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Migraine in men

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Abstract

Background Migraine is a common primary headache disorder, less frequently affecting men than women, and often regarded as predominantly a "women's disease." Despite this, migraine in men presents with unique characteristics in terms of symptoms, treatment responses, comorbidities, and pain perception. Historically, research has focused more on migraine in women, overlooking critical male-specific aspects.

Results This review delves into the epidemiology, clinical presentation, and particular challenges of diagnosing and managing migraine in men. It addresses sex-specific triggers, hormonal influences, and comorbid conditions affecting migraine prevalence and severity in men. Additionally, the review evaluates current therapeutic strategies, underscoring the necessity for individualized approaches. Men with migraine often exhibit atypical symptoms compared to the ICHD-3 criteria and are less likely to report common associated symptoms. They also tend to have fewer psychological comorbidities, respond more favorably to pharmacological treatments, yet are less likely to seek medical support. The reasons for these sex disparities are complex, involving biological, psychosocial, and cultural factors, such as brain structural differences, differences in functional responses to painful stimuli, hormonal effects, and behavioral influences like adherence to masculine norms and stigma.

Conclusion Men are underrepresented in clinical migraine research. In contrast, preclinical studies often focus solely in male animals as a result of various misconceptions. This disparity necessitates greater focus on sex-specific aspects of migraine to enhance diagnosis, treatment, and research. Addressing stigma, increasing healthcare access, and ensuring balanced sex and gender representation in future studies is crucial for a comprehensive understanding and effective management of migraine for all patients.

Introduction

Migraine is a highly prevalent primary headache disorder affecting 15% of the global population, with a prevalence three times lower in men than in women [1]. The cumulative incidence of lifetime migraine amounts to 18% for men and 48% for women [2]. This disparity in prevalence emerges during puberty, suggesting a potential influence of sex hormones. While the one-year prevalence of migraine in children is comparable, ranging from 2 to 5% among 7–9-year-olds, it increases to 4% in boys and 6.4% in girls aged 13–15 years, with the largest disparity occurring at the age of 30 years [3, 4].

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However, differences between men and women in migraine extend beyond prevalence. There appear to be variations in clinical manifestations and burden, including duration, frequency, pain characteristics, and accompanying symptoms [5–9]. Known sex-specific distinctions in pharmacokinetics and -dynamics can influence the effectiveness and side effects of acute and prophylactic treatments [10, 11]. Studies on preclinical migraine models have demonstrated disparities in migraine-like symptoms and pain responses, indicating sex-specific migraine mechanisms [12].

The underlying causes for sex-specific differences in migraine remain largely unknown but are likely multifactorial, with the influence of sex hormones being a prominent and frequently discussed factor [13–15]. Besides sex-specific effects, also gender-related factors influencing for instance healthcare seeking behaviour, pain reception and -reporting as well as differences in stress may influence a difference in the presentation of migraine in men and women [3].

Numerous studies and reviews have examined the evident sex differences in migraine, focusing predominantly on the female perspective [16–18]. As personalized medicine becomes increasingly the desired standard of care, recognizing differences in clinical presentation, response to acute medication, and underlying pathophysiological mechanisms is crucial. Therefore, this review aims to summarize the distinct aspects of clinical presentation, therapy, pathophysiology, and the impact of social stigma in migraine, specifically highlighting the male perspective to emphasize the need to acknowledge sex-specific aspects in migraine, as they can impact diagnostic accuracy, treatment efficacy and research outcomes. Differences between men and women are not necessarily due to biological sex differences, but may also be caused by differences in gender, which represents a social construct. As there is an interaction between sex and gender, and the definition of the two terms is still under debate [3, 19], we mainly refer to the term 'sex' in this review to indicate (mainly biological) differences between men and women, unless we specifically indicate 'gender'.

Methods

For this narrative review, we conducted searches in Pubmed and Google Scholar between March 2024 and October 2024. The literature search was based on, but not limited to the following terms: migraine, attack, male, man/men, sex, gender, accompanying symptoms, prodromal, CGRP, trigeminal, trigeminovascular, pathophysiology, testosterone, sex hormones, pain modulation, pain processing, neuroimaging, acute treatment, prevention, preventive treatment, prophylaxis, comorbid*, trigger, and cardiovascular. Additionally, we examined the reference lists of the selected articles to identify any relevant studies not initially retrieved. No limitations were applied during the search to ensure comprehensiveness.

Clinical perspective of men-specific aspects on migraine

Men-specific characteristics in clinical presentation of migraine headache

Migraine features

Characteristic migraine features, defined by the International Classification of Headache Disorders 3 (ICHD-3) [20], include unilateral pain, pulsating quality, and aggravation by movement. Some studies suggest that the frequency of these characteristic symptoms does not differ between men and women [21–24]. However, other studies reveal that men experience unilateral pain, pulsating quality, and aggravation by movement less frequently [5, 6]. Regarding the duration of migraine attacks, the vast majority of studies suggest a difference between the sexes. Men, both with and without aura, experience shorter migraine attacks, whether medicated or not, compared to women [5–8, 22]. This finding remains significant even when compared to postmenopausal women, suggesting that it is independent of hormonal influences [7]. Conversely, another study found that while migraine attacks in men lasted shorter than menstrual attacks in women, non-menstrual attacks were of similar duration in men and women [9]. While most studies did not differentiate between episodic migraine (EM) and chronic migraine (CM), one cross-sectional study analysing 184 migraine patients (28% men; 61.4% with EM) identified a difference in migraine duration between the sexes for patients with EM but not CM [23]. To our knowledge, only one study, a population-based Korean cross-sectional study involving 147 migraine patients (25% men), found no difference in headache duration between men and women [21].

Pain intensity

Previous evidence suggests that men have lower pain intensity, higher pain tolerance, and higher pain thresholds than women when exposed to noxious stimuli [25, 26], which appears to extend to the intensity of migraine headaches. Without differentiating between EM and CM, current literature indicates that men report lower migraine pain intensity compared to women, as measured by the visual analogue scale (VAS), and that women have higher pain sensitivity, regardless of cycling hormone levels [5, 6, 23, 27, 28]. In one study that differentiated between EM and CM, men with EM report lower pain intensity than women, while no difference in pain intensity was observed between sexes for patients with CM [23]. Although fewer in number, there are also studies suggesting no difference in headache intensity between men and women [7, 21, 22]. Corresponding to

the clinical data, in a preclinical CM model, male rodents required a higher dose of inflammatory soup to the dura to exhibit locomotor activity changes and remained sensitive for a shorter duration compared to females [12]. However, male rodents also required fewer applications than female rodents to exhibit behavioural changes. This has been argued to be a sex difference in the sensitization of the trigeminal system, with males experiencing sensitization more peripherally and females more centrally [12]. When testing mechanical allodynia, male animals showed increased withdrawal responses to sensory testing of the perimasseter region but not the periorbital region, whereas females responded more to both [12].

Headache frequency

Similar to headache characteristics, the literature is divided regarding differences in the frequency of migraine headaches between men and women. A Korean population-based study including 147 migraine patients (25% men) found no sex difference in the frequency of migraine headaches per month [21]. Likewise, a recent prospective cohort study analysing 184 patients (28% men; 61.4% with EM) reported no difference in monthly headache and monthly migraine days between the sexes [9]. However, a population-based study of 62,672 Danes, of which 12,618 fulfilled a migraine diagnosis (27% men), reported a lower headache frequency in men [5]. Although men experienced migraine headaches less frequently, they had a higher frequency of non-migraine headaches. This discrepancy might be related to the suggested atypical presentation of migraine in men. The characteristics of these non-migraine attacks, however, were not further described, leaving their nature unclear. In a different study that analysed 16,789 migraine patients (25.6% men) via a web questionnaire, men likewise reported significantly fewer headache days per month (4.3 vs. 5.3 days) [28].

In summary, studies regarding sex-specific headache characteristics in migraine are contradictory and often oriented towards the female sex. The analyses mainly involve post-hoc evaluations, which are not powered in the initial experimental design, resulting in uneven sample sizes and thereby increasing the risk of bias.

Men-specific characteristics in migraine attack accompanying symptoms

Accompanying symptoms such as nausea, vomiting, photophobia, and phonophobia are core criteria of a migraine attack [20]. Current literature predominantly indicates that men are less likely than women to suffer from nausea, vomiting, osmophobia, phonophobia, photophobia, allodynia, and cranial autonomic symptoms, also when compared to postmenopausal women [5, 8, 9, 22, 23, 29, 30]. Interestingly, while a sex difference in the incidence of nausea was consistently observed, this was not always the case for vomiting [22, 31], as one study reported that vomiting and phonophobia occurred more often in boys than in girls [24]. Nevertheless, this study was performed in children and adolescents, which severely limits the transferability, as children can differ fundamentally from adults in the phenotypic presentation of migraine attacks [21]. Migraine aura symptoms were more common among men compared to both perimenstrual and non-perimenstrual attacks in women in a study including 1,631 migraine patients (18% men) [9]. In addition, a higher proportion of migraine attacks with aura symptoms occurred in men diagnosed with migraine with aura compared to women diagnosed with migraine with aura [9].

Men-specific characteristics in prodromal symptoms

Pro- and postdromal symptoms in migraine affect 30–80% of all migraine patients and commonly include fatigue, irritability, yawning, and neck stiffness [32, 33]. Several studies found no differences in premonitory symptoms, prodrome frequency, or duration between the sexes [34–38]. One cross-sectional questionnaire study [39] of 2,223 individuals meeting migraine criteria and a questionnaire-based study [33] including 374 migraine patients reported that men experienced prodromal symptoms less frequently and with a fewer number of different symptoms compared to women.

Men-specific migraine comorbidities

Migraine is comorbid with various medical conditions, including cardiovascular diseases, hypothyroidism, asthma, allergies, epilepsy, and stroke, as well as psychiatric disorders such as depression or anxiety, and functional somatic conditions such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome [40–42]. Research on sex differences in comorbidities is limited and conflicting. A Danish twin study of 8,044 patients with self-reported migraine revealed that men had fewer comorbidities than women (7 vs. 18) [43]. Another study of 223 migraine patients (16% men) revealed distinct sex-based comorbidity profiles; while men were more likely to have somatic conditions including hypertension, hyperlipidaemia and hypothyroidism, women were more prone to have psychiatric conditions such as depression and anxiety [44]. In addition, men with migraine are more often diagnosed with coronary thrombosis, Scheuermann's disease, and kidney stones than women [45, 46]. These findings must be interpreted with caution due to the potential gender bias in diagnosing somatic versus psychiatric conditions—with the same symptoms, men tend to receive somatic diagnoses, whereas women are more often diagnosed with psychiatric or psychosomatic conditions [47, 48]. This bias

could increase the likelihood of overlooking psychiatric illnesses in men. However, the literature on psychiatric comorbidities is divided, with some studies [49] indicating higher prevalence in women and other studies finding no significant gender differences [41, 50].

Cardiovascular comorbidities

The association between cardiovascular disease and migraine with aura is well established [51, 52]. While the female sex is considered an independent risk factor for the development of ischaemic events in migraine patients and a large meta-analysis reported a lower risk for men compared to women [53], men with migraine still have an increased risk for major cardiovascular disease and myocardial infarction [54]. Compared to men without migraine, men under the age of 60 with migraine were shown to have an increased risk of iscahemic stroke [55] and men with migraine with aura were reported to have increased all-cause mortality and mortality from cardiovascular disease, attributed to higher mortality rates from coronary heart disease and stroke [46]. Interestingly, a national, prospective, population-based cohort study in Sweden found that young men with lower cardiovascular fitness had a higher long-term risk of developing migraine requiring pharmacological treatment [56]. Nevertheless, studies in men are limited and more data are necessary to draw reliable conclusions on the cardiovascular risk in men and women with migraine.

Evidence on men-specific triggers in migraine

Many migraine patients report various factors as triggers for their migraine attacks, including stress, loud noises, fasting, food, menstruation, weather changes, sleep disturbances, odours and alcohol [57–59]. Limited data suggest sex differences in the prevalence and types of triggers. While stress, wind, hunger, and sleep deprivation are equally reported by men and women [60–62], a study from 2020 of 871 migraine patients (27% men) found odour to be a more frequent trigger for women and excessive sleep for men [60]. Another cross-sectional study investigating 6,786 migraine patients revealed that men reported fewer trigger factors than women, even when menstruation was disregarded in the analysis [63]. Out of 11 triggers, only alcoholic beverages, physical exercise, and certain foods were more frequently reported by men, while the remaining triggers were more common in women. However, disregarding menstruation, the most common primary triggers for both men and women were stress and bright light. One hypothesis for sex differences in migraine triggers is the influence of fluctuating sex hormones [13, 63]. Although the exact pathophysiological mechanism is unclear, it has been suggested that hormonal fluctuations may alter neuronal excitability, thereby lowering the migraine threshold in women and increasing their susceptibility to external triggers [63–65]. This hypothesis is supported by the finding that postmenopausal women report a similar number of triggers as men [63–65].

Provocation studies in men with migraine

Human experimental provocation studies have identified various substances capable of inducing migraine-like headaches (thoroughly reviewed in [66]). However, with the exception of one study on CGRP-induced migraine attacks, which found no association between CGRP hypersensitivity and sex [67], human provocation studies did not differentiate between women and men, failed to report gender-specific results [68–71], or predominantly included women [72, 73], thereby preventing any meaningful analysis of sex differences.

Migraine features in ageing men

Migraine prevalence in men peaks between the ages of 20 and 45 years, simultaneous to the peak of prevalence in women, and decreases again with ageing [74]. Migraine symptoms can differ with age [75], more often presenting as bilateral migraine attacks [76] with fewer associated symptoms such as vomiting and photo- or phonophobia at higher age [76, 77]. Moreover, migraine aura becomes more common with increasing age, although its features tend to be less typical concerning the frequency and duration of symptoms [77]. Unfortunately, a distinction between ageing men and women was not made in these studies. A different study looking into age-related migraine characteristics in men and women (35% men) detected an increase in headache frequency and duration in ageing men, whereas women only had an increase in headache duration with ageing [78]. Due to the limited number of male participants, significant changes in pain characteristics and associated symptoms could not be detected. Larger studies in men are needed to detect age-related changes in migraine.

Changes with age have also been observed in preclinical studies. A recent study demonstrated that the maximum response of human middle meningeal arteries to exogenous calcitonin gene-related peptide (CGRP), which is a relevant structure and functional response for the pathophysiology of migraine, decreases with age in men, whereas the maximum response increases with age in women [79]. This decrease in maximum effect to CGRP is hypothesized to be caused by a decrease in CGRP receptor expression, possibly induced by changing levels of sex hormones [79]. Decreased CGRP receptor expression could subsequently result in decreased migraine susceptibility in elderly men. Future research should confirm the exact relationship between sex hormones, CGRP levels, and CGRP receptor expression in migraine-relevant structures.

Men-specific pathophysiological perspective on migraine

Brain structural differences between men and women

Differences between brain structures of subjects with and without migraine have been reported for regions such as the hypothalamus, insula, brainstem, and amygdala [80]. Most neuroimaging studies, however, have either only included women with migraine or have not investigated sex differences, leading to less knowledge about the male-specific neuropathology of migraine (reviewed in [80]). An interaction between sex and migraine concerning brain structural differences has been observed by Maleki and colleagues [81] who discovered that men had migraine-related structural changes to the parahippocampal gyrus volume, whereas women with migraine had a thicker posterior insula and precuneus. In addition, functional responses to noxious heat stimuli were smaller in men compared to women with migraine in regions involved in emotional processing, including the amygdala and parahippocampus [81]. The incidence of white matter abnormalities was higher in women with migraine compared to healthy controls, whereas no such difference was observed in men [82].

In summary, there is an insufficient number of studies addressing the anatomical differences between men and women with migraine. As there are known sex-specific differences in brain anatomy in healthy subjects, stratifying migraine patients by sex may improve our knowledge about the interaction between sex and disease-related alterations in migraine.

The influence of sex hormones in men with migraine

Pathophysiological influences of sex hormones

Testosterone has antinociceptive effects [83]. Preclinical evidence suggests that testosterone during early life is essential for the development of well-balanced antinociceptive responses [84, 85]. Neuroimaging has shown that in women who have low endogenous oestradiol resulting from using the combined oral contraceptive pill, activity of key regions of descending pain pathways increased with increasing testosterone, and that this activity was significantly reduced compared to controls [86]. Via this route, testosterone may play a crucial role in modulating pain sensitivity in these women.

In familial hemiplegic migraine (FHM)1 knock-in mice, females had a higher susceptibility for cortical spreading depression (CSD), the neuronal substrate thought to underly migraine aura [87, 88], which diminished after ovariectomy. Vice versa, susceptibility was increased after orchiectomy and restored after testosterone replacement in male mice [89, 90]. This demonstrates that susceptibility for CSD was influenced in opposite direction by sex steroids, with androgens suppressing and oestrogens increasing susceptibility.

Progesterone is believed to exert a neuroprotective effect by attenuating nociception in the trigeminovascular system [91]. The number of cells in the trigeminal ganglion (TG) system expressing progesterone has been found to be lower in male than female rats [92]. The same study showed that pretreatment with progesterone did not alter basal CGRP release, but it slightly decreased capsaicin-induced CGRP release from the male TG, though not from the dura. In the female dura or TG, progesterone did not increase capsaicin-induced CGRP release [92], although it has been shown by others to increase basal CGRP release [93]. Additionally, capsaicin-induced vasodilation was more potent after incubation with progesterone in the male but not female basilar artery. On the other hand, substance P release has been shown to be reduced in the TG of female but not male animals [93].

Progesterone can be rapidly converted into allopregnanolone, a neuroprotective neurosteroid that also plays a role in the modulation of nociceptive pain, however, via a different mechanism than progesterone [94, 95]. Allopregnanolone is a potent positive allosteric modulator of $GABA_A$ receptors and is possibly able to decrease nociception via this route [94, 95].

Although the modulatory direction of oestrogens on nociception is a matter of debate [15], there is a large body of evidence indicating that a decline in oestrogen levels may increase susceptibility to migraine attacks [16, 91]. Oestrogen receptor (ER) expression was lower in the TG of male rats compared with female rats, with ERα being more abundant than ERβ [96, 97]. Relaxation induced by 17β-oestradiol, which activates both ERα and ERβ receptors, did not differ between sexes. However, an ERβ-selective agonist induced relaxation in female but not male middle cerebral arteries [97]. In a study that investigated dural vasodilator responses in ovariectomized female rats, supplementation of 17β-oestradiol increased neurogenic vasodilation, suggesting enhanced CGRP release from periarterial nerve endings [98].

It has also been reported that progesterone or 17β-oestradiol, but not their combination, increased basal CGRP release in male rat TG [93].

Sex hormone levels in men with migraine

Clinical data on the influence of testosterone in migraine are scarce. Shields et al. (2019) reported that men with CM had lower total testosterone levels compared to published levels of age-matched controls [99]. Conversely, another study found no difference in free testosterone levels during the interictal phase in nonobese men with migraine compared with healthy men, although they did observe clinical evidence of relative androgen deficiency and higher interictal levels of 17β-oestradiol compared to healthy controls [100]. Similarly, Li et al. (2018) found

no difference in testosterone levels between men with migraine and healthy men but observed higher levels of gonadotropin hormone-releasing hormone, which stimulates the testicles to produce testosterone, compared with healthy controls [101]. No differences were observed for plasma oestrogen levels in men with migraine versus healthy men. However, oestrogen levels were negatively correlated with the Migraine Disability Assessment Score (MIDAS), a tool to evaluate the impact of migraine on the individual's life [102], indicating that higher oestrogen levels were associated with lower migraine-related disability. In one study, serum progesterone levels were lower in men with migraine compared to healthy controls and negatively correlated with migraine disease duration [101]. Levels of allopregnanolone appeared lower in patients with migraine compared to healthy controls in a study that did not stratify by sex [103], as well as in a study comparing women with migraine to men and women without migraine [104]. Furthermore, in a study that included postmenopausal women, allopregnanolone levels were lower in those with migraine than in those without migraine [105]. Prolactin levels have shown mixed results, with studies reporting both higher and lower levels in men with migraine compared to healthy men and those with non-migraine headaches [101, 106].

One study suggests that the prenatal ratio between oestrogen and testosterone might be a risk factor for developing migraine. They found that men with migraine had a higher second-to-fourth digit ratio, a proxy for prenatal sex steroids, suggesting a lower testosterone-to-oestrogen proportion compared with controls [107]. These results suggest that alterations in the delicate balance between sex hormones may alter the susceptibility of developing migraine.

Headache in the transgender population

The transgender population, especially those treated with gender-affirming hormone therapy (GAHT), allows us to investigate how the introduction of sex hormones may influence migraine patterns and helps to disentangle the importance of sex hormones versus sex chromosomes. In transgender men (i.e. women at birth identifying as a man), there are several reports of an improved frequency and intensity of migraine or headache after GAHT with testosterone [108, 109]. Conversely, in transgender women (i.e. men at birth identifying as a woman), headaches may worsen after initiation of GAHT [108]. In addition, a small uncontrolled study reported that transgender women taking GAHT had similar rates of migraine as cisgender women (i.e. women at birth identifying as a woman) [110]. For a comprehensive review on migraine in the transgender population we refer the reader to Martinez et al. (2023) [111]. Collectively, these results suggest that sex hormones contribute to the severity and prevalence of migraine. Nevertheless, it is also possible that these effects result from an altered hormonal balance that the body is not accustomed to. Additionally, other physiological or neurological processes unique to transgender individuals may already be in progress before the initiation of GAHT, potentially leading to differences in hormone balance or functional brain responses compared to the cisgender population. Until controlled studies have been conducted on the relationship between GAHT and migraine, no firm conclusions can be drawn about the causality of changes in sex hormone balance on migraine prevalence and severity. Moreover, the transgender population may also offer a unique perspective on how gender contributes to sex differences in migraine.

Evidence on sex-specific differences in migraine pathophysiology

The trigeminovascular system

Sex differences have been observed for the release, receptor expression, and functional responses of CGRP. In the dura mater, basal CGRP release is lower in male compared with female rats, but potassium-evoked CGRP release from the dura and TG is not different per sex [97, 112]. Expression of the CGRP receptor subunits RAMP1 and RCP is lower in male rats compared with female rats, but CLR expression is similar [92, 113]. In a preclinical model for chronic migraine, the mRNA levels of RAMP1, CLR, and RCP were higher at baseline in male rats than female rats, however, after application of inflammatory soup or, somewhat surprisingly, phosphate buffered saline, these levels increased more in female than male rats, demonstrating an interaction between sex and disease [12]. Application of CGRP to the dura induces female-specific facial and hind paw hypersensitivity, demonstrating stronger pain-related responses [114]. Functional responses to CGRP in human middle meningeal arteries are smaller in women than men in a population younger than 50 years, but this difference is absent in older age groups or in human coronary arteries [79]. These sex-specific responses may be due to alterations in the CGRP pathway itself, or through mechanisms modulating CGRP release and signalling.

PACAP-38 is a potent vasodilator that plays a role in pain transmission and migraine [115]. PACAP-38 and its receptors are expressed in the TG and can be regulated by oestrogens, with higher oestrogen levels potentially leading to a greater response to PACAP-38 in women than in men [116, 117]. It is yet unclear whether sex-dependent variations in PACAP-38 signalling contribute to the sex differences found in migraine [118].

Transient receptor potential (TRP) channels are involved in transducing sensory signals, including thermal and nociceptive stimuli [119]. Several families of

TRP channels have been implicated in the pathophysiology of migraine in a sex-specific manner, and their activation can trigger a migraine attack [120]. Activation of TRPV1 channels by capsaicin stimulates the release of CGRP. This concept has, therefore, been widely used as an experimental migraine model. Healthy men have a lower response to capsaicin than women, indicating less sensitization [121]. Men with migraine have a similar response to healthy controls, whereas women with migraine had a higher response than healthy controls, suggesting a sex-disease interaction [121, 122]. Mechanisms that may underly the sex-specific activation of TRP channels include their modulation by sex hormones (reviewed in [123, 124]). Briefly, the sensitivity of TRPV1 and TRPA1 channels can be enhanced by oestrogens but reduced by progesterone. Similarly, activation of the oestrogen receptors ERα and ERβ can induce upregulation of TRPV1 channels, whereas progesterone may downregulate TRPV1 channels [125]. Another potential sex-specific modulator of TRPV1 channels is serotonin, or 5-HT, which is known to be involved in the pathophysiology of migraine. In human dental pulp, which is innervated by the mandibular branch (V3) of the TG, 5-HT increased capsaicin-induced CGRP release in women but not men, possibly via differential modulation of TRPV1 [126]. Notably, the TG of male mice exhibits higher levels of key enzymes involved in 5-HT synthesis compared with females [127].

The temperature-sensitive TRPM8 channels have been linked to migraine in large GWAS studies [128–132]. These channels are less sensitive in the TG of male compared with female mice [133, 134]. Testosterone can regulate TRPM8 both via genomic regulation and as an agonist, whereas oestrogen and progesterone can reduce TRPM8 activity [123].

Pain modulation and processing

Recent research has identified a dysregulation of the endocannabinoid system in migraine [135]. The endocannabinoid system is influenced by gonadal hormones, potentially underlying sex-specific responses of this system. The main receptors, CB1 and CB2, modulate pain and inflammation and display a sex-specific pattern in expression and responses. CB1 receptor upregulation has been shown to be testosterone-dependent in men but not women during inflammatory situations in the trigeminal ganglia [125]. In contrast, women are more susceptible to effects of tetrahydrocannabinol (THC), which is a partial agonist at CB1 and CB2 receptors [136]. When compared to healthy controls, plasma concentrations of anandamide, a primary endocannabinoid, are lower in patients with migraine, particularly in those with chronic migraine. This effect is more pronounced in women with migraine, where degradation of anandamide occurs at a faster rate, leading to reduced levels [137]. Preclinical data has demonstrated higher levels of anandamide and 2-AG in healthy female animals compared with male animals [138]. Consequently, differences between healthy subjects and patients may be much larger in women compared to men.

The opioid system involves endogenous opioid peptides that modulate pain perception by acting on mu, delta, and kappa opioid receptors, which regulate nociceptive pathways and can influence the sensitivity and transmission of pain signals [85]. A dysregulation of the opioid system has been suggested to be implicated in the pathophysiology of migraine [139]. There is evidence that women have a better response to treatment with opioids than men, even though opioids should not be part of the treatment plan for migraine [140, 141]. The opioid system can be modulated by sex hormones, thereby altering pain sensitivity and opioid receptor function. While oestrogen can enhance the function of several opioid receptors, thereby facilitating nociception, testosterone has been suggested to inhibit hyperalgesia, in part via modulation of mu opioid receptors [140, 141].

The pituitary-derived hormone prolactin has a pronociceptive effect and has been reported to play a modulating role in migraine and contribute to its sex-dependent differences via a female-specific mechanism [142, 143]. The hypothalamic neuropeptide oxytocin is thought to play an anti-nociceptive role, with men potentially being more perceptive to its analgesic effects [144, 145].

Clinical perspective of men-specific aspects on migraine treatment

Men-specific characteristics of pharmacokinetics and pharmacodynamics

Pharmacokinetics and pharmacodynamics may show sex-specific differences due to several underlying reasons. On average, men have higher body weight, length, and surface area, resulting in a larger volume of distribution (Vd). The Vd may also show sex-dependent differences depending on the lipophilicity of a drug, because men have a lower percentage of body fat and higher body water content [10, 11]. Plasma-protein binding also shows sex-dependent differences, with men generally having a smaller free fraction of a drug [11]. As a result from faster hepatic and renal metabolism, men have faster clearance for most drugs. Hepatic clearance consists of two phases: for phase 1, the majority of drugs are metabolized by the cytochrome P450 superfamily of enzymes, which demonstrate complex sex-dependent disparities [146]. Most enzymes responsible for phase 2 metabolism have higher activity in men, and it is suggested that some of these enzymes may be regulated by oestrogens and androgens. Other pharmacokinetic parameters that may differ across

sexes include drug absorption and cardiac output [11, 147]. Differences on the level of pharmacodynamics may also exist, e.g., through distinct receptor expression or binding, as well as signalling pathways. In summary, sex-specific characteristics of pharmacokinetics and pharmacodynamics may impact drug efficacy and adverse effects [148]. While men generally exhibit faster drug clearance and larger volumes of distribution, women may show heightened sensitivity to certain treatments. However, the clinical relevance of these sex differences remains unclear for many migraine therapies.

Men-specific characteristics in acute and prophylactic treatment

Sex disparities in the pharmacokinetics and -dynamics of migraine treatment prompt consideration of potential differences in medication efficacy and tolerability. However, only very few publications have investigated these differences specifically, with studies often featuring low male participation and lacking the statistical power to discern sex-specific outcomes.

Non-specific acute migraine treatment

Findings regarding non-specific acute medication are contradictory and the available evidence focuses on other pain conditions rather than migraine. For instance, while one older study hinted at a heightened efficacy of ibuprofen in relieving pain among men in experimental settings [149], another suggested a more favourable response among women following tooth extraction [150]. Ibuprofen belongs to the pharmacological class of non-steroidal anti-inflammatory drugs (NSAIDs), which function by inhibiting the enzyme cyclooxygenase, thereby blocking the conversion of arachidonic acid to prostaglandins. Although some evidence points to sex-specific efficacy of NSAIDs, its direct relevance to migraine is unclear [151]. Additionally, acetylsalicylic acid is absorbed and cleared more slowly in men, but its impact on sex-specific efficacy remains unknown [151].

Specific acute migraine treatment

For specific acute migraine treatments, the evidence remains scant, with a lack of dedicated studies and reliance exclusively on pooled results. A meta-analysis examining sex differences in triptan response, drawing from 19 publications, included data from 2,280 men and 13,899 women [152]. Men and women exhibited similar rates of 2-hour pain freedom. Men, however, despite having lower drug exposure than women, had a 36% lower risk of headache recurrence compared to women, and they were also 18% less likely to report adverse events [152]. Triptans reduce CGRP release, neuronal excitability and sensitization via agonism of the 5-$HT_{1B/1D(/1F)}$ receptor [153]. Oestrogens can modulate 5-HT levels, receptor expression, and functional responses, which may contribute to the sexual dimorphism in sumatriptan sensitivity observed in rats, with females being more sensitive at lower concentrations than males [151, 154]. So far, no clinically meaningful pharmacokinetic sex-specific variation has been reported for the ditans, which are 5-HT_{1F} receptor agonists [155].

In contrast, a meta-analysis for gepants as acute treatment revealed statistically significant effects in women but not in men [156]. While the lack of statistically significant treatment effects in men may easily be assigned to a lower statistical power in the group of men because of less male (only 17% of the pooled cohort) than female participants in the clinical trials, the number needed to treat in men was notably higher at 36 compared to 11 for women, indicating a preferential effect of gepants in women.

Non-specific prophylactic migraine treatment

Regarding migraine prevention, the available evidence for sex-specific treatment outcomes for unspecific medications such as beta-blockers, ACE inhibitors, calcium channel blockers, antidepressants, or anticonvulsive drugs is limited. Studies examining sex differences in other conditions have yielded varied results. For instance, no sex differences were found for the efficacy of beta-blockers and ACE inhibitors in heart failure [157]. Beta blockers are, however, cleared more rapidly in men compared with women [11]. Furthermore, the Vd of most beta blockers is reported to be larger in men, resulting in lower systemic exposure [11], although one study suggests that this may not hold true for propranolol [158]. Nevertheless, a study in healthy controls found that acute administration of propranolol mediates the trigeminovascular system in a sex-dependent manner, possibly via interactions with sex hormones. They found that capsaicin-induced dermal blood flow could be attenuated by propranolol in men, but not women on contraceptives, possibly via agonism of the 5-HT_1 receptor [159]. In idiopathic generalized epilepsy, men tend to exhibit superior seizure remission under valproate treatment compared to women [160]. Notably, there has been no dedicated study exploring sex-specific responses to migraine treatment. In epilepsy patients, age and sex are significant factors that influence the volume of distribution of topiramate [161]. Sex-specific differences in drug clearance for calcium channel blockers depend on the method of administration, and selective serotonin-reuptake inhibitors (SSRIs) tend to have lower plasma concentrations in men due to faster hepatic clearance [151].

While it is crucial to recognize the potential higher prevalence of adverse events in women [162], men are not exempt from adverse events. For instance, amitriptyline-associated sexual dysfunction occurs up to six times

more often in men compared to women [163], and the use of beta-blockers poses a risk of erectile dysfunction in over 10% of men [164].

Specific prophylactic migraine treatment

In terms of preventive treatment with CGRP-targeted treatments, pooled results from Food and Drugs Administration (FDA) reviews have consistently favoured drug treatment over placebo in both sexes, although the improvements from baseline for primary endpoints appear to be higher in women compared to men [156]. In a dedicated post-hoc analysis of the FOCUS study including 837 individuals with 2–4 prior preventive treatment failures, reductions in migraine and headache days, acute medication use, and disability were comparable between men and women [165]. Similarly, in a real-world pooled analysis of 1,140 participants from 16 centres (18% men), response rates with erenumab after three months of treatment were similar for men and women [166]. In a pooled meta-analysis of real-world trials, the sex of the participants did not emerge as a predictor of response, confirming similar treatment outcomes across genders [167]. One case report has demonstrated erectile dysfunction as a potential, overlooked side effect of CGRP-targeted treatments, although this needs to be studied further [168]. So far, no clinically meaningful pharmacokinetic sex-specific variation has been reported for the gepants and monoclonal antibodies that target the CGRP pathway [169–174], despite the sex-related differences in the pharmacology of CGRP, as discussed above.

Differences in behaviour

Sex- and gender-specific differences in behaviour can significantly impact how men with migraine navigate their condition and seek support. Due to adherence to traditional masculine gender norms, men may be deterred from seeking help [175]. Traditional norms such as stoicism, self-reliance, and restrictive emotionality are consistently observed in men across different ethnic backgrounds and age groups [176]. Furthermore, given the historical perception of migraine as a predominantly women's disease, men may find it challenging to seek care, facing stigma surrounding a "feminized" condition [3].

The apparent lower burden of migraine experienced by men compared to women may be influenced by underreporting, potentially leading to inadequate diagnosis and treatment. Studies indicate that men are less likely to seek professional help for their migraine and are less inclined to discuss their condition with their general practitioner [177].

In the 2004 American Migraine Prevalence and Prevention Study, men with migraine reported lower headache-related disability compared to women. They were less likely to report inability to perform household tasks, poor work and school productivity, or missed social activities [49]. Additionally, men were more likely to function despite their migraine, whereas women often required bed rest and sought medical attention at emergency departments for severe headaches. Conversely, however, the lower reported burden experienced by men with migraine could be counterproductive, potentially resulting in poorer care. In fact, men who met diagnostic criteria for migraine were less likely to receive a diagnosis and also to have ever received preventive treatment [49].

Data on patient-reported outcome measures, such as the impact of headaches on daily life measured by scores like the Headache Impact Test-6 (HIT-6), are scarce. A Korean population-based study found no difference in the HIT-6 score between men and women with migraine, except for probable migraine, where men scored lower [21]. Men scored also significantly lower on the "consequences" (how much the illness affects the patient's life) and "emotional response" (how much the illness causes unpleasant emotions) items of the Brief IPQ than women [178].

In addressing these disparities, future strategies should aim to raise awareness and reduce stigma surrounding migraine, also among men. By promoting open dialogue and challenging traditional gender norms, all individuals should feel empowered to seek help and receive appropriate care for their migraine symptoms.

Understanding of the role of men-specific aspects in migraine attacks, treatment, and research

Attacks and treatment

Although the literature is divided on this issue, there is evidence suggesting that the clinical presentation of migraine attacks in men differs from that in women. In men, the symptoms may be less typical than those described in the ICHD-3 criteria and less frequently accompanied by the typical associated symptoms (Fig. 1) [5–9]. Coupled with the widespread social stigma, not only among the general population but also within medical circles, that migraine is a "women's disease", it seems likely that men are underrepresented and neglected in the accurate diagnosis of migraine [3]. It may also possible that the criteria for diagnosing migraine may, to some extent, have been developed under the assumption that migraine is primarily a "women's disease". Consequently, ICHD-3 criteria may represent 'female' symptoms more comprehensively than 'male' symptoms. This bias could result in a diagnostic framework that better identifies and addresses symptoms typically experienced by women, potentially overlooking or underrepresenting the symptoms more commonly reported by men.

The stigma of migraine as a "women's disease" further complicates the issue, leading to men being less likely to

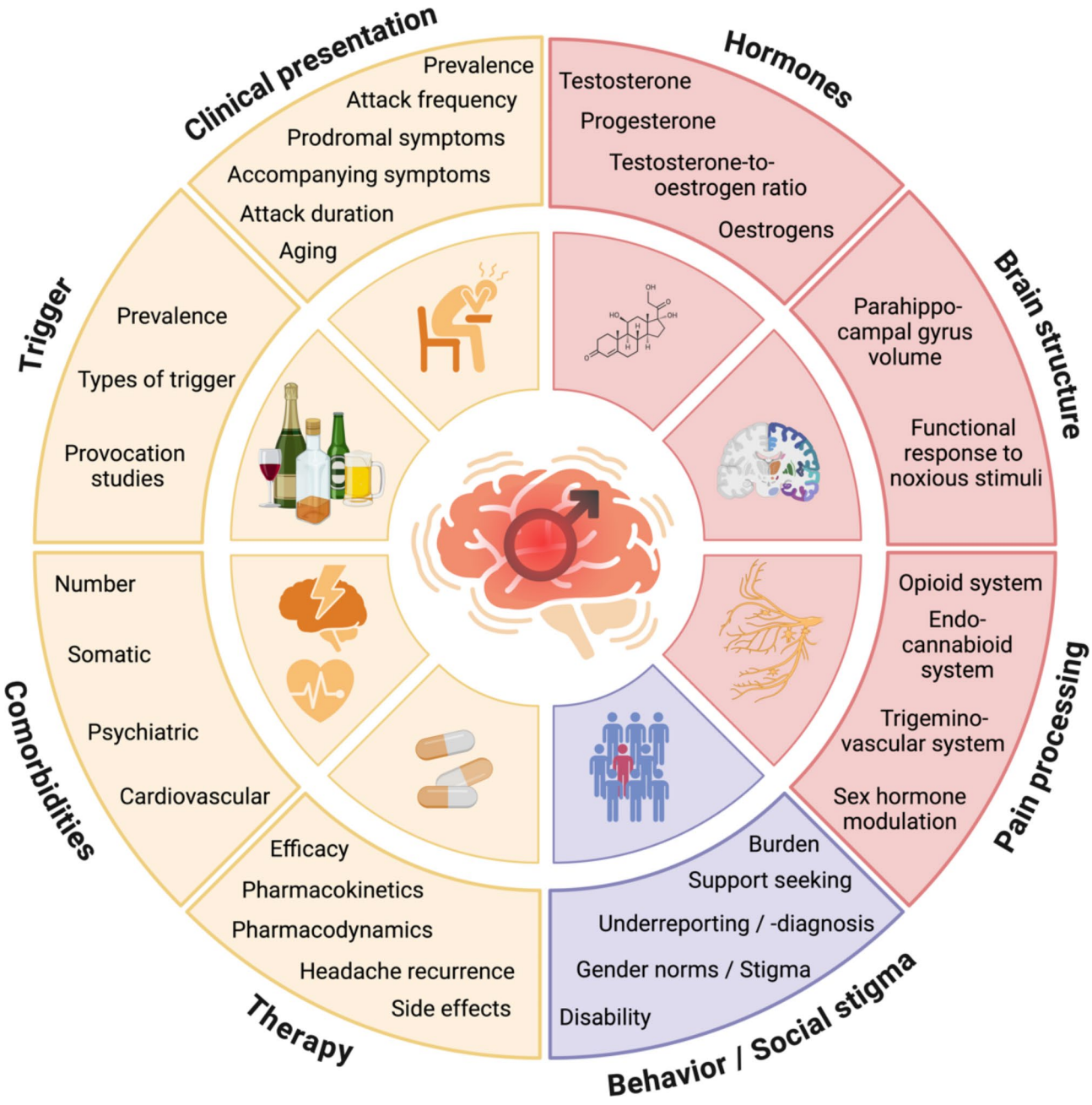

Fig. 1 Levels and sources of men-specific features of migraine

seek medical advice [3, 175, 177]. This delay increases individual suffering and exacerbates the overall socioeconomic burden of migraine due to decreased productivity and increased healthcare costs [49]. Addressing this issue requires not only educating the general public to reduce stigma but also ensuring that healthcare providers, including emergency room staff, are trained to recognize and treat migraine in men without bias. This focus on education could help to ensure that men receive appropriate and timely diagnosis and treatment for migraine, mitigating the biases that currently exist.

In terms of treatment, additional research towards personalized, or at least sex-specific, treatment strategies is needed to improve care. Meanwhile, clinicians should be mindful of potential side effects, including stigmatized side effects such as erectile dysfunction [164, 168]. Overall, reducing stigma, revising diagnostic criteria, and conducting sex-specific research are essential to better meet the needs of men with migraine.

Research

Given the natural differences in migraine prevalence and the current focus on women in migraine research, men are often underrepresented in migraine studies, leading to a lack of statistical power, as well as an increased risk of bias. Preclinical studies, on the other hand, often include solely male animals, with the aim of minimizing the impact of cycling hormones in female animals [179]. In addition, this sex bias in preclinical research stems from two misconceptions: firstly, that a loss of power occurs when assessing both sexes [180, 181]. Secondly, that variability will be less in male than in female animals [182]. The approach of only including male animals diminishes the opportunity to investigate sex differences in the pathophysiology of migraine. As sex-specific aspects can impact research outcomes, diagnostic accuracy, and treatment efficacy, these differences should be acknowledged.

Sex differences are evident in systems that play a role in migraine, including the trigeminovascular system, the endocannabinoid system, and the opioid system [65, 85, 91, 120, 125, 135–138]. In addition, sex hormones may act in different ways in men and women [93, 97]. The potentially altered hormonal balance in men with migraine may increase the susceptibility for migraine features and affect sex differences in migraine [100, 107, 111]. Nevertheless, a large body of evidence indicates that hormonal influences are not the only influences at play. Sex differences in the pathophysiology of migraine may also arise from other factors, including genetic influences which are consistently present or interactions between sex and the underlying disease processes, as well as gender-related factors.

The use of healthy people and animals in preclinical research towards sex differences may bypass certain sex-specific variations observed in migraine, as this approach omits the possibility of studying interactions between migraine and sex. Therefore, it is important to not only investigate the role of sex in the pathophysiology of the systems involved in migraine, but also to work with suitable preclinical disease models.

Conclusions

In conclusion, considering the reported differences in migraine of men and women (Fig. 1) and the fact that men are often underrepresented in migraine studies, limiting the understanding of male-specific pathophysiology and symptom presentation, we must acknowledge that men with migraine may be underdiagnosed and overlooked in a research landscape primarily focused on female characteristics. It is important, though, to consider sex-specific aspects in migraine research, as they can impact diagnostic accuracy, treatment efficacy and research outcomes. Hence, there is a clear need for dedicated studies that examine the influence of sex and gender on migraine. In addition, men should be supported in accessing appropriate migraine care, while efforts are made to reduce the social stigma associated with migraine in men. Future research should ensure adequate representation of both men and women to allow comprehensive analyses of the sex- and gender-specific aspects of migraine.

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Figure 1 was created using BioRender.com.

Author contributions

MF and DMB took the lead in writing the manuscript. MF, DMB, TdV, CH, HF, and BR wrote the main manuscript text. MF and DMB prepared Fig. 1. MF, DMB, TdV, BR, and AMvdB prepared the outline of the review. MF and DMB share the first authorship. BR and AMvdB share the last authorship. All authors provided critical feedback and helped shape the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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