Headaches, hormones, and transgender individuals: current evidence and knowledge gaps

Olga Grodzka[1,2]*, Anna K. Szewczyk[3], Marta Antkowiak[4], Arnold Kukowka[5], Piotr Woźniak[6], Monika A. Białecka[5], Izabela Domitrz[1]

[1]Department of Neurology, Faculty of Medicine and Dentistry, Medical University of Warsaw, Poland
[2]Doctoral School, Medical University of Warsaw, Poland
[3]Department of Neurology, Medical University of Lublin, Poland
[4]Department of Otorhinolaryngology and Oncological Laryngology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland
[5]Department of Pharmacokinetics and Therapeutic Drug Monitoring, Pomeranian Medical University, Szczecin, Poland
[6]Department of Psychiatry, Bielanski Hospital, Warsaw, Poland

***Corresponding author:**
Olga Grodzka MD
Department of Neurology
Faculty of Medicine
and Dentistry
Medical University of Warsaw
80 Cegłowska St
01-809 Warsaw, Poland
E-mail: olga.grodzka.124@gmail.com

Submitted: 10 April 2026; **Accepted:** 18 June 2026
Online publication: 5 September 2026

Arch Med Sci 2026
DOI: https://doi.org/10.5114/aoms/224765

Abstract

Migraine is a prevalent primary headache disorder affecting 14–17% of the global population and is strongly influenced by sex hormones. However, its characteristics in transgender individuals remain poorly understood and insufficiently studied. This review synthesizes evidence from 126 publications across neurology, otorhinolaryngology, pharmacology, and psychiatry to explore potential relationships between migraine and transgender health. Findings suggest that sex-related differences in migraine extend beyond epidemiology to clinical presentation, severity, and management, and may manifest uniquely in transgender patients. Factors such as gender-affirming hormone therapy, psychosocial stress, internal conflict, minority stress, and societal stigma may contribute to an increased headache burden. Additionally, barriers to healthcare access and limited provider knowledge may further complicate diagnosis and treatment. Despite these insights, data remain limited and fragmented. Greater awareness, interdisciplinary collaboration, and further research are needed to improve understanding and to develop more personalized, inclusive, and effective approaches to migraine management in transgender populations.

Key words: gender diverse individuals, gender diverse population, primary headache disorders, transgender individuals.

Introduction

Migraine constitutes a primary, recurrent headache disorder characterized by unilateral pulsating pain of moderate or severe intensity aggravated by routine physical activity with concurrent autonomic symptoms and/or photo- or phonophobia [1]. Despite the high prevalence of migraine disorder (estimated at 14–17% depending on the global region) and its substantial socio-economic and personal impact [1, 2], the condition remains underdiagnosed and undertreated [3].

Gender incongruence is defined by the World Health Organization's International Classification of Diseases (ICD-11) as a marked and persistent incongruence between an individual's experienced gender and the sex assigned at birth, often accompanied by a strong desire to transition socially, legally, or medically. This terminology replaces the ICD-10 category of "transsexualism" and reflects a global shift toward a non-pathologizing, affirming classification of gender diversity [4]. In parallel, the American Psychiatric Association's DSM-5 replaced the earlier diagnosis of "gender identity disorder" with gender dysphoria, emphasizing that it is not the incongruence itself but rather the associated psychological distress that warrants clinical attention [5]. Regarding the terminology, the term transgender and gender diverse (TGD) refers to people whose gender identity or expression does not match the sex they were assigned at birth. This includes transgender men and women, as well as non-binary and other gender-expansive individuals. In medical and scientific writing, the terms assigned female at birth and assigned male at birth are used to describe someone's recorded sex at birth. These labels help researchers and clinicians talk about biological and hormonal factors that may affect health, without making assumptions about a person's gender identity. Using such terms improves clarity and supports respectful, inclusive communication in transgender health research.

The proportion of TGD individuals worldwide ranges from 0.3% to 4.5% (including 0.3–0.5% who specifically identify as transgender), with an observable increase in this percentage in recent years, especially among adolescents [6, 7]. TGD individuals might require medically necessary gender-affirming hormone therapy (GAHT) to align physical characteristics with their gender identity [6, 7]. GAHT (testosterone for masculinizing GAHT, and estrogen with androgen-lowering medications for GAHT aimed at feminine embodiment) aims to equalize serum levels of the sex steroids with the values characteristic of one's gender identity [6, 7].

Regarding the search for biological features underlying identification with a gender other than that assigned at birth, the primary aim is to find evidence for the enduring nature of transgender identity. Based on the current state of knowledge, it can be concluded that biological factors, genetic, hormonal, and immunological, play a significant role in the development of gender identity and sexual orientation. However, there is still insufficient evidence to precisely define the interrelationships among these factors, or between biological and epigenetic influences [8–10].

Considering headaches, the suggested hormonal effects on headache characteristics in cisgender individuals, together with the increasing proportion of transgender patients receiving GAHT, raises the issue of potential associations between hormonal interventions and headache morbidity in the TGD community [11, 12]. It has been postulated that GAHT might impact the frequency and severity of migraine episodes due to the possible pro-nociceptive and anti-nociceptive character of estrogen and testosterone, respectively [11, 13]. Also, based on our experience, even headache characteristics can transform in the same patient before, during, and after GAHT.

The objective of this review was to analyze the existing literature regarding the impact of hormonal fluctuations on nociceptive processing and thus examine the potential relationships between headaches in general, focusing on migraine, and GAHT in transgender patients. The presented summary of the unique aspects of headache and migraine management in transgender individuals might potentially contribute to the overall improvement of neurologic care for the TGD population.

Material and methods

The review was written as a narrative review; however, some crucial methodological principles were applied to enhance transparency and rigor. The literature search, selection, and interpretation of findings were performed by experts from different fields relevant to the topic, such as neurology, psychiatry, otorhinolaryngology, and pharmacology, to ensure a comprehensive approach and a multidisciplinary perspective.

A literature search was performed in the PubMed database. The search strategy was designed to cover both neurological and hormonal aspects of headache disorders in TGD populations. The following Medical Subject Headings (MeSH) terms were used during the search, listed in alphabetical order: "estrogens", "gender-affirming care", "gender-affirming procedures", "gender identity", "gonadal hormones", "hormones", "migraine disorders", "oxytocin", "pregnancy", "progesterone", "prolactin", "sexual and gender minorities", "testosterone", "transgender persons", and "vasopressin". Additionally, one non-MeSH term, "gender affirming hormone therapy", was used. Study selection was performed by the authors, and any discrepancies were resolved by discussion.

Regarding inclusion and exclusion criteria, no restriction was placed on the type of publications, unless they were not officially published and authorized. To be included, an article had to address the broad topic of the current review, including hormones, headaches, and the TGD population. Also, peer-reviewed articles were considered for

inclusion only if the full text was available in English, so all the references remain understandable for the reader. A total of 126 adequate studies were finally included in the analysis.

Given the narrative nature of the review, a formal risk-of-bias assessment was not performed. However, the included studies were critically appraised by the multidisciplinary author team with attention to study design, sample size, and potential confounding factors. Heterogeneity across original studies, particularly in terms of study populations, hormonal status, stage of transition, and outcome measures, was addressed through a descriptive synthesis approach. Such data were provided, where applicable, throughout the work to ensure clarity and transparency. Findings were interpreted cautiously, with consideration of these limitations.

Results

Hormonal background of migraine

Sex hormones regulate pain through various mechanisms, including modulation of descending antinociceptive pathways, influence on neuroinflammatory processes, control of neurotransmitter release involved in pain perception, and impact on emotional state, especially mood [14, 15]. The lower pain threshold observed in females typically emerges during puberty. Interestingly, in older age (postmenopause and andropause), pain perception between sexes tends to converge again [16, 17]. The specific roles of estrogen, progesterone, and testosterone in shaping pain sensitivity remain incompletely understood. Among these hormones, estrogens are particularly enigmatic and multifaceted in their role in pain perception.

Estrogens

The role of estrogens in the pathogenesis of migraine is complex. Research findings have demonstrated both pro-nociceptive and antinociceptive effects, likely reflecting the diversity of estrogenic compounds. Estrogen receptor (ER) expression has been demonstrated in several areas of the spinal cord and brain involved in pain perception and modulation, with ER-α predominantly identified in these nociceptive structures. One theory posits that the divergent effects of estrogens on pain perception are dependent on receptor subtype: stimulation of ER-$\alpha$is typically associated with analgesic effects, whereas activation of ER-β may be pro-nociceptive [18]. Furthermore, high estrogen levels are generally associated with antinociceptive effects, possibly due to activation of inhibitory pathways in the spinal cord. Consequently, it is not only the concentration of estrogens that matters, but also their stability. Stable levels are associated with improved pain control [19–21].

Clinical and experimental data suggest that estrogen fluctuations across the menstrual cycle and throughout a woman's lifespan may influence both the frequency and intensity of migraine pain. Raffaelli *et al*. found that women with migraines and regular menstrual cycles exhibited significantly higher levels of calcitonin gene-related peptide (CGRP), a neuropeptide implicated in neurogenic inflammation with a well-established role in migraine, during menstruation compared to women without migraines. Furthermore, suppression of hormonal fluctuations with oral contraceptives was associated with lower CGRP concentrations in tear fluid than physiologic menstruation [22]. These findings reinforce a mechanistic connection between estrogen fluctuations and increased CGRP signaling, a hallmark of migraine pathogenesis. Importantly, this effect seems to apply specifically to fluctuations in endogenous estrogen levels rather than to the consistently low levels seen in menopause. A second theory, also supported by animal models, suggests that estrogen withdrawal may enhance cortical spreading depression [23], which may result from estrogen's effects on neuronal excitability and hypothalamic gene expression. Additionally, estrogens influence energy homeostasis via proopiomelanocortin neurons in the hypothalamic arcuate nucleus [24].

Progesterone

Despite a common assumption regarding its pro-nociceptive properties, findings from both experimental models and clinical observations remain inconclusive. In fact, most studies point toward a potential antinociceptive effect of progesterone, particularly through its capacity to reduce neuroinflammatory activity [25–27]. Chuang *et al*. reported that neurosteroids derived from progesterone may reduce nociceptive transmission within the trigeminovascular system [28]. Elevated levels of sex steroids observed post-ovulation and during pregnancy are associated with a state of "luteal analgesia," during which progesterone may dampen the emotional component of pain and suppress pain-related cortical activation [29].

Allopregnanolone, an active metabolite of progesterone, is a potent positive allosteric modulator of gamma-aminobutyric acid A (GABA-A) receptors, leading to an antinociceptive effect confirmed in preclinical studies [30, 31]. Currently, progesterone is thought to exert a protective role, lowering the risk of migraine attacks by modulating nociceptive signaling. However, despite high progesterone levels during the early luteal phase, proinflammatory mediators, including CGRP, are simultaneously synthesized. This paradoxical situation may promote neuroinflammation [32, 33]. Moreover, like estrogen, progesterone levels drop

just before menstruation, which may contribute to migraine initiation. Despite the potential benefits of progesterone and its metabolites in pain modulation, clinical trials have not confirmed a clear therapeutic advantage of progesterone supplementation in migraine prevention [34].

Testosterone

In animal studies, gonadectomy or pharmacological blockade of androgen receptors consistently results in heightened sensitivity to nociceptive stimuli [35, 36]. These findings align with clinical observations. In patients with chronic pain, testosterone supplementation has been shown to reduce pain intensity and improve pain sensitivity [37–39]. Observational data also suggest that men with lower androgen levels may be more susceptible to cluster headaches [40].

Compared to other sex hormones, the role of testosterone in migraine remains less well understood [14, 41]. In a study by Kobus *et al*., women with migraine were more likely to have been exposed prenatally to higher levels of testosterone relative to estrogen, whereas men with migraine showed the reverse pattern, greater prenatal exposure to estrogen relative to testosterone [42]. Mattsson *et al*. assessed the influence of sex hormone levels on migraine in postmenopausal women who were not undergoing hormone replacement therapy. No significant differences were found between patients with migraine and controls in serum levels of androstenedione, total testosterone, or free testosterone [41]. Nonetheless, isolated reports suggest that testosterone supplementation, including via subcutaneous implants, may be effective. In a study involving 27 women, both pre- and postmenopausal participants experienced a reduction in migraine intensity following testosterone therapy, with a mean level of improvement of 3.3 points on a 5-point scale [43].

Shields *et al*. found significantly lower testosterone concentrations in men with chronic migraine compared to healthy controls [44]. In contrast, Li *et al*. found no significant differences in testosterone levels between migraineurs and healthy men [45]. Similarly, another study found no difference in free testosterone levels during the interictal phase among non-obese men with migraine [46]. Dourson *et al*. in their review summarized the effect of testosterone on migraine through several mechanisms: (a) the influence on sensory neurons and reduction of CGRP level, (b) activation of the immune system by decreasing the concentration of pro-inflammatory cytokines and increasing the concentration of anti-inflammatory cytokines, (c) stimulation of the vasculature to dilate blood vessels, constrict blood vessels or by influencing vascular signaling, (d) the influence on limbic areas involved in pain processing and migraine pathophysiology, (e) stress reduction and (f) mood improvement [47]. Overall, the effects of sex hormones on migraine and headaches appear to be heterogeneous, with both beneficial and adverse outcomes reported across studies, although some consistent trends may be observed within specific hormonal contexts. A summary of the role of the three main sex hormones in pain perception is presented in Figure 1.

Other hormones

In animal models, elevated prolactin levels have been shown to increase trigeminal meningeal pain sensitivity, notably through the selective modulation of CGRP signaling in female rodents [48]. Clinical data on prolactin are more equivocal. Studies have alternately reported no differences in prolactin levels between patients with migraine and controls, elevated prolactin in those with migraine, or increased prolactin concentrations specifically during migraine attacks [49–51]. For instance, Alia *et al*. found significantly higher prolactin levels in women with chronic migraine compared to those with episodic migraine [52]. There is mounting evidence linking elevated endogenous prolactin levels and increased expression of prolactin receptors to a greater risk of developing migraine. Intriguingly, several case reports have described remission of chronic migraine-like headaches following treatment with dopamine agonists in patients with hyperprolactinemia, suggesting that this pathway could present novel therapeutic possibilities [53, 54].

Given the central role of the hypothalamus in migraine pathophysiology, there is growing interest in neurohormones such as vasopressin and oxytocin [14]. Maddahi *et al*. highlighted sex differences in vasopressin receptor (VR) distribution, showing that V1aR- and V1bR-expressing cells are more abundant in female than male rats and are expressed in both the hypothalamus and trigeminal ganglion [55]. Clinical observations further support vasopressin's relevance to migraine. Platelets from women with migraine exhibit increased expression of VR, and elevated vasopressin levels during migraine attacks may contribute to associated symptoms such as pallor and reduced urine output [56]. The potential involvement of vasopressin in migraine pathogenesis should also be considered in the context of known modulators; for example, stress and alcohol suppress vasopressin secretion, whereas sleep and some prophylactic migraine treatments, such as tricyclic antidepressants, may increase vasopressin levels [57]. Although intranasal administration of vasopressin has been explored in headache manage-

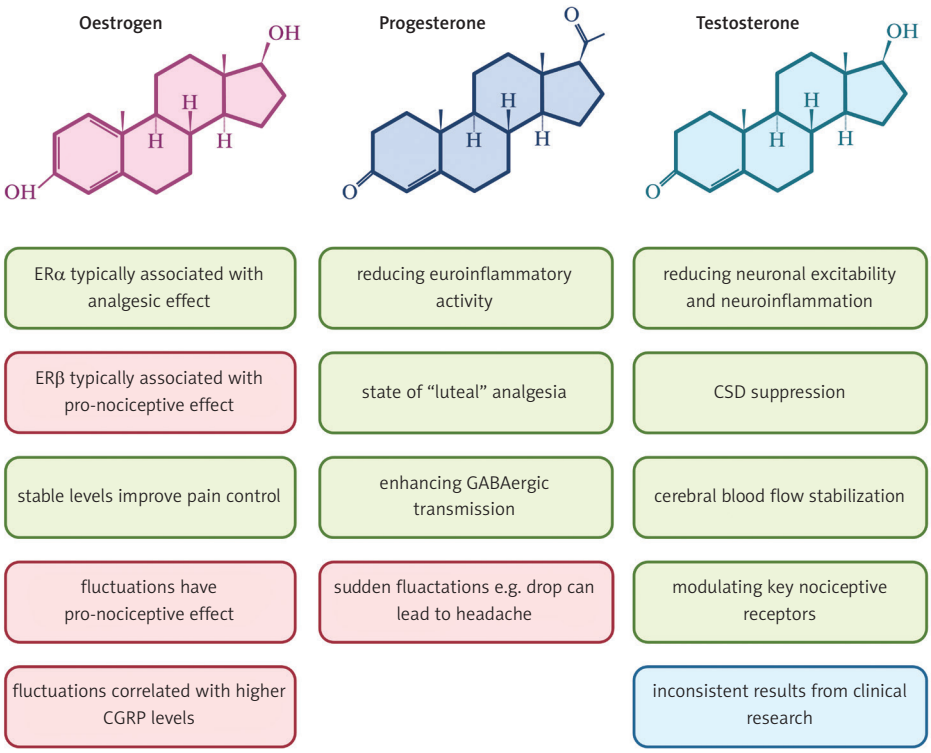

Figure 1. A graphical summary of the role in nociception of estrogen, progesterone, and testosterone. The figure illustrates the complex and, in some cases, opposing effects of sex hormones on pain modulation, highlighting the importance of hormonal balance and fluctuations rather than absolute hormone levels alone. It should be noted that these mechanisms are context-dependent and may differ depending on physiological state, hormonal dynamics, and individual susceptibility. The red color represents a pro-nociceptive effect, the green color stands for an anti-nociceptive effect, and the blue is reserved for inconsistent findings across the studies

CGRP – calcitonin gene-related peptide, CSD – cortical spreading depression, ER – estrogen receptors, GABA – gamma-aminobutyric acid.

ment, there are currently no formal recommendations for its clinical use in migraine treatment [14].

Furthermore, one prevailing theory suggests that estrogen withdrawal is accompanied by a reduction in oxytocin levels, which may contribute to the onset of menstrual migraines [58, 59]. Phillips *et al.* described complete relief of acute migraine pain in two patients following intravenous oxytocin infusion [60]. Subsequent studies have confirmed the effectiveness of intranasal oxytocin in relieving migraine pain in both men and women [57, 61]. However, oxytocin's analgesic mechanism is multifaceted. Oxytocin's analgesic action in migraine is believed to arise from activation of oxytocin receptors localized in the trigeminal nucleus and trigeminal ganglia [62]. This suggests that oxytocin may reduce both the frequency and intensity of migraine attacks by inhibiting CGRP release from trigeminal nociceptive neurons [62].

Differences in migraine course between females and males

Epidemiological studies of children and adolescents reveal significant regional differences in the prevalence and subtypes of headaches. In particular, the prevalence of migraine in this group has increased significantly in recent years due to lifestyle factors and social isolation [63, 64]. Migraines are relatively rare among pre-pubertal children and do not show significant gender differences or only a slight predominance among boys. Some data show that compared to females, male youth present earlier with migraine symptoms [65, 66]. In children between 5 and 15 years, migraine occurs in up to 10.6% and between 15 and 19 years in up to 28% [67]. In childhood, the prevalence of migraine increases with age, usually affecting girls aged 8–14 years and boys aged 9–15 years [68]; however, there is a perceptible age-related gender difference in presentation at this time. Specifically, after puberty, the prevalence of migraine increases dramatically in females [67]. Interestingly, Maleki *et al.* reported early puberty as a risk factor for developing migraine. Regardless of age or family history of migraine, each year's delay in menarche reduces the risk of migraine by 7% [69]. Migraine with aura is more common in girls, while migraine without aura is more common in boys. Also, adolescent females, compared to adolescent males, had a higher frequency of headaches and a higher rate of chronic migraine [66]. The preva-

lence of chronic migraine in children aged 12 to 17 years is estimated at 0.8–1.8% [70].

These sex differences show that physiological concentration and type of sex hormone are crucial for headache [71]. This is well reflected in epidemiological studies of adult primary headaches, which show that migraine has a three times higher predilection in females compared to males (18% vs. 6%) [72] and occurs 3–4 times more often in post-pubertal women than in men [73], while cluster headaches are two to three times more common in males [74]. However, in both sexes, migraine prevalence peaks occur between the ages of 20 and 45 years, and decrease again with ageing [75].

Data suggest that, due to sex disparities, men are often underrepresented in migraine studies. In a narrative review on migraine in men, the authors found that adult males, compared to females, experience shorter migraine attacks (with and without aura), both treated and untreated, lower migraine pain intensity, and are less likely to suffer from accompanying symptoms [16]. Perhaps, symptoms such as aggravation by movement, unilateral pain, and pulsating quality are less frequent in men [16]. An atypical clinical migraine presentation is also possible in men, as they experience migraine headaches less frequently but non-migraine headaches more frequently [16]. Nevertheless, some data indicate a higher proportion of migraine with aura attacks in men diagnosed with migraine with aura than in women with the same diagnosis [16].

Differences in migraine course in view of the other genders

Undoubtedly, there is a gap in the neurological health of sexual and gender minorities (SGM) due to long-standing stigma and prejudice, as well as a lack of data collection or awareness. A few cohort studies indicate that headaches may be more common among SGM compared to cisgender counterparts, but the collected data did not include gender minorities [76, 77]. For SGM, it remains crucial to understand and identify the underlying factors, including unique stressors for this population, contributing to migraine, and to develop effective and/or personalized interventions based on these factors [78, 79].

In a cross-sectional self-reported study from the United States, the authors stated that SGM adults had higher odds of experiencing migraine compared to heterosexual adults. It may be caused by greater physical and mental problems, as well as barriers to access to health care [80]. Rosendale *et al*. also reported depression, anxiety, and post-traumatic stress disorder as significant and potentially modifiable factors for migraine in SGM. Nevertheless, almost 94% of respondents reported a history of discrimination and trauma, both of which were associated with higher odds of moderate-severe migraine disability [81, 82]. Also, in gender-diverse adolescents, a higher risk of frequent headaches may be related to psychological factors (such as anxiety, depression, suicidality, and peer victimization), which are potentially amenable to prevention and treatment, rather than to gender differences per se [83].

Neurobiological considerations in headache among transgender individuals

Clinical experiences of the authors suggest that headaches in transgender individuals occur frequently but represent a heterogeneous phenomenon. From a theoretical standpoint, headaches in transgender individuals may be considered within four clinical contexts related to the developmental phase of gender incongruence and the initiation of gender-affirming interventions: 1) the exploratory stage, accompanied by uncertainty, anxiety, and ambivalence toward sexual impulses, lack of acceptance, feelings of guilt, and attempts to resolve the internal conflict; 2) the realization of incongruence between one's physical (and, in some cases, psychological) characteristics and experienced gender, characterized by increasing distress up to the level of gender dysphoria; 3) the initial phase of transition, associated with the commencement of hormone therapy; and 4) the definitive phase of transition, encompassing multi-stage surgical procedures and, in some cases, additional hormonal interventions.

In the context of headaches, the question arises whether headaches in transgender individuals have a distinct biological basis compared with those in other patient populations with such symptoms. Addressing this requires consideration of possible differences in nervous system function in transgender individuals.

The development of gender identity and sexual orientation constitutes distinct components of brain development prior to birth. Sexual differentiation of the human brain begins in the second trimester of gestation [84, 85]. According to classical organizational theory, prenatal and early postnatal exposure to testosterone promotes the development of a gynephilic orientation (sexual interest in females), whereas an androphilic orientation (sexual interest in males) develops under conditions of relatively low testosterone exposure. In humans, testosterone appears to influence the development of gender identity and sexual orientation directly (i.e., without mediation by metabolites), whereas in rodents, these processes occur primarily via estradiol generated through aromatization of circulating testosterone [84–86]. Postna-

tally, these features are subject to environmentally influenced epigenetic processes [84, 85].

Neuroimaging studies have identified specific anatomical differences more strongly associated with gender identity than with biological sex. These differences involve certain hypothalamic nuclei, particularly the red nucleus of the stria terminalis and the uncinate nucleus [87, 88]. Differences in the microstructure of grey and white matter have also been reported [89–91], along with localized differences in neuronal populations, especially those in the hypothalamus secreting kisspeptin and neurokinin B within the pituitary infundibulum [92, 93]. Anatomical variations in brain structure among transgender individuals may translate into functional differences, such as impairments in visuospatial coordination [94]. Another promising research avenue is the study of differences in neural responses to odorants with pheromonal (sexual attractant) properties in transgender individuals [94, 95]. It has been suggested that gender incongruence may be associated with functional differences in neural networks underlying self-perception and self-awareness.

Discussion

Having established the theoretical background based on the available body of research, the authors in the following discussion aim to further explore the nature of headaches in transgender individuals. Drawing on both existing literature and their own clinical experience, they will analyze potential mechanisms underlying these conditions. Particular attention will be given to the multifactorial origins of headache disorders in this population, including hormonal therapy influence, psychosocial factors, and broader environmental determinants.

Difference in headache characteristics before and after the sexual conversion process

As suggested by practice and our own experience, the headache profile in the same patient before and after the transition, especially before and after beginning GAHT, may be different. Headaches are common health problems that exhibit marked sexual dimorphism. Cisgender women report a higher prevalence and severity of headaches, mainly migraine, tension-type headache, paroxysmal hemicrania, and hemicrania continua than cisgender men, suggesting a significant role for sex hormones in the pathophysiology of these conditions [11]. In the context of transgender individuals undergoing medical transition involving GAHT, the question arises as to how hormonal changes affect the clinical course of headaches. Before starting hormone therapy, transgender individuals often report headaches of varying nature, but the frequency and type of headaches appear to be similar to those in the population of their assigned sex at birth [96]. Psychosocial factors such as minority stress, gender dysphoria, and limited access to adequate medical care may contribute to increased headache frequency and intensity [97]. The use of exogenous estrogen and antiandrogenic agents may contribute to headache risk [87]. These agents are known to influence circulating nitric oxide levels, which in turn may promote vasodilation and migraine symptoms [98–100]. The available literature suggests that the influence of hormones on headache may be similar across cisgender and TGD populations, with GAHT appearing to exacerbate headache symptoms in transfeminine individuals, while potentially alleviating them in transmasculine individuals [101–104]. Furthermore, in transgender men, testosterone use may have both a protective effect (predominantly) and, much less commonly, a provocative effect (headache attributed to a substance or its withdrawal [1] in the context of various types of headaches. Todd *et al*. described two cases of chronic migraine without aura in transmasculine patients who used masculinizing hormone therapy with testosterone [105]. The first described patient experienced a migraine disability assessment (MIDAS) score reduction of over 50% after starting GAHT with testosterone without changes in migraine frequency, while the second patient noted a reduction from 9 to 6 in monthly migraine days and an improvement in MIDAS score from 17 to 14 after beginning testosterone supplementation. In transwomen, the use of estrogens and antiandrogens may increase the risk of migraine, which is confirmed by observations of cisgender populations [103]. Aloisi *et al*. found that 6 out of 11 transgender individuals experienced a decrease in pain symptoms after the beginning of GAHT with testosterone [102]. In a recent study, transgender men receiving masculinizing GAHT had lower odds of headache overall (odds ratio (OR) = 0.20, 95% confidence interval (CI): 0.05–0.85) and tension type headaches (OR = 0.18, 95% CI: 0.07–0.45), but significantly higher odds of migraine (OR = 3.93, 95% CI: 1.60–9.63) [106]. A study conducted in 2023 by Hranilovich *et al*. partially supported these findings [107]. Transfeminine individuals had a significantly higher risk of experiencing headache during GAHT compared to those not receiving hormone therapy (7% vs. 1%; OR = 5.84, 95% CI: 1.24–27.6). Interestingly, transmasculine individuals also showed a higher risk of headache than their GAHT-naïve counterparts (12% vs. 5%; OR = 2.71, 95% CI: 1.37–5.4), which challenges the commonly pro-

posed antinociceptive effects of testosterone [102, 105]. This paradox may be explained by the developmental stage of these individuals, both in terms of pubertal status and maturation of the nervous system [107].

Taken together, these apparently contradictory findings, where some studies show a reduction in migraine frequency and severity in transmasculine individuals receiving testosterone, while others indicate an increased risk of headache during GAHT or a higher prevalence of migraine in transgender compared to cisgender men, likely reflect significant heterogeneity across studied populations rather than a consistent effect of testosterone on headache, as it was initially suggested. Several factors may account for these differences. The timing of GAHT initiation and developmental stage, particularly in relation to pubertal status and maturation of the nervous system, may influence individual susceptibility to headache. In addition, treatment duration and hormonal alterations, including early fluctuations versus long-term stabilization of testosterone levels, may differentially affect headache patterns; therefore, the stage of GAHT may play a role. The impact of testosterone may also depend on baseline headache phenotype and prior hormonal sensitivity, especially the tendency to experience hormone-dependent headaches, as well as interactions with endogenous estrogen levels, which may remain variable regardless of GAHT and contribute to increased activity of migraine-related pathways, primarily within the trigeminovascular system. Furthermore, psychosocial factors, including stress, mental health burden, and healthcare-related disparities, may act as important confounders in this population. Altogether, these observations suggest that the effect of testosterone on headache is presumably individualized and dependent on various factors, underscoring the need for longitudinal studies that cover both biological and non-biological determinants. Compared to testosterone, the effects of estrogen in feminizing GAHT are more consistently associated with an increased frequency or severity of migraine, although individual variability should be acknowledged.

Interestingly, in pediatric patients receiving GAHT, transmasculine youth appeared more consistently to have a higher prevalence of headache. The authors explained it by different effects of GAHT initiated in adolescence than in adulthood, while puberty is a critical period for brain development and sex-specific divergence. Moreover, researchers reported an increased rate of headaches in patients on GAHT compared to those who were not [11]. Nevertheless, it seems that sex steroids interact with the regional brain structures differently in girls and boys, and this impact may be influenced by such factors as sex hormone genes or exposure during the pre- or perinatal period [108, 109]. Also, the hypothesis of migraine as a sex-steroid programmed in fetal disease should be considered, as described above [42]. The level of sex hormones in transgender patients may also vary in concentration depending on the timing of initiation of gender-affirming hormones [110].

Based on these observations, the impact of GAHT on headache in transgender adolescents cannot be interpreted without the broader developmental context. As shown in cisgender populations, puberty represents an important point in migraine epidemiology, with a marked increase in prevalence associated with hormonal maturation and fluctuations. Thus, the introduction of exogenous sex steroids within GAHT during adolescence may further modulate headache patterns, particularly during active brain development and maturation. Importantly, adolescence is also a period of increased vulnerability to psychosocial stressors, including anxiety, depression, and identity-related distress, which have been shown to contribute to headache burden in gender-diverse youth. Therefore, the higher prevalence of headaches observed in transmasculine adolescents receiving GAHT, including masculinizing GAHT, may reflect a combined effect of hormonal, age-related, and psychosocial factors rather than a direct and homogeneous influence of hormones alone. Taken together, these findings suggest that headache manifestations during gender transition in adolescents may be influenced by a complex interplay of biological and environmental factors.

Finally, reduced distress related to gender dysphoria and increased satisfaction with identity after initiating medical transition may contribute to reduced pain, which highlights the importance of the biopsychosocial model of pain understanding [111]. Further well-designed prospective studies involving transgender people are needed to allow the development of individualized diagnostic and treatment guidelines [11].

Migraine misdiagnosis

For transgender people undergoing GAHT, the diagnosis and treatment of headaches may be further complicated by the unique interactions between sex hormones and the nervous system, coexisting psychiatric conditions, and potential systemic biases in health care. Hormone therapy in transgender individuals may affect the occurrence and nature of headaches. In such cases, headaches may present with migraine-like features, potentially leading to misdiagnosis as migraine. However, Todd et al. described two cases of chronic migraine without aura in transmascu-

line patients who received masculinizing hormone therapy with testosterone [105]. In transmen, testosterone use may have both a protective effect and, less commonly, a provocative effect (i.e. headache attributed to a substance or its withdrawal [1]) in the context of various types of headaches. In transwomen, the use of estrogens and antiandrogens may increase the risk of migraine, which is confirmed by observations of cisgender populations [103]. Also, an effect of estrogen use may be headache that is incorrectly diagnosed as migraine because its phenotype resembles migraine attacks or chronic migraine. On the other hand, a complication of treatment with sex hormones, especially estrogens in high doses, is cerebral venous thrombosis, during which there may be a symptomatic headache, resembling migraine. Transgender people are still underrepresented in studies on headaches and migraine, which leads to a lack of reliable and credible data and diagnostic and therapeutic guidelines [106].

Psychological aspects of headaches in transgender and gender diverse populations

Primary headaches, similar to other somatization symptoms, may arise from the experience of internal conflict or may represent an expression of psychological pain, whether consciously perceived or not. Thus, the diagnostic process for headaches should include inquiries into the nature of the distress and an exploration of the specific sources of the experienced psychological pain [112]. During adolescence (as well as in the years immediately preceding and following this period, i.e., early adulthood), uncertainty about gender identification may form part of more broadly understood identity challenges resulting from developmental processes. Belonging to a group facilitates self-definition, fosters acceptance, and, most importantly, enables the articulation and redefinition of personal identity-related concerns. According to Steiner's theory of the "psychic retreat", the benefit of group membership lies in avoiding confrontation with psychological pain and certain internal conflicts, while the cost is the emergence of various masking symptoms, which may include somatic manifestations such as headaches [113]. A study involving one of the largest cohorts of TGD individuals to date in the context of pain demonstrated a higher prevalence of chronic pain within this population, particularly among those undergoing GAHT. Importantly, the authors found that chronic pain in TGD individuals was closely associated with coexisting mental health conditions, notably depression and anxiety disorders [114].

Heterogeneous nature of headache in transgender individuals

Biological sex is one of the most consistent predictors of pain sensitivity, with cisgender women reporting a higher prevalence and severity of many pain conditions than cisgender men. This difference is observed across multiple domains, including clinical pain syndromes, experimental pain thresholds, and pain-related disability [115–118]. These disparities are not solely attributable to social or psychological factors; rather, accumulating evidence implicates sex hormones [45, 119–124] (Table I) as important modulators of nociceptive processing [125, 126].

The topic of headache in TGD individuals remains poorly studied, particularly concerning epidemiological data. The limited availability of large-scale studies makes it difficult to accurately estimate the true burden of headache in this population, especially in determining whether transgender individuals, transfeminine people in particular, have an increased predisposition to headache disorders [11, 127]. Pringsheim *et al.* found that the prevalence of migraine in transfeminine individuals was comparable to that of cisgender women (26% vs. 25.5%) [101]. For comparison, migraine prevalence among men in the Dutch population has been estimated at 7.5%.

Given the elevated prevalence of mental health conditions in the TGD population, emphasis should be given to the critical need for integrated care

Table I. Summary of hormonal influence on headaches in cisgender individuals

Hormone	Headache influence	Key mechanisms
Estrogen	Fluctuations, especially withdrawal (e.g., perimenstrual drop), are associated with migraine onset [119–121]	Modulation of serotonin receptors, nitric oxide pathways, and vascular reactivity
Progesterone	Potentially modulates GABAergic systems and may have a stabilizing effect on neuronal activity, thus reducing the nociception but evidence is inconsistent [45, 122]	May enhance GABA activity and dampen CNS excitability; exact mechanisms remain unclear
Testosterone	Associated with reduced headache and migraine frequency [123, 124]	Inhibits pro-inflammatory cytokines, modulates opioid receptors, reduces neuronal sensitization

CNS – central nervous system, GABA – gamma-aminobutyric acid.

approaches that address not only pain symptoms but also the psychological and social determinants of health that may exacerbate pain severity and treatment resistance [128–132]. Furthermore, it is important to note that access to adequate headache treatment within the TGD population is often limited, largely due to social determinants such as discrimination, stigma, and healthcare bias. These barriers can lead not only to suboptimal pain management but also to avoidance of medical care altogether, thereby worsening overall health outcomes. As a result, individuals may self-medicate with analgesics, sometimes excessively, potentially resulting in medication overuse headache and perpetuating a vicious cycle of pain and ineffective treatment.

Thus, it is essential to recognize that the exacerbation of headache in TGD individuals may be influenced not only by GAHT but also by a complex interplay of social stressors, internalized stigma, and fear of healthcare settings. Moreover, this population has a higher baseline prevalence of comorbid mental health conditions, which are independently associated with increased headache frequency and may complicate pharmacologic management [111, 133–138]. Overall, as traditional pain management models often fail to meet the specific needs of TGD individuals, this contributes to underdiagnosis, treatment avoidance, and poor outcomes. There is an urgent need for trans-inclusive, equity-based approaches to pain care, particularly as GAHT may interact with nociceptive pathways in underexplored ways, demanding tailored clinical strategies and further research [139].

This study has some limitations. The paucity of data on the topic of headaches in TGD is the main limitation. Also, if such research is undertaken, it is generally conducted on a markedly small and narrowly defined population sample. Additionally, the available data are fragmented, with substantial heterogeneity in study populations and outcome measures; thus, comparability across studies is highly restricted, and any conclusions should be drawn with great caution. Moreover, the current evidence is based on observational and retrospective studies, with an absence of prospective controlled trials, which limits the ability to establish causal relationships. A further limitation is that a proportion of the included literature consists of review articles, which tend to summarize general trends rather than provide precise quantitative data, thereby limiting the ability to derive exact numerical estimates.

This is a narrative review, and there is a risk that some relevant articles were omitted. However, the substantial number of included references increases the likelihood that all key studies have been captured. Additionally, only English-language studies have been included; therefore, some potentially relevant articles written in other languages may have been excluded.

In conclusions, the issue covered in this narrative review is very complex and remains highly understudied. The need for high-value research in the transgender population on larger group samples is undoubtedly mounting. Current evidence indicates that both hormonal factors, especially their fluctuations, and psychosocial influences play a central role in shaping headache patterns in TGD individuals, although their relative contributions remain incompletely understood. Future research should focus on well-designed prospective studies with larger and more diverse populations, standardized outcome measures, and careful consideration of hormonal regimens and developmental factors, optimally in a prospective controlled trials format.

Regarding the clinical practice, this review highlights several essential points which should be taken into consideration by all clinicians taking care of members of the TGD population, especially those suffering from headaches: 1) A significant role in headaches among TGD people is played not only by sex hormones *per se* but also their fluctuating levels, causing and influencing migraine headaches. 2) Changes in estrogen and progesterone levels are considered factors aggravating migraine headaches, while testosterone is suggested to have mainly an antinociceptive role. 3) However, transmasculine people in some studies presented a higher headache rate than the control group not receiving testosterone; thus, not only hormones have an impact on headaches in the TGD population. Emotional and psychosocial aspects may have a critical role. 4) Psychosocial factors such as minority stress, gender dysphoria, and limited access to adequate medical care, which are often present during this phase of life, also contribute to increased headache frequency and intensity. 5) Importantly, traditional pain management models often fail to meet the specific needs of TGD individuals, which contributes to underdiagnosis, treatment avoidance, and poor outcomes. A dedicated focus on the TGD group is highly required. 6) A specific patient group is a pediatric TGD population, in whom headache patterns may differ from adults and demand special care. 7) Headaches that are likely to be present in the TGD population, especially before and during the transition process, may have a complex pathogenesis, not limited only to hormonal changes or psychological aspects. Further research should be oriented toward this specific headache, looking for unique traits that could distinguish it from other well-known types.

Building on these observations, several practical considerations may support clinicians in the management of headaches in TGD individuals. From a clinical perspective, care should be individualized and multidisciplinary. Clinicians are encouraged to regularly and thoroughly monitor headache characteristics before and during GAHT, with particular attention to associations between headache patterns and hormonal changes, which are usually temporal. In cases of worsening symptoms, especially with a migraine phenotype, adjusting GAHT parameters, including dosage, formulation, or route of administration, should be considered. Moreover, it ought to be performed in collaboration with an endocrinologist, aiming to minimize hormonal fluctuations and adverse events based on them. Importantly, headaches which begin during GAHT should not be automatically classified as primary disorders, even if they clearly resemble a specific phenotype. Secondary causes, including hormone-related complications, should always be excluded. Furthermore, a complex etiology, comprising primary and secondary causes, is possible. Psychosocial factors may substantially contribute to headache burden; therefore, close collaboration between not only neurologists and endocrinologists, but also with mental health professionals, is essential. Finally, a patient-focused approach that combines effective headache management with the goals of gender-affirming care remains fundamental.

Funding

No external funding.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018; 38: 1-211.
2. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. J Headache Pain 2022; 23: 34.
3. Agosti R. Migraine burden of disease: from the patient's experience to a socio-economic view. Headache 2018; 58 Suppl. 1: 17-32.
4. Drescher J, Cohen-Kettenis P, Winter S. Minding the body: situating gender identity diagnoses in the ICD-11. Int Rev Psychiatry 2012; 24: 568-77.
5. Cohen-Kettenis PT, Pfäfflin F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. Arch Sex Behav 2010; 39: 499-513.
6. Poteat T, Davis AM, Gonzalez A. Standards of care for transgender and gender diverse people. JAMA 2023; 329: 1872-4.
7. Coleman E, Radix AE, Bouman WP, et al. Standards of care for the health of transgender and gender diverse people, version 8. Int J Transgend Health 2022; 23 (Suppl. 1): S1-s259.
8. Balthazart J. Minireview: hormones and human sexual orientation. Endocrinology 2011; 152: 2937-47.
9. Bailey JM, Vasey PL, Diamond LM, Breedlove SM, Vilain E, Epprecht M. Sexual orientation, controversy, and science. Psychol Sci Public Interest 2016; 17: 45-101.
10. Fisher AD, Ristori J, Morelli G, Maggi M. The molecular mechanisms of sexual orientation and gender identity. Mol Cell Endocrinol 2018; 467: 3-13.
11. Hranilovich JA, Kaiser EA, Pace A, Barber M, Ziplow J. Headache in transgender and gender-diverse patients: a narrative review. Headache 2021; 61: 1040-50.
12. Winter S, Diamond M, Green J, et al. Transgender people: health at the margins of society. Lancet 2016; 388: 390-400.
13. Pace A, Barber M, Ziplow J, Hranilovich JA, Kaiser EA. Gender minority stress, psychiatric comorbidities, and the experience of migraine in transgender and gender-diverse individuals: a narrative review. Curr Pain Headache Rep 2021; 25: 82.
14. Godley F, 3rd, Meitzen J, Nahman-Averbuch H, et al. How sex hormones affect migraine: an interdisciplinary preclinical research panel review. J Pers Med 2024; 14: 184.
15. Gulati M, Dursun E, Vincent K, Watt FE. The influence of sex hormones on musculoskeletal pain and osteoarthritis. Lancet Rheumatol 2023; 5: e225-e38.
16. Fitzek MP, Boucherie DM, de Vries T, et al. Migraine in men. J Headache Pain 2025; 26: 3.
17. van Lohuizen R, Paungarttner J, Lampl C, Maassen-VanDenBrink A, Al-Hassany L. Considerations for hormonal therapy in migraine patients: a critical review of current practice. Expert Rev Neurother 2023; 24: 1-21.
18. Spooner MF, Robichaud P, Carrier JC, Marchand S. Endogenous pain modulation during the formalin test in estrogen receptor beta knockout mice. Neuroscience 2007; 150: 675-80.
19. Athnaiel O, Cantillo S, Paredes S, Knezevic NN. The role of sex hormones in pain-related conditions. Int J Mol Sci 2023; 24: 1866.
20. Reddy N, Desai MN, Schoenbrunner A, Schneeberger S, Janis JE. The complex relationship between estrogen and migraines: a scoping review. Syst Rev 2021; 10: 72.
21. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. Neurology 2006; 67: 2154-8.
22. Raffaelli B, Storch E, Overeem LH, et al. Sex hormones and calcitonin gene-related peptide in women with migraine: a cross-sectional, matched cohort study. Neurology 2023; 100: e1825-e35.
23. Kudo C, Harriott AM, Moskowitz MA, Waeber C, Ayata C. Estrogen modulation of cortical spreading depression. J Headache Pain 2023; 24: 62.
24. Stincic TL, Grachev P, Bosch MA, Rønnekleiv OK, Kelly MJ. Estradiol drives the anorexigenic activity of proopiomelanocortin neurons in female mice. eNeuro. 2018; 5: ENEURO.0103-18.2018.
25. Lacroix-Fralish ML, Tawfik VL, Nutile-McMenemy N, DeLeo JA. Progesterone mediates gonadal hormone differences in tactile and thermal hypersensitivity follow-

ing L5 nerve root ligation in female rats. Neuroscience 2006; 138: 601-8.
26. Kim MJ, Shin HJ, Won KA, et al. Progesterone produces antinociceptive and neuroprotective effects in rats with microinjected lysophosphatidic acid in the trigeminal nerve root. Mol Pain 2012; 8: 16.
27. Carvalho B, Granot M, Sultan P, Wilson H, Landau R. A longitudinal study to evaluate pregnancy-induced endogenous analgesia and pain modulation. Reg Anesth Pain Med 2016; 41: 175-80.
28. Chuang SH, Reddy DS. 3β-Methyl-neurosteroid analogs are preferential positive allosteric modulators and direct activators of extrasynaptic δ-subunit γ-aminobutyric acid type a receptors in the hippocampus dentate gyrus subfield. J Pharmacol Exp Ther 2018; 365: 583-601.
29. Vincent K, Stagg CJ, Warnaby CE, Moore J, Kennedy S, Tracey I. "Luteal analgesia": progesterone dissociates pain intensity and unpleasantness by influencing emotion regulation networks. Front Endocrinol (Lausanne) 2018; 9: 413.
30. Krause DN, Warfvinge K, Haanes KA, Edvinsson L. Hormonal influences in migraine – interactions of oestrogen, oxytocin and CGRP. Nat Rev Neurol 2021; 17: 621-33.
31. Hornung RS, Benton WL, Tongkhuya S, Uphouse L, Kramer PR, Averitt DL. Progesterone and allopregnanolone rapidly attenuate estrogen-associated mechanical allodynia in rats with persistent temporomandibular joint inflammation. Front Integr Neurosci 2020; 14: 26.
32. Gupta S, McCarson KE, Welch KM, Berman NE. Mechanisms of pain modulation by sex hormones in migraine. Headache 2011; 51: 905-22.
33. Al-Hassany L, van Drie RWA, Boucherie DM, MaassenVanDenBrink A. Unraveling the paradox: cardiovascular risk profiling in migraine- a correspondence. J Headache Pain 2025; 26: 113.
34. Somerville BW. The influence of progesterone and estradiol upon migraine. Headache 1972; 12: 93-102.
35. Aloisi AM, Ceccarelli I, Fiorenzani P. Gonadectomy affects hormonal and behavioral responses to repetitive nociceptive stimulation in male rats. Ann N Y Acad Sci 2003; 1007: 232-7.
36. Ceccarelli I, Scaramuzzino A, Massafra C, Aloisi AM. The behavioral and neuronal effects induced by repetitive nociceptive stimulation are affected by gonadal hormones in male rats. Pain 2003; 104: 35-47.
37. Lashkari M, Noori A, Oveisi S, Kheirkhah M. Association of serum testosterone and dehydroepiandrosterone sulfate with rheumatoid arthritis: a case control study. Electron Physician 2018; 10: 6500-5.
38. Pikwer M, Giwercman A, Bergström U, Nilsson J, Jacobsson LT, Turesson C. Association between testosterone levels and risk of future rheumatoid arthritis in men: a population-based case-control study. Ann Rheum Dis 2014; 73: 573-9.
39. White HD, Brown LA, Gyurik RJ, Manganiello PD, Robinson TD, Hallock LS, et al. Treatment of pain in fibromyalgia patients with testosterone gel: Pharmacokinetics and clinical response. Int Immunopharmacol 2015; 27: 249-56.
40. Verhagen IE, Brandt RB, Kruitbosch CMA, MaassenVanDenBrink A, Fronczek R, Terwindt GM. Clinical symptoms of androgen deficiency in men with migraine or cluster headache: a cross-sectional cohort study. J Headache Pain 2021; 22: 125.
41. Mattsson P. Serum levels of androgens and migraine in postmenopausal women. Clin Sci (Lond) 2002; 103: 487-91.
42. Kobus M, Sitek A, Antoszewski B, Rożniecki J, Pełka J, Żądzińska E. Prenatal oestrogen-testosterone balance as a risk factor of migraine in adults. J Headache Pain 2021; 22: 119.
43. Glaser R, Dimitrakakis C, Trimble N, Martin V. Testosterone pellet implants and migraine headaches: a pilot study. Maturitas 2012; 71: 385-8.
44. Shields LBE, Seifert T, Shelton BJ, Plato BM. Testosterone levels in men with chronic migraine. Neurol Int 2019; 11: 8079.
45. Li W, Diao X, Chen C, Li C, Zhang Y, Li Y. Changes in hormones of the hypothalamic-pituitary-gonadal axis in migraine patients. J Clin Neurosci 2018; 50: 165-71.
46. van Oosterhout WPJ, Schoonman GG, van Zwet EW, et al. Female sex hormones in men with migraine. Neurology 2018; 91: e374-e81.
47. Dourson AJ, Darken RS, Baranski TJ, Gereau RW, Ross WT, Nahman-Averbuch H. The role of androgens in migraine pathophysiology. Neurobiol Pain 2024; 16: 100171.
48. Avona A, Mason BN, Burgos-Vega C, et al. Meningeal CGRP-prolactin interaction evokes female-specific migraine behavior. Ann Neurol 2021; 89: 1129-44.
49. Parashar R, Bhalla P, Rai NK, Pakhare A, Babbar R. Migraine: is it related to hormonal disturbances or stress? Int J Womens Health 2014; 6: 921-5.
50. Guldiken S, Guldiken B, Demir M, et al. Soluble CD40 ligand and prolactin levels in migraine patients during interictal period. J Headache Pain 2011; 12: 355-60.
51. Masoud SA, Fakharian E. Serum prolactin and migraine. Ann Saudi Med 2005; 25: 489-91.
52. Alia S, Ali RS, Nafiseh E, Ehsan K. Comparison the serum level of prolactin among patients with chronic and episodic migraine. J Neurol Res 2013; 3: 68-72.
53. Hartman N, Voron SC, Hershman JM. Resolution of migraine following bromocriptine treatment of a prolactinoma (pituitary microadenoma). Headache 1995; 35: 430-1.
54. Cavestro C, Rosatello A, Marino MP, Micca G, Asteggiano G. High prolactin levels as a worsening factor for migraine. J Headache Pain 2006; 7: 83-9.
55. Maddahi A, Edvinsson L, Warfvinge K. Expression of vasopressin and its receptors in migraine-related regions in CNS and the trigeminal system: influence of sex. J Headache Pain 2022; 23: 152.
56. Buschmann J, Leppla-Wollsiffer G, Nemeth N, Nelson K, Kirsten R. Migraine patients show increased platelet vasopressin receptors. Headache 1996; 36: 586-8.
57. Bahadoram M, Mahmoudian-Sani M-R, Keikhaei B, Alikhani K, Bahadoram S. The antimigraine action of arginine-vasopressin: a theoretical basis. Future Neurology 2020; 15. DOI: 10.2217/fnl-2020-0017.
58. Tzabazis A, Kori S, Mechanic J, et al. Oxytocin and migraine headache. Headache 2017; 57 Suppl. 2: 64-75.
59. Szewczyk AK, Ulutas S, Aktürk T, et al. Prolactin and oxytocin: potential targets for migraine treatment. J Headache Pain 2023; 24: 31.
60. Phillips WJ, Ostrovsky O, Galli RL, Dickey S. Relief of acute migraine headache with intravenous oxytocin: report of two cases. J Pain Palliat Care Pharmacother 2006; 20: 25-8.
61. Wang YL, Yuan Y, Yang J, et al. The interaction between the oxytocin and pain modulation in headache patients. Neuropeptides 2013; 47: 93-7.

62. Warfvinge K, Krause DN, Maddahi A, et al. Oxytocin as a regulatory neuropeptide in the trigeminovascular system: Localization, expression and function of oxytocin and oxytocin receptors. Cephalalgia 2020; 40: 1283-95.
63. Özge A, Peres MFP, Burstein R. Pediatric migraine care: bridging gaps, overcoming barriers, and advancing solutions. Eur J Pediatr 2025; 184: 362.
64. Lu G, Xiao S, Wang Y, et al. Global epidemiology and burden of headache disorders in children and adolescents from 1990 to 2021. Headache 2025; 65: 1170-9.
65. Fonseca E, Torres-Ferrús M, Gallardo VJ, Macaya A, Pozo-Rosich P. Impact of puberty in pediatric migraine: a pilot prospective study. J Clin Neurol 2020; 16: 416-22.
66. Eidlitz-Markus T, Zeharia A. Symptoms and clinical parameters of pediatric and adolescent migraine, by gender - a retrospective cohort study. J Headache Pain 2017; 18: 80.
67. Maleki N, Bernstein C, Napadow V, Field A. Migraine and puberty: potential susceptible brain sites. Semin Pediatr Neurol 2016; 23: 53-9.
68. Khan A, Liu S, Tao F. Current trends in pediatric migraine: clinical insights and therapeutic strategies. Brain Sci 2025; 15: 280.
69. Maleki N, Kurth T, Field AE. Age at menarche and risk of developing migraine or non-migraine headaches by young adulthood: a prospective cohort study. Cephalalgia 2017; 37: 1257-63.
70. Greene K, Irwin SL, Gelfand AA. Pediatric migraine: an update. Neurol Clin 2019; 37: 815-33.
71. Martinez CI, Liktor-Busa E, Largent-Milnes TM. Molecular mechanisms of hormones implicated in migraine and the translational implication for transgender patients. Front Pain Res (Lausanne) 2023; 4: 1117842.
72. Peterlin BL, Gupta S, Ward TN, Macgregor A. Sex matters: evaluating sex and gender in migraine and headache research. Headache 2011; 51: 839-42.
73. Al-Hassany L, Haas J, Piccininni M, Kurth T, Maassen Van Den Brink A, Rohmann JL. Giving researchers a headache – sex and gender differences in migraine. Front Neurol 2020; 11: 549038.
74. Allena M, De Icco R, Sances G, et al. Gender differences in the clinical presentation of cluster headache: a role for sexual hormones? Front Neurol 2019; 10: 1220.
75. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018; 17: 954-76.
76. Simmasalam R, Zuniga MC, Hinson HE. Neurological health in sexual and gender minority individuals. Semin Neurol 2024; 44: 193-204.
77. Heslin KC. Explaining disparities in severe headache and migraine among sexual minority adults in the United States, 2013-2018. J Nerv Ment Dis 2020; 208: 876-83.
78. Lane IA, Zempsky WT. Capturing the experiences of sexual and gender minorities with migraine headache. Headache 2023; 63: 971-4.
79. Eitel KB, Hodax JK. Evaluation and medical care of intersex and gender diverse youth. Pediatr Radiol 2024; 54:1352-62.
80. Nagata JM, Ganson KT, Tabler J, Blashill AJ, Murray SB. Disparities across sexual orientation in migraine among US adults. JAMA Neurol 2020; 78: 117-8.
81. Rosendale N, Guterman EL, Obedin-Maliver J, et al. Migraine, migraine disability, trauma, and discrimination in sexual and gender minority individuals. Neurology 2022; 99: e1549-e59.
82. Volpe SG, Ahmad J, Patel RA, Rosendale N. Neurological care for LGBT+ people. Nat Rev Neurol 2024; 20: 288-97.
83. Nilles C, Williams JVA, Patten S, Pringsheim T, Orr SL. Association between peer victimization, gender diversity, mental health, and recurrent headaches in adolescents: a Canadian population-based study. Neurology 2023; 101: e1654-e64.
84. Savic I, Garcia-Falgueras A, Swaab DF. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. Prog Brain Res 2010; 186: 41-62.
85. Hines M, Constantinescu M, Spencer D. Early androgen exposure and human gender development. Biol Sex Differ 2015; 6: 3.
86. Roselli CE. Neurobiology of gender identity and sexual orientation. J Neuroendocrinol 2018; 30: e12562.
87. Zhou JN, Hofman MA, Gooren LJ, Swaab DF. A sex difference in the human brain and its relation to transsexuality. Nature 1995; 378: 68-70.
88. Garcia-Falgueras A, Swaab DF. A sex difference in the hypothalamic uncinate nucleus: relationship to gender identity. Brain 2008; 131 (Pt 12): 3132-46.
89. Simon L, Kozák LR, Simon V, et al. Regional grey matter structure differences between transsexuals and healthy controls – a voxel based morphometry study. PLoS One 2013; 8: e83947.
90. Hoekzema E, Schagen SE, Kreukels BP, et al. Regional volumes and spatial volumetric distribution of gray matter in the gender dysphoric brain. Psychoneuroendocrinology 2015; 55: 59-71.
91. Kranz GS, Hahn A, Kaufmann U, et al. White matter microstructure in transsexuals and controls investigated by diffusion tensor imaging. J Neurosci 2014; 34: 15466-75.
92. Taziaux M, Staphorsius AS, Ghatei MA, Bloom SR, Swaab DF, Bakker J. Kisspeptin expression in the human infundibular nucleus in relation to sex, gender identity, and sexual orientation. J Clin Endocrinol Metab 2016; 101: 2380-9.
93. Taziaux M, Swaab DF, Bakker J. Sex differences in the neurokinin B system in the human infundibular nucleus. J Clin Endocrinol Metab 2012; 97: E2210-20.
94. Burke SM, Kreukels BP, Cohen-Kettenis PT, Veltman DJ, Klink DT, Bakker J. Male-typical visuospatial functioning in gynephilic girls with gender dysphoria – organizational and activational effects of testosterone. J Psychiatry Neurosci 2016; 41: 395-404.
95. Berglund H, Lindström P, Dhejne-Helmy C, Savic I. Male-to-female transsexuals show sex-atypical hypothalamus activation when smelling odorous steroids. Cereb Cortex 2008; 18: 1900-8.
96. Yalinay Dikmen P, Ertas M, Kosak S, et al. Primary headaches among gender dysphoric female-to-male individuals: a cross-sectional survey on gender transition experience. Headache 2021; 61: 1194-206.
97. White Hughto JM, Reisner SL, Pachankis JE. Transgender stigma and health: a critical review of stigma determinants, mechanisms, and interventions. Soc Sci Med 2015; 147: 222-31.
98. Badaeva A, Maiolino L, Danilov A, et al. Neurogasobiology of migraine: carbon monoxide, hydrogen sulfide, and nitric oxide as emerging pathophysiological trinacrium relevant to nociception regulation. Open Med (Wars) 2025; 20: 20251201.

99. Hoskin KL, Bulmer DC, Goadsby PJ. Fos expression in the trigeminocervical complex of the cat after stimulation of the superior sagittal sinus is reduced by L-NAME. Neurosci Lett 1999; 266: 173-6.
100. Valenti S, Fazzuoli L, Giusti M. Circulating nitric oxide levels increase after anti-androgen treatment in male-to-female transsexuals. J Endocrinol Invest 2003; 26: 522-6.
101. Pringsheim T, Gooren L. Migraine prevalence in male to female transsexuals on hormone therapy. Neurology 2004; 63: 593-4.
102. Aloisi AM, Bachiocco V, Costantino A, et al. Cross-sex hormone administration changes pain in transsexual women and men. Pain 2007; 132 Suppl. 1: S60-s7.
103. MacGregor EA. Oestrogen and attacks of migraine with and without aura. Lancet Neurol 2004; 3: 354-61.
104. Ahmad SR, Rosendale N. Sex and gender considerations in episodic migraine. Curr Pain Headache Rep 2022; 26: 505-16.
105. Todd CM, Yu A, Lay C, Lagman-Bartolome AM. Effect of testosterone therapy on migraine frequency and disability in two transgender patients: a case report. BMJ Case Rep 2023; 16: e251895.
106. Trovão Diniz E, Rocha Leite JB, Ribeiro Coutinho Madruga C, Maia Arca V, Macedo Cavalcanti Albuquerque JA, Sampaio Rocha-Filho PA. Headache in transgender men using gender-affirming hormone therapy: a case-control study. Headache 2025: 65: 1449-56.
107. Hranilovich JA, Millington K. Headache prevalence in transgender and gender diverse youth: a single-center case-control study. Headache 2023; 63: 517-22.
108. Peper JS, Brouwer RM, Schnack HG, et al. Sex steroids and brain structure in pubertal boys and girls. Psychoneuroendocrinology 2009; 34: 332-42.
109. Koolschijn PC, Peper JS, Crone EA. The influence of sex steroids on structural brain maturation in adolescence. PLoS One 2014; 9: e83929.
110. Roberts CM, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E. Continuation of gender-affirming hormones among transgender adolescents and adults. J Clin Endocrinol Metab 2022; 107: e3937-e43.
111. Bockting WO, Miner MH, Swinburne Romine RE, Hamilton A, Coleman E. Stigma, mental health, and resilience in an online sample of the US transgender population. Am J Public Health 2013; 103: 943-51.
112. Holroyd KA, Stensland M, Lipchik GL, Hill KR, O'Donnell FS, Cordingley G. Psychosocial correlates and impact of chronic tension-type headaches. Headache 2000; 40: 3-16.
113. Steiner J. Psychic Retreats: Pathological Organizations in Psychotic, Neurotic and Borderline Patients. Routledge, London 2003.
114. Tabernacki T, Gilbert D, Rhodes S, et al. The burden of chronic pain in transgender and gender diverse populations: evidence from a large US clinical database. Eur J Pain 2025; 29: e4725.
115. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL, 3rd. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009; 10: 447-85.
116. Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain 2008; 9: 883-91.
117. Bimpong K, Thomson K, McNamara CL, et al. The gender pain gap: gender inequalities in pain across 19 European countries. Scand J Public Health 2022; 50: 287-94.
118. Keogh E. Men, masculinity, and pain. Pain 2015; 156: 2408-12.
119. Martin V, Wernke S, Mandell K, et al. Medical oophorectomy with and without estrogen add-back therapy in the prevention of migraine headache. Headache 2003; 43: 309-21.
120. Calhoun AH. Understanding menstrual migraine. Headache 2018; 58: 626-30.
121. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol 2017; 16: 76-87.
122. Epstein MT, Hockaday JM, Hockaday TD. Migraine and reporoductive hormones throughout the menstrual cycle. Lancet 1975; 1: 543-8.
123. Vincent K, Warnaby C, Stagg CJ, Moore J, Kennedy S, Tracey I. Brain imaging reveals that engagement of descending inhibitory pain pathways in healthy women in a low endogenous estradiol state varies with testosterone. Pain 2013; 154: 515-24.
124. Moehlig RC. Methyl testosterone for migraine of women; report of sixty cases. J Mich State Med Soc 1955; 54: 577-9.
125. Keogh E. Sex and gender differences in pain: past, present, and future. Pain 2022; 163 (Suppl. 1): S108-s16.
126. Craft RM, Mogil JS, Aloisi AM. Sex differences in pain and analgesia: the role of gonadal hormones. Eur J Pain 2004; 8: 397-411.
127. Institute of Medicine (US) Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. National Academies Press (US), Washington (DC) 2011.
128. Ólason M, Andrason RH, Jónsdóttir IH, Kristbergsdóttir H, Jensen MP. Cognitive behavioral therapy for depression and anxiety in an interdisciplinary rehabilitation program for chronic pain: a randomized controlled trial with a 3-year follow-up. Int J Behav Med 2018; 25: 55-66.
129. Verma S, Gallagher RM. The psychopharmacologic treatment of depression and anxiety in the context of chronic pain. Curr Pain Headache Rep 2002; 6: 30-9.
130. Songer D. Psychotherapeutic approaches in the treatment of pain. Psychiatry (Edgmont) 2005; 2: 19-24.
131. Hajek A, König HH, Buczak-Stec E, Blessmann M, Grupp K. Prevalence and determinants of depressive and anxiety symptoms among transgender people: results of a survey. Healthcare (Basel) 2023; 11: 705.
132. De La Rosa JS, Brady BR, Ibrahim MM, et al. Co-occurrence of chronic pain and anxiety/depression symptoms in U.S. adults: prevalence, functional impacts, and opportunities. Pain 2024; 165: 666-73.
133. Martinez CI, Liktor-Busa E, Largent-Milnes TM. Problems in management of medication overuse headache in transgender and gender non-conforming populations. Front Neurol 2024; 15: 1320791.
134. Weitzer D. How to provide effective pain management to LGBTQ individuals. Pract Pain Manag 2019; 19.
135. Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental health outcomes in transgender and nonbinary youths receiving gender-affirming care. JAMA Netw Open 2022; 5: e220978-e.
136. Hughto JM, Restar AJ, Wolfe HL, et al. Opioid pain medication misuse, concomitant substance misuse, and the unmet behavioral health treatment needs of

transgender and gender diverse adults. Drug Alcohol Depend 2021; 222: 108674.
137. Gordon AR, Krieger N, Okechukwu CA, et al. Decrements in health-related quality of life associated with gender nonconformity among U.S. adolescents and young adults. Qual Life Res 2017; 26: 2129-38.
138. Abd-Elsayed A, Heyer AM, Schatman ME. Disparities in the treatment of the LGBTQ population in chronic pain management. J Pain Res 2021; 14: 3623-5.
139. Anger JT, Case LK, Baranowski AP, et al. Pain mechanisms in the transgender individual: a review. Front Pain Res (Lausanne) 2024; 5: 1241015.