

Headaches, hormones, and transgender population: current evidence and knowledge gaps.

Keywords

migraine, transgender individuals, gender diverse individuals, gender diverse population, primary headache disorders

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.

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Running title: Headaches in transgender population.

Preprint

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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% identifying specifically as transgender), with an observable increase in this percentage in recent years, especially among adolescents (6, 7). TGD population might require medically necessary gender-affirming hormone therapy (GAHT) to align physical characteristics with their gender identity (6, 7). GAHT (testosterone in masculinizing GAHT, and estrogen with androgen-lowering medications in GAHT with feminine embodiment goals) 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 impact on headache characteristics in cisgender individuals and an increasing proportion of transgender patients receiving GAHT raises the issue of potential associations between the 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, according to own 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 has been written in a narrative manner; however, some crucial methodological principles were applied to enhance transparency and rigor. The literature search, selection, and interpretation of findings were performed by the experts in 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 throughout 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 have been applied during the search, listed in the 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 following 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 was given, 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- α is typically associated with analgesic effects, whereas activation of ER- β may be pro-nociceptive (18). Furthermore, high estrogen levels are generally linked 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 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. demonstrated 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 summarize the effect of testosterone on migraine through several mechanisms: (a) 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 signalling, (d) 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 has been 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 management, 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 in boys. Also, adolescent females, compared to adolescent males, had a higher frequency of headaches and a higher rate of chronic migraine (66). The prevalence 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 the epidemiological studies of adult primary headaches that state 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 disparity, men are often underrepresented in migraine studies. In the narrative review on migraine in men, the authors found that adult males, compared to females, experience shorter migraine attacks (with and without aura) either treated or 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 compared to women diagnosed (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

didn't 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 the 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 adolescence, a higher risk of frequent headaches may be related to psychological factors (such as anxiety, depression, suicidality, and peer victimization), which are available for 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;
- 4) and the definitive phase of transition, encompassing multi-stage surgical procedures and, in some cases, additional hormonal interventions.

In the context of headaches, the question should be raised of whether headaches in transgender individuals have a distinct biological basis compared with other patient populations with such symptoms. Addressing this requires consideration of possible differences in the functioning of the nervous system 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 the 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 relative absence of testosterone. In humans, testosterone appears to influence the development of gender identity and sexual orientation directly (i.e., without metabolite mediation), whereas in rodents, these processes occur primarily via estradiol generated through aromatization of circulating testosterone (84-86). Postnatally, these features are subject to environmentally dependent epigenetic influences (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, 102)(103) (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 the recent study, transgender men receiving masculinizing GAHT presented lower risk than cisgender man of all headache types overall (odds ratio (OR) 0.20, 95% confidence interval (CI) 0.05–0.85); however, while the risk for tension type headaches was lower (OR 0.18, 95% CI 0.07–0.45), they had significantly higher prevalence of migraine (OR 3.93, 95% CI 1.60–9.63) comparing to cisgender men. (106). A study conducted in 2023 by Jennifer A. Hranilovich et al. partially supported these findings. Transfeminine individuals had a significantly higher risk of experiencing headache during GAHT compared to those not receiving hormone therapy (7% versus 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% versus 5%; OR 2.71, 95% CI 1.37-5.4), which challenges the commonly proposed 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, youth transmasculine 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).

Concluding, 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 homogenous influence of hormones alone. Taken together, these findings suggest that headache manifestations during transition in adolescents are presumably influenced by a complex interplay of biological and environmental aspects.

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, they may be symptomatic headaches with a migraine phenotype, and the diagnosis of migraine is incorrect. However, Todd et al. described two cases of chronic migraine without aura in transmasculine patients who used masculinizing hormone therapy with testosterone (105). In transmen, testosterone use may have both a protective effect and, less commonly, a provocative effect (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, a side effect of estrogen use is headaches incorrectly diagnosed as migraine, because their phenotype is like 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 in gender identification may form part of more broadly understood identity disturbances 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). Another 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 compared to 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 1*) as important factors 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, the emphasis should be given to the critical need for integrated care 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).

Limitations

The very limited 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.

The review was written narratively; thus, the risk arises that some appropriate 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 high-value articles written in other languages may have been excluded.

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 plays not only 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, the 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.

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Migraine and other headaches, hormones, and transgender population.

A state-of-the-art review.

Olga Grodzka, Anna K. Szewczyk, Marta Antkowiak, Arnold Kukowka, Piotr Woźniak, Monika Białecka, Izabela Domitrz

This **narrative review** examines the current evidence on migraine and headache disorders in transgender individuals, with a focus on the roles of sex hormones, psychosocial factors, and clinical management challenges.



Conclusions:

Transgender individuals may experience distinct patterns of migraine and headache burden influenced by hormonal therapies, stress, and social factors. However, the existing literature is sparse and fragmented, limiting the ability to draw firm clinical recommendations. Increased research efforts and greater clinical awareness are needed to improve personalized and effective headache care for transgender patients.

Takeaway: Migraine in transgender individuals remains understudied and requires greater clinical awareness.

Preprint

Table 1. 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

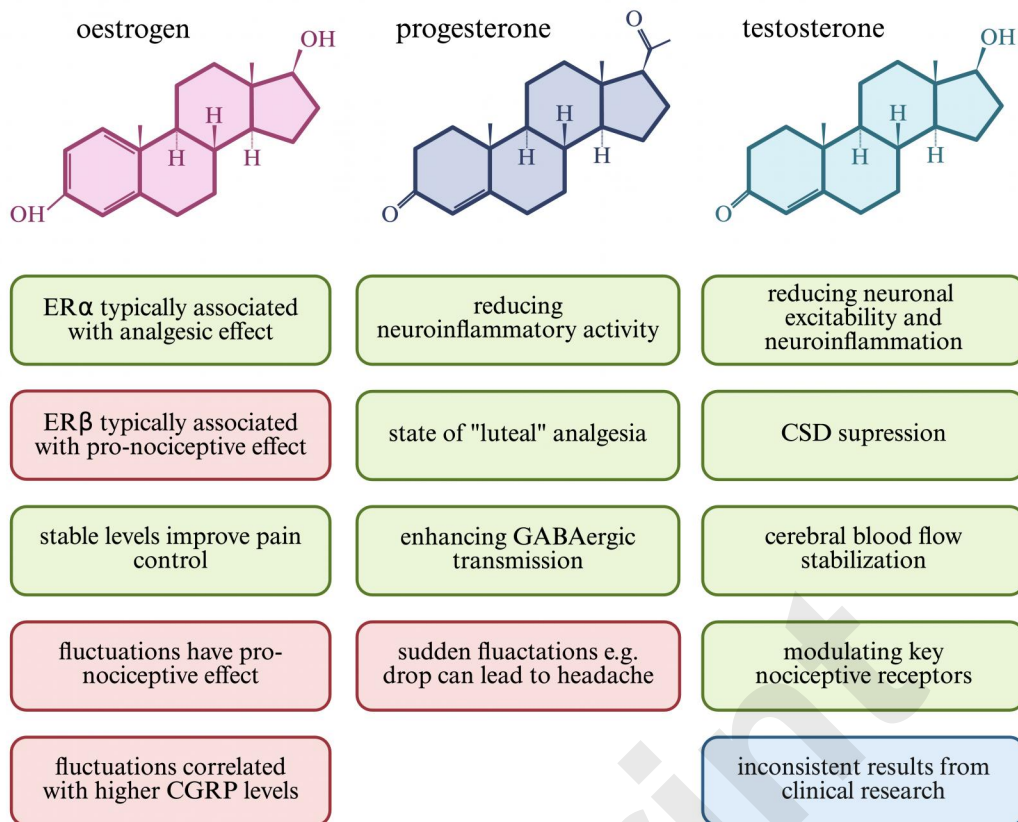


Figure 1. A graphical summary of the role in nociception of estrogen, progesterone, and testosterone. The figure illustrates the complex and, in some cases, opposing effects of sex hormones on pain modulation, highlighting the importance of hormonal balance and fluctuations rather than absolute hormone 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