Current Perspectives on Sex Differences in Tension Type Headache

Abstract

Introduction: Clinical and experimental evidence supports the presence of several gender differences in the pain experience.

Areas covered: The current paper discusses biological, psychological, emotional, and social differences according to gender and their relevance to TTH. Gender differences have also been observed in men and women with tension-type headache and they should be considered by clinicians managing this condition. It appears that multimodal treatment approaches lead to better outcomes in people with tension-type headache; however, management of tension-type headache should consider these potential gender differences. Different studies have observed the presence of complex interactions between tension-type headache, emotional stress, sleep and burden and that these interactions are different between men and women

Expert Opinion/Commentary: Based on current results, we hypothesize that treatment of men with tension-type headache should focus on improvement of sleep quality and the level of depression whereas treatment of women with TTH should focus on nociceptive mechanisms and emotional/stressful factors. Future trials should investigate the proposed hypotheses.

Keywords: Gender, tension type headache, sleep quality, pain, depression, treatment.

Article highlights

1. Evidence supports the presence of biological, psychological, emotional, and social differences between men and women which could affect the pain experience.
2. The relationships between headache, sleep, mood disorders and related-burden are highly complex in patients with tension-type headache.
3. The interactions between headache, sleep, mood disorders and burden are slightly different between men and women with tension-type headache.
4. The presence of musculoskeletal disorders is more prevalent in women than in men with tension-type headache and are associated with anxiety and hyperalgesia.
5. A hypothesis that management of men with tension-type headache should focus on improvement of the sleep quality (coping strategies or physical activity) and depressive levels (psychological management) is provided.
6. A hypothesis that treatment of women with TTH should focus on nociceptive pain mechanisms (non-pharmacological physical therapy) and emotional or stressful (coping strategies or cognitive behavior interventions) factors is also provided.

Current Perspectives on Sex Differences in Tension Type Headache

1. Introduction

Headache is a neurological condition highly prevalent in the society. Globally, in 2016, neurological disorders were the leading cause of disability-adjusted life-years and second leading cause of deaths worldwide [1]. Additionally, in the Global Burden of Disease Study 2017, headache was found to be the second most prevalent disorder in both men and women [2]. Headaches are mainly classified as primary or secondary. The International Headache Society (IHS) defines primary headaches as those that are not the result of an underlying medically specific condition and mainly include migraine, TTH and trigeminal autonomic cephalalgias [3]. Tension type headache (TTH) is probably the most common and the most neglected primary headache seen by neurologists in clinical practice [4]. It has been estimated that TTH has a point prevalence of 42% in the general population [5]. In a recent longitudinal study, it has been found that the one-year prevalence of TTH has increased in the last decades from 16% to 21% [6]. Since headaches have the greatest impact in middle-age active workers, they are associated with loss of work productivity and an important socio-economic impact [7]. In fact, indirect costs, including missed working days associated to headache burden, accounted for 92% of the overall financial costs of TTH [8].

In general, gender differences are usually found in some chronic pain conditions. For instance, women are two times at a greater risk to develop temporomandibular pain as compared to men in all the diagnostic groups (muscle disorders, disc displacement, or arthralgias) [9]. Similarly, it seems that TTH is more prevalent in women than men (female: male ratio 3:1) [10]. In fact, female gender is a key factor for poor prognosis in headaches, independently of the diagnosis [6]. Interestingly, women have a greater odds ratio (OR 1.25) of suffering from TTH associated with ischemic stroke than men [11].

However, not all headaches have a female predominance. For example, cluster headache is considered a male disorder; although there is an increasing identification in women with a progressive reduction of the male-to-female ratio from 5:1 to 2-3:1 [12]. However, it has been recently described that there exist gender differences in clinical manifestations since women with cluster headache exhibit more phenotypical features of migraine, particularly nausea, than men with cluster headache [13].

It has been previously suggested that headache features could be different between men and women since the gender influence on headache phenotype is a complex process [14]. A better understanding of the differences between men and women with TTH could assist clinicians in determining more specific therapeutic strategies according to gender [15]. The current paper discusses biological, psychological, emotional, and social differences according to gender and their relevance to TTH by proposing hypotheses in relation to current clinical reasoning.

2. Gender Differences in Nociceptive Pain Mechanisms

The fact that women are more likely to experience several chronic musculoskeletal pain syndromes suggests the presence of gender differences in nociceptive processing. The systematic review conducted by Racine et al. [16] found differences in some, but not all, quantitative sensory testing (QST) between men and women. For instance, ischemic pain thresholds were similar between men and women, while pressure pain and thermal pain thresholds were lower in women than in men [16]. No gender differences in tolerance thresholds were observed either [16]. Nevertheless, some comparisons included in this review maybe underpowered due to small sample sizes of published studies.

Some hypotheses for explaining these gender differences in pain perception have been proposed. We will briefly discuss those mostly related to headaches. First, the role of hormones on pain modulation should be considered. There is evidence supporting that hormones can influence nociceptive pain processing by complex interactions including the peripheral and central nervous systems and both excitatory and inhibitory pathways [17]. Although review of these mechanisms is beyond the scope of the current paper, we will briefly discuss those more relevant. First, the role of hormone in pain perception is mainly based on the fact that clinical manifestations of several chronic pain disorders are worse during the late luteal or early follicular phases of the menstrual cycle and that thresholds are different depending on which phase of the menstrual cycle are assessed [18]. However, results are heterogeneous and no association between pain thresholds and menstrual cycle phases is clear. The role of hormones and headache is clearly observed in migraine headaches where the age of menarche and changes in estrogen levels during the late luteal phase play a relevant role [19]. In fact, a female-only migraine type is menstrual migraine supporting the relevance of hormones in this condition. However, this association seems to be clearer in migraine than in TTH. Obviously, hormones can also affect the female affective state, and this may be another mechanism for modulating pain sensitivity. For instance, hormone changes could be associated with potential depressive or anxiety states in some women. In such a scenario, a depressive state contributes to chronic pain via supra-spinal mechanisms and emotional modulation of pain, creating a vicious cycle [20].

It has been also hypothesized that gender differences in pain perception could also be related to differences in brain structure development and function. Ingalhalikar et al. [21] suggested that male brain seems to be structured mostly to facilitate connectivity between perception and coordinated actions, whereas the female brain seems to be mainly

designed to facilitate communication between analytical and intuitive processing modes. These results provide a potential anatomical substrate for emotional gender differences. Ritchie et al. [22] reported interesting results in relation to nociceptive pain mechanisms. These authors found gender differences in the volume of different cortical areas related to pain, e.g., the pain neuromatrix, such as the cingulate gyrus, the insula, or the precentral gyrus); nevertheless, there was a considerable distributional overlap between both sexes [22]. Readers are referred to other texts for further discussion on these mechanisms underlying potential gender differences [16-22].

3. Gender Differences in Psychological, Emotional, and Social Aspects

Cognitive, emotional, and affective factors may also influence pain responses and, again, gender differences can be observed [23]. Evidence suggests that women are more likely and more vulnerable than men to experience mood disorders such as depression and anxiety; however, both disorders are highly comorbid and share several symptoms and risk factors [24,25]. Similarly, women also experience worse sleep quality than men [26]. These gender differences could be related to a potential hormone effect [27]. In addition, there is evidence that men and women cope differently with adversity, which may be related to the fact that certain resilience factors are more effective for women than for men [28]. Other psychological aspects such as personality also influence pain perception. Thorn et al. [29] revealed that gender differences in response to pain stimuli were partially attributed to personality traits differences between men and women.

There are also gender differences in social factors which could also be involved in the emotional status and, therefore, in pain perception. For instance, life experiences and cultural and social expectations are slightly different between men and women [30]. For instance, women are more likely than men to seek support from others, including

family an and friends [31]. This social "pressure" explains why women are also more likely to suffer from social anxiety [32]. Social anxiety is characterized by a marked fear to social situations (e.g., talking to a stranger, going to a party) or public activities (e.g., giving a speech) to unfamiliar people [32]. The emotional stress induced by social events could lead to an increase in anxiety levels which could promote pain in a vicious circle.

Cultural factors can also be involved in gender perception of the world and, hence, influence pain perception [33]. In some cultures, women view overt pain expression as more acceptable than men [34], which could be associated to the idea that men should be more tolerant to pain than the woman (masculinity culture factor) [35]. These cultural factors could lead to differences in pain perception between women and men leading to women experiencing higher intensities of pain but with lower external manifestation to the others.

Finally, the type of work can also have an influence. Women have higher levels of job strain than men; however, no gender differences of effect on adverse job situations on depressive symptoms have been found [36]. Another potential labor differences, such as lower income, could also have an influence on pain perception. Chu et al. [37] found that women were more influenced by socioeconomic status on the development of TTH than men. These authors found that living in rural areas and having college-level of education were related to decreased risk of TTH, particularly in women [37].

In conclusion, consistent evidence supports that psychological, emotional, social and cultural gender differences should be considered in the maintenance of chronic pain.

4. Tension Type Headache, Nociceptive Muscle Pain and Gender Differences

There is consistent evidence supporting that mechanical pain thresholds, i.e., pain thresholds to pressure, are lower in women than in men [16]. Interestingly, mechanical pain hypersensitivity is one of the main clinical features of TTH. Consistent evidence suggests that both peripheral or central mechanisms are involved in the etiology of TTH and that patients presenting with the frequent form are typically more peripheral dominant whereas those with the chronic are more central dominant [38]. Different systematic reviews reported evidence supporting the presence of hypersensitivity to pressure pain, i.e., lower pressure pain thresholds, in patients with TTH as compared to healthy people, particularly in the trigeminal area [39,40]. Further, women with TTH had consistently higher sensitivity to pressure pain than men with TTH [39, 40].

The International Headache Society describes the pain features of TTH as follows: 1, bilateral location; 2, pressing or tightening pain quality, although patients also describe their pain as dull, heaviness, pressure or soreness; 3, moderate intensity; 4, no aggravation of headache during physical activity [3]. Some features, e.g., photophobia, phonophobia, nausea or vomiting, which are mostly associated with migraine, are sometimes permitted in patients with the chronic form of the disease [3]. All these clinical features are similar to the pain descriptors commonly used for describing muscle referred pain. In fact, TTH is considered a prototype of headache where muscle tissues can play a relevant role in the pathogenesis [41]. In fact, it is formally accepted that the presence of musculoskeletal disorders of the cervical spine in this type of headache [42]. In such a scenario, muscular trigger points (TrPs) have received increasing attention in the last two decades [43]. Fernández-de-las-Peñas et al. [44] proposed a pain model where the referred pain elicited by TrPs located in muscles mainly innervated by the trigeminal nerve and upper cervical roots (C1-C3 segments) could be the main responsibility for peripheral nociception

198 arriving to trigemino-cervical nucleus caudalis. According to this model, a continuous
199 nociceptive afferent barrage from these TrPs into the trigeminal nerve nucleus caudalis
200 could sensitize the central nervous system and thereby contribute to generation of
201 widespread sensitization found in TTH. Recent studies showing the association of muscle
202 TrPs with central sensitization have supported, at least partially, this pain model in TTH
203 [45].

204 It has recently been recently that gender differences in the presence of referred
205 muscle pain in patients with TTH. Cigarán-Mendez et al. [46] found that women suffering
206 from TTH exhibited higher number of TrPs than men and that the association between
207 TrPs, anxiety and sensitivity to pressure pain was more pronounced in women than in
208 men. These authors suggested that gender differences in muscle architecture could
209 explain the higher prevalence of myofascial pain syndrome in women [46]. Other
210 extrinsic factors such as differences in physical activity and muscle strength between men
211 and women could also be involved. More interesting was the more pronounced
212 association between muscle pain, anxiety, and pressure pain hyperalgesia in women than
213 in men. This interaction is highly relevant for understanding the development and
214 maintenance of TTH in women. For instance, it has been found that stress can promote
215 hyperalgesic responses in the central nervous system [47]. In fact, general distress has
216 been identified as a risk factor for referred muscle pain [48]. These results would support
217 that emotional factors such as anxiety can lead to higher muscle responses in women with
218 TTH than in men with TTH. Further, gender differences in the presence of muscle
219 referred pain could also be related to the fact that experimental-induced muscle pain is
220 able to activate diffuse noxious inhibitory pain mechanisms in men, but not in women
221 [49]. Current findings would suggest that muscle pain development could be different

between men and women with TTH and, therefore, should be considered in the management of this condition.

5. Tension Type Headache, Emotional Trigger Factors and Gender Differences

Several trigger factors can potentially precipitate a headache attack. It appears that emotional stress and sleep disturbances are trigger factors most commonly self-reported by patients with TTH [50]. Consistent evidence supports that people with TTH exhibit co-morbid mood disorders (depression or anxiety) [51] and sleep disturbances [52]. These factors could promote pain sensitivity in primary headaches [53]. In fact, poor sleep or other sleep disturbances are considered a risk factor for progression from the episodic to the chronic form of TTH [54]. A recent study reported that insufficient sleep or poor sleep quality was associated with higher intensity of headache and more disability in patients with TTH [55].

Some studies have previously investigated the association between depression and the burden of headache, but most of them focussed on migraine, and not TTH [56, 57]. Recent studies have revealed several complex interactions between mood disorders (i.e., anxiety or depression) and sleep disorders with headache burden in a large cohort of patients with TTH. Palacios-Ceña et al. [58] found that depression and sleep quality mediated the association between headache frequency and emotional burden of headache and pain interference in patients with chronic TTH. The results of this study support that depression and sleep play a more relevant role in headache burden than anxiety; however, this was a cross-sectional study. In a longitudinal design, Fuensalida-Novo et al. [59] found that depression and the emotional burden of headache mediated the effects of pain interference with global burden of headache one-year after, again, in individuals with chronic TTH. Similarly, Benito-González et al. [60] also observed that sleep quality

exhibits complex interactions with emotional factors since depression and emotional burden are associated with sleep quality, whereas widespread pressure sensitivity over extra-trigeminal areas was associated with the quality of sleep one-year after. These studies support a complex relationship between emotional aspects in patients with chronic TTH; however, we do not know if these findings would be similar in individuals with the episodic form.

Interestingly, two recent studies have demonstrated that these associations are also slightly different by sex in TTH. Cigarán-Méndez et al. [61] found that depressive symptoms and emotional burden were associated with sleep quality in men, whereas depression and headache intensity were associated in women with chronic TTH. Similarly, Fuensalida-Novo et al. [62] showed that sleep quality was associated with the burden of headache in men with TTH, whereas the levels of depression and headache pain intensity were most associated with the burden of headache in women with TTH. Both studies found that depression was an emotional factor highly important for TTH. In fact, depression has a marked impact on the burden perceived by headache since it increases the risk of feeling less understood by the society, including family and friends, as well as increased risk of avoiding to tell other people about the headache [63]. Nevertheless, it seems that depressive levels can be slightly more relevant in men than in women with TTH. In such a scenario, cultural and social factors can explain this. For instance, men could perceive depressive symptoms like a debility (not a masculine feature), developing more fear to its social consequences, and leading to a higher influence in the perceived burden [31]. On the contrary, women are more likely to seek support from others, including family and friends, and are more likely to receive positive social reinforcement when expressing concerns about their symptoms that could encourage self-focused attention. Similarly, under some conditions of perceived threat,

men are more likely to escape or cope by taking action, but women are more likely to express social behavior and seek support from others [31].

Similarly, the association of sleep quality with headache burden in men, but not women, with TTH found by Fuensalida-Novo et al. [62] can help to understand potential gender differences. For instance, a greater effect of sleep quality in men with TTH could be associated to greater physical demands in men and worse quality of sleep could lead to tiredness or lack of energy in a greater extent in men. In conclusion, several gender differences between men and women with TTH are also observed in emotional and psychological factors.

6. Tension Type Headache, Clinical Implications and Gender Differences

Independently of the biological mechanisms underlying these gender differences, several potential implications for clinical practice can be drawn from the current review since mood disorders, sleep and pain represent modifiable risk factors implicated in the chronicity of headaches [64]. Therefore, biological, psychological, emotional, social, and cultural factors discussed in the current paper should be integrated into a multimodal and multidisciplinary approach of TTH, but considering these gender differences [65].

Based on current data we would like to propose the hypotheses that management of men with TTH should mainly focus on interventions targeting to improve sleep quality (by using copying strategies, relaxation techniques, and promotion of physical activity) and depressive levels by psychological or self-management approaches (**Fig. 1**) whereas treatment of women with TTH should mainly focus on interventions targeting nociceptive mechanisms related to pain (i.e., physical therapy approaches) and psychological and/or emotional approaches (i.e., copying and cognitive strategies) (**Fig. 2**).

There is substantial evidence in favor of psychological treatments for headaches; however, no consensus on which intervention, e.g., cognitive-behavior therapies, coping strategies, relaxation training, biofeedback, mindfulness-based treatment, or autogenic treatment, is more indicated since their effectiveness seem similar [66]. Nevertheless, clinicians should consider that there are several approaches targeting each emotional or psychological factor, therefore, treatment personalization is highly relevant. As example, different coping strategies (e.g., diverting attention, coping self-statements, focusing on or reinterpreting pain sensations, or suppression of pain-related thoughts) can be adopted to better manage pain. Therefore, the clinician should adapt therapeutic strategies to each patient considering gender differences. First, women with TTH exhibit pessimistic coping strategies more frequently than men with TTH [67]. Second, women tend to cope better with pain than men when employing pain attention focus or reinterpreting sensation strategies, whereas men work better with the distraction strategies [68]. These gender differences may be relevant for choosing strategies aimed at eliminating the stressor event (problem focused coping) or strategies aimed at reducing the emotional impact of the stressor (i.e., emotion-focused coping). The first strategy could be more effective in men and the second one more effective in women with TTH.

Improvement of sleep quality seems to be also an important target for treatment. In fact, sleep disturbances, such as insomnia, can be treated pharmacologically and non-pharmacologically, while short sleep duration can be relieved by ensuring a sufficient sleep duration and good sleep hygiene, that is, with education and coping strategies [69]. In fact, going to sleep earlier is the most commonly used self-management strategy (81%) by individuals with TTH and also rated as the most effective strategy [70]. One non-pharmacological treatment strategy that can modulate sleep quality is exercise/physical activity since it activates descending inhibitory pain pathways [71]. In fact, the inclusion

of regular exercise into the therapeutic approach for TTH has been previously proposed for normalizing the potential excitability of the central nervous system [72]. Although there is evidence supporting positive effect of exercise for TTH [73], the most appropriate therapeutic exercise program can be different depending on each headache, e.g., TTH, migraine, cluster headache [74]. Clinicians should differentiate between aerobic exercise, which influences the central nervous system, and specific and localized exercise, targeting specific musculoskeletal disorders of the cervical spine. Both treatment options should be implemented for the management of TTH [75]. In fact, evidence suggests that the application of muscle strengthening or motor control exercise programs is effective in TTH [76,77]. According to gender differences discussed in the current paper, aerobic exercise may be more indicated for men (for improving sleep quality and energy) whereas localized exercises may be more indicated for women (for managing local tissue-based impairments) with TTH. Future studies should investigate this hypothesis.

Another important factor to consider in the management of women with TTH is management of tissue-based musculoskeletal disorders. It has been found that muscular impairments seem to be more relevant in women with TTH [46]. This study observed a greater number of TrPs in women with TTH and, importantly, these TrPs were associated to higher widespread pressure pain hyperalgesia and anxiety levels [46]. These results would suggest a higher spatial summation of TrP activity in women with TTH, therefore, proper identification of all potentially affected muscles maybe more relevant in women than in men with TTH. A recent meta-analysis provided preliminary evidence suggesting that manual interventions targeting muscle TrPs can be effective for the management of TTH; however, the quality of evidence was low due to inconsistent results [78]. This lack of effect may explain the fact that higher presence of muscle pain in women with TTH is associated with anxiety levels and widespread mechanical hyperalgesia, therefore,

346 management of women with TTH should also include psychological aspects and central
347 nervous system therapeutic strategies and not just localized tissue-based (manual therapy)
348 interventions. In such a scenario, biofeedback could be an effective therapeutic strategy
349 to be included in treatment of women with TTH. In fact, there is evidence supporting that
350 biofeedback is effective for reducing headache intensity and frequency in TTH, but again
351 with low evidence [79]. Since the objective of biofeedback is to teach the patients to
352 manage muscle tension in those activities that they associate with their headaches,
353 biofeedback would be mostly effective in those individuals with headache associated to
354 pericranial tenderness and maybe more indicated for women, but not men, with TTH.
355

356 ## 7. Conclusions

357 This paper has summarized the biological, psychological, and emotional aspects
358 that are different between men and women with TTH and proposes a therapeutic model.
359 These gender differences should be considered by clinicians for the management of
360 individuals with headache. It seems that treatment of TTH patients should include
361 multimodal therapeutic approaches, considering, gender differences. Based on current
362 evidence, we hypothesize that sleep and depressive levels should be the main therapeutic
363 targets in the management of men with TTH whereas nociceptive mechanisms and
364 emotional factors should be the therapeutic targets in women with TTH. Future trials
365 should investigate the proposed hypotheses.
366

367 ## Declaration of Interest

368 No funds were received for this study. No conflict of interest is declared by the authors
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Expert Opinion

There is clinical and scientific evidence demonstrating the presence of gender differences in pain mechanisms. In fact, women are more susceptible to develop chronic pain than men. Tension-type headache (TTH) is a primary headache with a female predominance. Previous research has not consistently considered the potential influence of gender in the development and chronification of TTH. This paper has discussed the presence of important differences between men and women with TTH which has not been previously considered when managing these patients. Current evidence investigating the effects of the different therapeutic strategies for TTH is heterogeneous. Interestingly, previous studies have not considered gender differences when designing a treatment plan. We have proposed two models for managing women/men with TTH according to the identified potential gender differences: sleep and depressive levels should be the main targets in the management of men with TTH, whereas musculoskeletal pain disorders associated to pain mechanisms and anxiety/emotional stress should be the main targets in women with TTH. Clinicians treating patients with headache should consider the differences discussed in this paper for improving the effectiveness of their treatment approaches when treating patients with TTH. Future studies are clearly needed for confirming or refuting these hypotheses.

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Legend of Figures

Figure 1: Proposal model of relevant events (INPUT, sleep and depression) integrating the cognitive processes (INTEGRATION PLAN) and potential OUTPUT in men with tension-type headache.

Figure 2: Proposal model of relevant events (INPUT, musculoskeletal impairments and anxiety) integrating the cognitive processes (INTEGRATION PLAN) and potential OUTPUT in women with tension-type headache.