J. The pharmacokinetics of the antimigraine compound zolmitriptan in Japanese and Caucasian subjects. Eur J Clin Pharmacol 2002;58:247–252.
12. Buchan P, Keywood C, Wade A, Ward C. Clinical pharmacokinetics of frovatriptan. Headache 2002;42(suppl 2):S54–S62.
13. Ho TW, Rodgers A, Bigal ME. Impact of recent prior opioid use on rizatriptan efficacy. A post hoc pooled analysis. Headache 2009;49:395–403.
14. Smith DA, Cleary EW, Watkins S, Huffman CS, Dilzer SC, Lasseter KC. Pharmacokinetics and pharmacodynamics of zolmitriptan in patients with mild to moderate hypertension: a double-blind, placebo-controlled study. J Clin Pharmacol 1998;38:685–693.
15. Bell CF, Foley KA, Barlas S, Solomon G, Hu XH. Time to pain freedom and onset of pain relief with rizatriptan 10 mg and prescription usual-care oral medications in the acute treatment of migraine headaches: a multicenter, prospective, open-label, two-attack, crossover study. Clin Ther 2006;28:872–880.
16. Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. Br J Clin Pharmacol 1998;46:505–511.
17. Montastruc JL, Lapeyre-Mestre M, Bagheri H, Fooladi A. Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. Fundam Clin Pharmacol 2002;16:343–346.
18. Kumagai T, Nagayama H, Ota T, Nishiyama Y, Mishina M, Ueda M. Sex differences in the pharmacokinetics of levodopa in elderly patients with Parkinson disease. Clin neuropharmacology 2014;37:173–176.

19. Ronfeld RA, Tremaine LM, Wilner KD. Pharmacokinetics of sertraline and its N-demethyl metabolite in elderly and young male and female volunteers. Clin Pharmacokinet 1997;32(suppl 1):22–30.
20. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2009;48:143–157.
21. Seaber E, On N, Dixon RM, et al. The absolute bioavailability and metabolic disposition of the novel antimigraine compound zolmitriptan (311C90). Br J Clin Pharmacol 1997;43:579–587.
22. Seaber EJ, Peck RW, Smith DA, et al. The absolute bioavailability and effect of food on the pharmacokinetics of zolmitriptan in healthy volunteers. Br J Clin Pharmacol 1998;46:433–439.
23. Lee Y, Conroy JA, Stepanavage ME, et al. Pharmacokinetics and tolerability of oral rizatriptan in healthy male and female volunteers. Br J Clin Pharmacol 1999;47:373–378.
24. Musson DG, Birk KL, Panebianco DL, Gagliano KD, Rogers JD, Goldberg MR. Pharmacokinetics of rizatriptan in healthy elderly subjects. Int J Clin Pharmacol Ther 2001;39:447–452.
25. Peck RW, Seaber EJ, Dixon RM, et al. The pharmacodynamics and pharmacokinetics of the 5HT1B/1D-agonist zolmitriptan in healthy young and elderly men and women. Clin Pharmacol Ther 1998;63:342–353.
26. Anderson GD. Gender differences in pharmacological response. Int Rev Neurobiol 2008;83:1–10.
27. Catteau A, Bechtel YC, Poisson N, Bechtel PR, Bonaiti-Pellie C. A population and family study of CYP1A2 using caffeine urinary metabolites. Eur J Clin Pharmacol 1995;47:423–430.
28. Allais G, Tullo V, Omboni S, et al. Efficacy of frovatriptan versus other triptans in the acute treatment of menstrual migraine: pooled analysis of three double-blind, randomized, crossover, multicenter studies. Neurol Sci 2012;33(suppl 1):S65–S69.
29. Pinkerman B, Holroyd K. Menstrual and nonmenstrual migraines differ in women with menstrually-related migraine. Cephalalgia 2010;30:1187–1194.
30. Bhambri R, Martin VT, Abdulsattar Y, et al. Comparing the efficacy of eletriptan for migraine in women during menstrual and non-menstrual time periods: a pooled analysis of randomized controlled trials. Headache 2014;54:343–354.
31. Visser WH, Jaspers NM, de Vriend RH, Ferrari MD. Risk factors for headache recurrence after sumatriptan: a study in 366 migraine patients. Cephalalgia 1996;16:264–269.
32. Martin VT, Pavlovic J, Fanning KM, Buse DC, Reed ML, Lipton RB. Perimenopause and menopause are associated with high frequency headache in women with migraine: results of the American migraine prevalence and prevention study. Headache 2016;56:292–305.
33. Wang SJ, Fuh JL, Lu SR, Juang KD, Wang PH. Migraine prevalence during menopausal transition. Headache 2003;43:470–478.
34. Ibrahimi K, Couturier EG, MaassenVanDenBrink A. Migraine and perimenopause. Maturitas 2014;78:277–280.
35. Rubio-Beltran E, Labastida-Ramirez A, Villalon CM, MaassenVanDenBrink A. Is selective 5-HT1F receptor agonism an entity apart from that of the triptans in antimigraine therapy? Pharmacol Ther 2018;186:88–97.
36. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia 2002;22:633–658.
37. Dodick DW, Martin V. Triptans and CNS side-effects: pharmacokinetic and metabolic mechanisms. Cephalalgia 2004;24:417–424.
38. Buzzi MG. Pathways to the best fit of triptans for migraine patients. Cephalalgia 2008;28(suppl 2):21–27.
39. Tfelt-Hansen P, Edvinsson L. Pharmacokinetic and pharmacodynamic variability as possible causes for different drug responses in migraine. A comment. Cephalalgia 2007;27:1091–1093.
40. The long-term tolerability and efficacy of oral zolmitriptan (Zomig, 311C90) in the acute treatment of migraine. An international study. The International 311C90 Long-term Study Group. Headache 1998;38:173–183.
41. Tuchman M, Edvinsson L, Geraud G, Korczyn A, Mauskop A, Pfaffenrath V. Zolmitriptan provides consistent migraine relief when used in the long-term. Curr Med Res Opin 1999;15:272–281.
42. Edmeads JG, Millson DS. Tolerability profile of zolmitriptan (Zomig; 311C90), a novel dual central and peripherally acting 5HT1B/1D agonist. International clinical experience based on > 3000 subjects treated with zolmitriptan. Cephalalgia 1997;17(suppl 18):41–52.
43. Schoenen J, Sawyer J. Zolmitriptan (ZomigTM, 311C90), a novel dual central and peripheral 5HT1B/1D agonist: an overview of efficacy. Cephalalgia 1997;17(suppl 18):28–40.
44. Pascual J, Falk R, Docekal R, et al. Tolerability and efficacy of almotriptan in the long-term treatment of migraine. Eur Neurol 2001;45:206–213.
45. Ashford E, Salonen R, Saiers J, Woessner M. Consistency of response to sumatriptan nasal spray across patient subgroups and migraine types. Cephalalgia 1998;18:273–277.
46. Dodick DW, Lipton RB, Goadsby PJ, et al. Predictors of migraine headache recurrence: a pooled analysis from the eletriptan database. Headache 2008;48:184–193.
47. Franconi F, Finocchi C, Allais G, et al. Gender and triptan efficacy: a pooled analysis of three double-blind, randomized, crossover, multicenter, Italian studies comparing frovatriptan vs. other triptans. Neurol Sci 2014;35(suppl 1):99–105.
48. Sheftell F, Almas M, Weeks R, Mathew NT, Pitman V, Lipton RB. Quantifying the return of headache in triptan-treated migraineurs: an observational study. Cephalalgia 2010;30:838–846.
49. Goldberg MR, Lee Y, Vyas KP, et al. Rizatriptan, a novel 5-HT1B/1D agonist for migraine: single- and multiple-dose tolerability and pharmacokinetics in healthy subjects. J Clin Pharmacol 2000;40:74–83.

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