

REVIEW

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Hallmarks of primary headache: part 2– Tension-type headache

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Abstract

Background and aim Tension-type headache is the most prevalent primary headache disorder. While the episodic subtype is more common, chronic tension-type headache significantly impacts health-related quality of life and contribute to increased healthcare utilization and disability. Despite considerable advances in the understanding of tension-type headache, critical gaps persist. This paper aims to provide a comprehensive review of the hallmarks of tension-type headache, from its pathophysiology, comorbidities, treatment options, to psychosocial impact.

Main results Multiple factors are associated with tension-type headache, including peripheral mechanisms (increased muscle tenderness and myofascial trigger points), central sensitization, genetic predisposition, and psychological comorbidities such as anxiety and depression. Neuroimaging and neurophysiological studies demonstrated altered pain processing in cortical and subcortical regions in patients with tension-type headache. Regarding treatment strategy, in addition to pharmacological treatment, novel insights into non-pharmacological interventions such as cognitive behavioral therapy, neuromodulation techniques, physical therapy, mindfulness, lifestyle management, and patient education were highlighted as valuable components of comprehensive management strategies.

Conclusions A complex interplay between peripheral and central mechanisms and psychosocial stressors underpins tension-type headache. Integrated multidisciplinary approaches combining pharmacological and non-pharmacological interventions are critical for optimal patient outcomes. Further research should continue to refine

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the understanding of these mechanisms to improve targeted therapeutic strategies and reduce the global burden of tension-type headache.

Keywords Tension-type headache, Disease burden, Primary headache, Non-pharmacological treatments

Introduction

Tension-type headache (TTH) is the most prevalent primary headache disorder. TTH is highly prevalent worldwide, affecting a substantial portion of the global population. Prevalence estimates differ across studies and regions worldwide, mainly due to variations in case definitions, research methodologies, and demographic factors, including ethnicity and population characteristics. Literature shows that the global prevalence is approximately 26% [1, 2]. TTH exhibits a slight female predominance, with a sex ratio 1.2:1, notably lower than the 3:1 ratio observed in migraine. TTH can be clinically classified based on headache frequency into episodic (ETTH) and chronic (CTTH) types, whereas ETTH is further subdivided into infrequent and frequent ETTH [3] (Fig. 1). While ETTH is more common, CTTH significantly impacts health-related quality of life (HRQoL) [4], contributing to increased healthcare utilization [5] and disability [6]. Despite considerable advances in the understanding of TTH, critical gaps persist. Addressing these unresolved issues is urgently needed, given their potential impact on clinical decision-making and patient outcomes.

Challenges in TTH diagnosis: the dilemma of strict and non-strict criteria

TTH is characterized by bilateral, non-pulsating, pressing, or tightening pain of mild to moderate intensity, typically lacking the accompanying symptoms of nausea, vomiting, photophobia, and phonophobia, primarily seen in migraine. Currently, the diagnosis of TTH is based on the International Classification of Headache Disorders, third edition (ICHD-3) [3]. Despite the well-defined criteria for TTH, several limitations persist in clinical practice. One key challenge lies in the ambiguity of distinguishing TTH from mild forms of migraine, particularly when migrainous features are subtle or inconsistently reported. Although the current ICHD framework places TTH at a higher diagnostic hierarchy than probable migraine, this distinction may inadvertently lead to suboptimal clinical decisions. Clinicians may be less inclined to consider migraine-specific treatments, such as triptans or gepants, and the options for preventive treatment may be limited. This diagnostic shift may contribute to potentially avoidable disability, particularly when the underlying headache phenotype is more aligned with migraine pathophysiology. To address these challenges, some experts have proposed alternative diagnostic criteria—often called the *strict criteria* for TTH—which have

been included in the Appendix of both the ICHD-2 [7] and ICHD-3 [3]. These criteria aim to improve diagnostic specificity, enhancing the homogeneity of the TTH diagnosis. Evidence supports biological differences between strict-criteria TTH and migraine, showing variations in gray matter volume and distinct patterns of somatosensory cortex excitability [8, 9]. These findings offer biological evidence supporting the adoption of strict criteria to improve the diagnostic delineation between TTH and migraine. Field testing of the alternative criteria has provided valuable insights into the clinical profiles of patients diagnosed with TTH [10]. Among individuals meeting the standard (non-strict) criteria for TTH, only 40.6% also fulfilled the strict criteria. Of the remaining 59.4%, approximately one-third were reclassified as probable migraine, while the other two-thirds could not be classified within the current ICHD framework and were considered to have “unclassified headache.” Compared to those diagnosed with TTH under the standard criteria, subjects identified by the alternative (strict) criteria exhibited fewer migrainous features, as expected. Notably, they also had lower headache frequency and experienced less headache-related disability, as reflected by lower HIT-6 scores. These findings highlight the heterogeneity introduced by the current criteria while revealing a significant drawback of the strict criteria—their limited sensitivity. The large proportion of patients categorized as “unclassified headache” raises concerns about the clinical utility of such a narrow definition. If strict criteria are to be adopted, it will be necessary to refine the diagnostic framework for probable TTH and clarify the hierarchy between probable TTH and probable migraine. Given the growing role of AI-based diagnostic models, the need for clearly defined and standardized clinical input has become increasingly critical. Ambiguous descriptions from the patients, such as “sometimes I have this or another sign” may lead to misclassification. These discussions highlight the need for refinement of the diagnostic criteria of TTH, which may be addressed in the upcoming ICHD-4. Of note, based on the ICHD-3, a diagnosis of TTH can coexist with medication-overuse headache (MOH) if the criteria for both conditions are fulfilled.

Epidemiological data and diagnostic transitions between migraine and TTH

The GBD 2021 study [6] estimated TTH prevalence in individuals aged 5–9, 10–14, and 15–19 years at 8.0%, 26.7%, and 30.8% in females and 7.7%, 26.3%, and 30.0% in males, respectively. However, these estimates are

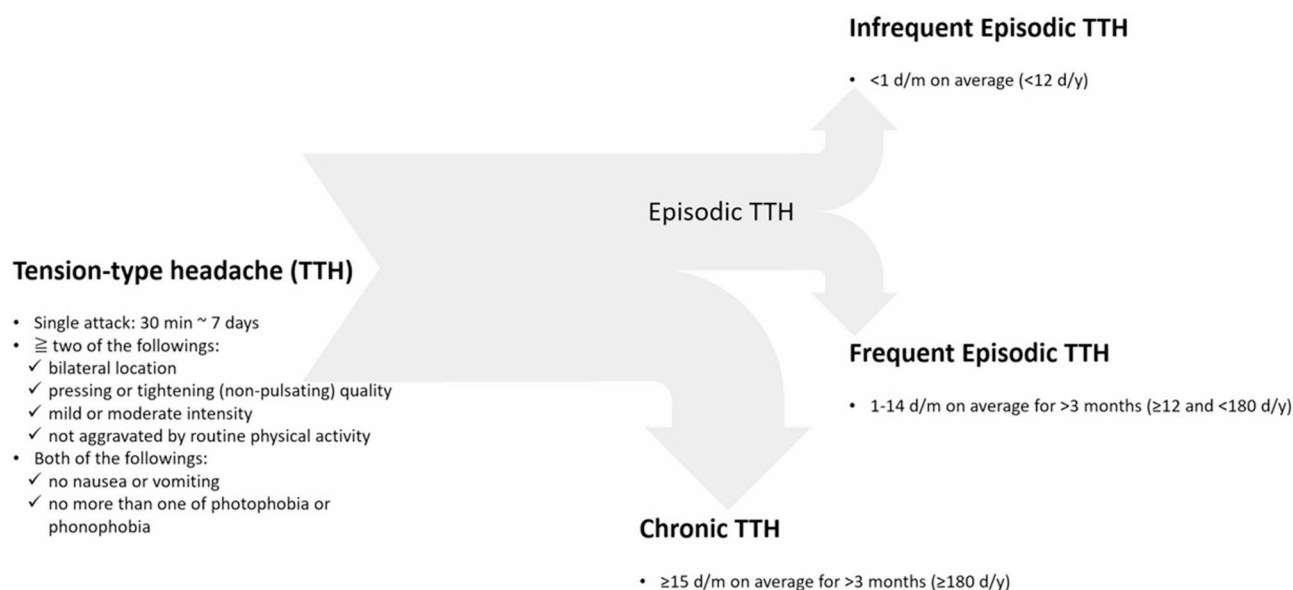


Fig. 1 The ICHD-3 criteria for tension-type headache and its subtypes. Tension-type headache includes episodic and chronic forms based on attack frequency. Episodic tension-type headache can be further divided into infrequent and frequent subtypes. TTH: tension-type headache

derived from cross-sectional data and do not capture the dynamic changes in headache diagnoses that may occur as children and adolescents age. Several longitudinal studies have provided insights into the age-related evolution of headache diagnoses [11–14]. One study reported that up to 71.3% of individuals experienced a change in their headache classification over a seven-year follow-up period [12]. Ozge et al. and Kienbacher et al. conducted longitudinal studies following children and adolescents over approximately six years [11, 12]. Both studies reported similar findings: among those initially diagnosed with TTH, about 20% were reclassified as migraine at follow-up. In contrast, Guidetti et al. reported a lower conversion rate of 8.3% from TTH to migraine after an eight-year follow-up [14]. Additionally, both Kienbacher et al. [11] and Guidetti et al. [14] observed that 38–44.4% of individuals with TTH became headache-free. In contrast, Ozge et al. reported a substantially lower rate of remission at 14.2%. Sillanpää et al. made a significant contribution through a 25-year longitudinal study that followed participants from age 7 to 32 [13]. Their findings revealed notable sex-related differences in headache transitions: among girls diagnosed with non-migraine headaches at age 7, 30% were later diagnosed with migraine by age 32; in contrast, only 12% of boys with non-migraine headaches at baseline received a migraine diagnosis in adulthood. It is important to note that this study began in 1974, predating the publication of the first edition of ICHD in 1988 [15]. Therefore, migraine diagnosis was based on the Vahlquist criteria [16]. Recurrent primary headaches not fulfilling the Vahlquist criteria for migraine were classified as non-migraine headaches,

which likely comprised a majority of TTH. Secondary headaches were excluded from the study. Sillanpää et al. further noted that a substantial proportion of adults with migraine—ranging from 29–35%—had a history of non-migrainous headaches in childhood, which in this context can reasonably be interpreted as predominantly TTH [13]. In contrast, only 2–5% of adults with non-migrainous headaches had migraine during childhood. The fluidity between the diagnoses of TTH and migraine presents a significant challenge for clinical classification and therapeutic decision-making.

The pathophysiology of TTH: peripheral or central origin?

One crucial aspect in understanding TTH is the interplay between central and peripheral pain mechanisms, contributing to its pathophysiology and clinical variability. While early hypotheses [17, 18] suggested that peripheral muscle tension was the primary cause of TTH, more recent research [19] indicates that central pain sensitization and dysregulated pain processing play a significant role, especially in CTTH. Neuroimaging [20] and neurophysiological [21] studies have provided compelling evidence that individuals with CTTH exhibit altered pain modulation networks, including changes in brainstem function, cortical excitability, and impaired descending inhibitory control. Genetic predisposition [22, 23], vascular factors [24], and inflammatory pathways [25] have been explored as potential contributors, though their roles remain incompletely understood. The complex nature of TTH, which involves an interplay between genetic, molecular, neurological, vascular, and

psychological factors [26], underscores the need for a multidisciplinary approach to research and management.

Given the complex and multifactorial nature of TTH, this review aims to present the hallmarks of TTH in all these fields. It is organized into a set of sub-sections, each aimed at reporting the elements that identify TTH-specific features, summarizing the most comprehensive and precise evidence possible for each topic.

Neuroimaging in TTH

TTH vs. non-headache control: evidences from structural neuroimaging studies

A limited number of studies have analyzed structural changes in TTH compared to non-headache controls [20]. Notably, the “TTH” group in different studies may vary in frequency and severity; some studies included ETTH, while others recruited CTTH, and some did not report the headache frequency [20]. Therefore, differences in results between these studies may also reflect the heterogeneity across these studies.

ETTH

Among studies focused on ETTH, one Italian study compared the white matter hyperintensities (WMH) between patients with ETTH (mean headache frequency 8.8 ± 3.3 days per month) and healthy controls [27]. The study found no differences between groups in the periventricular WMH, but two out of thirty ETTH patients had deep WMH. The study also found that ETTH patients with neurological soft signs (assessed by the Heidelberg scale) tend to present WMH [27, 28]. However, caution is warranted when interpreting the results of this study, as neurological soft signs assessed using the Heidelberg scale—such as sensory integration, motor coordination, and primitive reflexes—are not included in the diagnostic criteria for TTH [28]. Moreover, TTH patients exhibiting neurological soft signs may represent a distinct subgroup from the general TTH population [27]. Another Chinese study on treatment-naïve ETTH (mean headache frequency 5.3 ± 3.0 days per month) reported differences in gray matter density (GMD) between the headache and non-headache phases [29]. They found GMD was lower in the right primary somatosensory cortex during the headache phase compared to the non-headache phase, while the GMD was higher in the bilateral anterior cingulate cortices (ACC) and bilateral anterior insulae during the headache phase [29]. Additionally, GMD in the left ACC and left anterior insula showed a negative correlation with monthly headache days. However, no correlation was found between regional GMD and the Visual Analogue Scale in patients with ETTH [29].

CTTH

A German study analyzed the gray matter volume (GMV) in CTTH [30]. Their CTTH patients had a mean headache frequency of 27.0 ± 3.7 days per month, and patients were under preventive medications. This study found decreased total GMV in CTTH patients [30]. Also, a significant decrease in GMV was observed across various cortical and subcortical regions. These include the dorsal rostral and ventral pons; the perigenual ACC (BA 24), mid-ACC (BA 24/31), and right posterior cingulate cortex (PCC, BA 23); the bilateral anterior and posterior insulae; the right posterior temporal lobe; the bilateral orbitofrontal cortex and parahippocampus; and the right cerebellum [30]. Moreover, this study found that decreased GMV in aforementioned regions was positively correlated with increased disease duration [30].

Comparison between ETTH and CTTH

A Taiwan study compared the GMV between “strict-criteria” TTH, migraine, and non-headache control [31]. This study directly analyzed the effect of headache frequency (episodic vs. chronic) on GMV changes. Compared to controls, TTH patients exhibited increased GMV in the ACC, supramarginal gyrus, temporal pole, lateral occipital cortex, and caudate. Regarding differences between episodic and chronic headaches, the chronic group showed a GMV decrease in the bilateral insula and ACC. Notably, this study recruited TTH patients met the “strict criteria,” meaning they did not exhibit any migrainous features such as nausea, vomiting, photophobia, or phonophobia [31]. Therefore, this study may represent a “pure TTH” subgroup, excluding any potential confounding effects from migrainous features. Additionally, it compared neuroimaging differences between pure TTH and migraine, which will be discussed in the following “TTH vs. Migraine” section.

The heterogeneity of recruited TTH patients in these studies hampered the direct comparison between them, but we can still observe some consistency in their findings. First, nearly all studies reported changes in volume or density (increased or decreased) of grey matter in ACC in TTH. Second, the ‘headache frequency effect’ might be attributed to decreased GMV in the insula and ACC. Based on findings in ETTH, the ACC seems to play a pivotal role in the modulation of TTH. The reduced GMV in the ACC and insula observed in CTTH may reflect a common consequence of headache chronification or increased headache frequency.

TTH vs. non-headache control: evidences from functional neuroimaging studies

Compared to migraine, functional neuroimaging research on TTH remains limited. Additionally, these studies face similar challenges as structural imaging

studies, including heterogeneity in headache frequency and the inclusion of both ETTH and CTTH in study participants.

Honningsvag et al. used diffusion tensor imaging (DTI) to compare the difference in axonal diffusivity (AD) between TTH from the HUNT3 study and non-headache controls [32]. When only corrected for age and sex, TTH had higher AD than the headache-free group in several areas of the Tract-Based Spatial Statistics skeleton, most prominent in the corpus callosum, corticospinal tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and left superior longitudinal fasciculus [32]. When corrected with age, sex, Hospital Anxiety and Depression Scale (HADS) score, chronic pain, and consumption of alcohol and over-the-counter painkillers, only the left corticospinal tract and left superior longitudinal fasciculus showed higher AD [32]. If further corrected with WMH, they found no differences between TTH and headache-free groups [32]. However, one limitation of this study is the lack of information on headache frequency, which hindered the possibility of adjusting for headache frequency or analyzing ETTH and CTTH separately. This study also compared the white matter by DTI between TTH and migraine and will be discussed in the following “TTH vs. Migraine” section.

Functional magnetic resonance imaging (fMRI) studies have reported inconsistent findings across different studies. Li et al. observed altered amplitude of low-frequency fluctuations (ALFF) in the slow-5 frequency band (0.01–0.027 Hz) in patients with TTH, with decreased activity in the left ACC, left thalamus, and right middle frontal gyrus, and increased activity in the right superior parietal gyrus and left orbitofrontal cortex [33]. However, a limitation of this study is the lack of information on headache frequency, making it impossible to rule out the potential effect of headache frequency [33]. Among studies reporting headache frequency, Zhang et al. found increased regional homogeneity (ReHo) in the right medial superior frontal gyrus and middle frontal gyrus within the Slow-5 frequency band (0.01–0.027 Hz) in TTH patients with a mean headache frequency 15.4 ± 3.9 days per month [34]. Wang and Wang (2022) conducted a seed-based whole-brain resting-state functional connectivity (rsFC) analysis in TTH patients (mean headache frequency 7.7 ± 10.2 days per month), finding no significant differences in rsFC compared to non-headache controls [35]. Notably, the main purpose of this study was to analyze the differences in rsFC between migraine, TTH, and control [35]. A recent study by Yang et al. analyzed fractional amplitude of low-frequency fluctuations (fALFF) in patients with ETTH (mean headache frequency: 7.9 ± 2.6 days per month) and identified increased fALFF in the right posterior insula and anterior insula. Additionally, they

observed decreased fALFF in the posterior cingulate cortex [36].

Comparative studies in structural neuroimaging

Chen et al. (2018). offered an in-depth analysis of the structural differences between patients with “strict-criteria” TTH (25 ETTH, 24 CTTH), migraine (31 episodic, 25 chronic), and 43 non-headache controls [31]. Their findings revealed an overall increase in total GMV in TTH, whereas migraine was associated with a decrease in total GMV [31]. Regionally, TTH patients exhibited increased GMV in the right caudate, temporal pole, left ACC, supramarginal gyrus, and lateral occipital cortex, while migraine patients showed decreased GMV in the right orbitofrontal cortex [31]. Further comparisons between the two primary headache disorders demonstrated that TTH patients had larger superior and middle frontal gyri, cerebellum, dorsal striatum, and precuneus than those with migraine [31]. Additionally, receiver operating characteristic analysis identified the left superior frontal gyrus and right cerebellum lobule V as the most distinguishing volumetric markers between TTH and migraine [31]. Alterations in the prefrontal cortex may indicate dysfunction in the descending inhibitory pain modulation system and executive function deficits in migraine [37, 38]. The reduced cerebellum GMV might be linked to its role in pain modulation through its connectivity with the prefrontal region [39]. The reduced volume of prefrontal and cerebellum likely reflects the higher pain-related burden in migraine.

Comparative studies in functional neuroimaging

Honningsvag et al. used DTI to compare the difference between TTH from the HUNT3 study and migraine [32]. When adjusted only for age and sex, no significant differences in DTI measures were found between migraine and TTH. The study further adjusted for pain, alcohol consumption, and over-the-counter painkiller use, and even after accounting for WMH, none of the corrected data showed any differences in any DTI indices between migraine and TTH [32]. The comparison of functional neuroimaging between TTH and migraine warrants further investigation to elucidate the similarities and differences in the central mechanisms of the two headache disorders.

Trends in current research and future perspectives

In neuroimaging studies for TTH, the heterogeneity of recruited TTH patients in these studies hampered the direct comparison between them, but we can still observe some consistency in their findings. In structural imaging studies, we have the following observations.

First, nearly all studies found changes in volume or density (increased or decreased) of grey matter in ACC

in TTH. Second, the “headache frequency effect” might be attributed to decreased GMV in the insula and ACC. Based on findings in ETTH, the ACC seems to play a pivotal role in the modulation of TTH. The reduced GMV in the ACC and insula observed in CTTH may reflect a common consequence of headache chronification or increased headache frequency. In functional imaging studies, Wang et al. and Zhang et al. found changes in the superior frontal gyrus and middle frontal gyrus, and both regions belong to the descending pain modulation system, which suggests aberrant local brain activity in the frontal areas may enhance pain perception in TTH patients [33, 34]. The discrepancy between structural and functional neuroimaging findings highlights the need for further research on TTH.

Future neuroimaging studies on TTH should focus on improving standardization to reduce heterogeneity. This includes distinguishing between ETTH and CTTH, clearly reporting headache frequency, and better controlling for analgesic use and comorbid conditions. Standardizing diagnostic criteria (e.g., strict vs. standard ICHD-3 criteria) or separately analyzing subgroups based on clinical symptoms would also enhance study consistency.

Additionally, most current research did not focus on structural or functional changes in brainstem. The use of 7-Tesla MRI to investigate functional changes in the brainstem’s pain-processing pathways may offer deeper insights into its role in TTH. Furthermore, multi-modal approaches, such as integrating pain-threshold assessments with neuroimaging or combining structural and functional imaging, could further elucidate the underlying pathophysiology of TTH.

Closing remarks

Structural and functional MRI studies suggest that the ACC may play a crucial role in the pathophysiology of TTH, and a decreased ACC and insula volume may be associated with higher headache frequency or chronification. Compared to migraine, TTH exhibits less volume reduction in the frontal lobe and cerebellum. Currently, neuroimaging studies on TTH remain scarce, with significant variations in study design and protocols. Future research could focus on standardizing protocols, incorporating novel neuroimaging techniques, and integrating multi-modal approaches to enhance consistency and improve our understanding of the underlying mechanisms of TTH.

Neurophysiological aspects of TTH

The distinctive neurophysiological characteristics of TTH, revealed by electrophysiological studies, are based on the still controversial understanding of the pathophysiology of this primary headache and so require further validation in the future. The primary features to be

examined pertain to the peripheral engagement of myofascial tissues and the modification of central pain control systems, including central sensitization. These characteristics are mostly assessed using reflexological evaluations, algometry, and the recording of cortical evoked responses. The CTTH is the most extensively researched.

Myofascial involvement

The myofascial contribution to the pathogenesis of TTH was first noted through the measurement of electromyographic (EMG) activity and stiffness in the pericranial muscles. EMG and pericranial muscle tension were, on average, elevated in individuals with CTTH compared to healthy individuals. Nevertheless, no correlation was identified between EMG activity, headache presence or severity [40, 41], inflammatory status [25], and intramuscular lactate levels during rest and muscle exertion in individuals with CTTH compared to healthy subjects [42].

Nociceptive reflex responses

The examination of reflex response recordings did not produce compelling results in ETTH. Conversely, certain indirect evidence of sensitization was observed in CTTH, characterized by distinct nociceptive reflexes and evoked potentials.

Monitoring the activity of brainstem interneurons which silence masticatory muscle motor neurons by the observation of two consecutive exteroceptive suppressions (ES1 and ES2), referred to as “silent periods”, during masticatory muscle stimulation revealed no anomalies in patients with ETTH. Some researchers have reported a reduction in the second temporal interval of exteroceptive silent (ES2) in individuals with CTTH [41, 43–46], whereas other investigations have found it to be normal [47–51]. This reduction in ES2 is presumably due to insufficient activation or excessive inhibition of brainstem inhibitory interneurons, the latter regulated by limbic regions such as the periaqueductal grey matter, amygdala, hypothalamus, and orbitofrontal cortex. The discrepancies in the results may be attributed to methodological variations or variances in cohort selection among the studies.

The recording of the blink reflex, mediated by excitatory bulbo-pontine neurons, revealed normal amplitude, area, and latency [47, 52–56], along with a prolonged recovery cycle [47] of the R2 component in CTTH. Two distinct groups observed diminished latencies of the trigeminocervical reflex in individuals with CTTH [57, 58]. Employing a nociceptive-specific electrode, diminished values of the normalized mean square and area under the blink curve were observed in CTTH patients compared to control subjects [59].

Additional compelling evidence of central sensitization in CTTH is derived from investigations of pain sensitivity in pericranial or lower limb tissues. The flexion reflex elicited in the biceps femoris muscle following electrical stimulation of the sural nerve is a nociceptive response mediated by the spinal cord. The subjective pain thresholds and RIII reflex thresholds of the nociceptive flexion reflex RIII of the lower limb were found to be markedly reduced in individuals with CTTH compared to control subjects [60]. These findings were linked to a counterintuitive enhancement of the RIII reflex response during the cold pressor test, suggesting impaired descending inhibition, a deficiency also identified by other authors [61]. Prior research has identified normal pain pressure thresholds (PPTs) in ETTH [62, 63]. In CTTH, PPTs were observed to be diminished, particularly in the anterior region of the temporalis muscle and the superior region of the trapezius muscle. Cathcart et al. investigated temporal summation, characterized as the heightened perception of pain due to repeated noxious stimuli (an indirect measure of sensitization), utilizing an algometer and heterotopic noxious conditioning stimulation (HNCS) in patients with CTTH relative to controls [64]. Pain induced by repeated algometric pressure increased more in TTH participants compared to healthy controls, both in the fingers and shoulder, and was less mitigated by HNCS [64]. CTTH sufferers exhibited reduced pain thresholds in the cephalic area's muscles and skin, but not in the extracephalic region, alongside elevated ratings after single repetitive supra-threshold electrical stimulation (2 Hz) compared to healthy controls [65].

Cortical evoked responses

The limited investigations examining the dynamics of central activity by recording cortical evoked potentials did not yield definitive evidence of sensitization, namely an augmentation in response amplitude. This applied to ETTH about visual evoked responses [66], laser-evoked potentials (LEP) [67], event-related auditory P300 [68], and CTTH concerning visual P300 [69] and LEP [70]. In a LEP investigation, the heat pain threshold was comparable between CTTH patients and controls at both the hand and pericranial skin levels. Total tenderness scores (TTS) at pericranial locations were elevated in TTH patients compared to controls. The amplitude of the N2a-P2 LEP complex induced by pericranial stimulation was higher in TTH patients compared to controls, and this difference was substantially correlated with the TTS [71]. Notably, Chen et al. [8] enrolled patients who met "strict-criteria" for TTH, including the absence of any migraine-associated symptoms and the presence of three out of four TTH characteristics (bilateral, nonpulsatile, mild or moderate intensity, and not aggravated by physical activities). They studied brain excitability using a paired-pulse

electrical stimulation paradigm. The findings showed that the first response amplitude was increased in CTTH, and the gating ratio was increased in both ETTH and CTTH, as well as chronic migraine. Furthermore, headache frequency correlated with the strength of the first primary somatosensory response in all TTH patients.

Closing remarks

Electrophysiological investigations applied to patients with TTH have documented a substantial normality of responses in the episodic form. In contrast, chronic patients showed an electrophysiological pattern of increased peripheral muscle activity, increased excitability of the brainstem inhibitory circuits, a lowering of the sensitization threshold at the spinal level, but normal cortical evoked responses. All this evidence favors a sensitization confined to the brainstem level rather than the cortical level.

Mechanisms and pathophysiology (Fig. 2)

Genetic basis

The genetic influence in TTH pathogenesis has been recognized, mainly based on the findings from twin studies [22, 72, 73]. The heritability of TTH, nevertheless, varies with the presence of coexisting migraine. The heritability of TTH is higher in individuals without migraine (estimated at 48% in males and 44% in females) [72], as compared to individuals comorbid with both migraine and TTH (estimated at 19%) [22]. The headache frequency of TTH also matters. A more substantial genetic influence was shown in patients with higher headache frequency. The differences of concordance rates between monozygotic and same-gender dizygotic twin pairs were small in infrequent ETTH, while the differences were more substantial in patients with frequent ETTH (11–14% vs. 4–5%) [73]. For CTTH, heritability estimates from twin studies remain inconclusive due to small sample sizes [73]. However, a family aggregation study reported a threefold increased risk of CTTH in first-degree relatives, supporting a stronger genetic predisposition in chronic cases [74].

Several candidate genes have been proposed to be causative of TTH. Polymorphisms in monoaminergic neurotransmission-related genes, particularly the 5-HTT-gene-linked polymorphic region (5-HTTLPR) genotype [75] and the Val158Met *COMT* (encoding catechol-O-methyltransferase) polymorphism [76, 77], have been associated with CTTH risk and its clinical phenotype. These genes are involved in pain modulation and affective processing, suggesting that altered monoaminergic neurotransmission may contribute to TTH pathophysiology. In contrast, the APOE- ϵ 4 allele has been proposed as a protective factor against TTH [78].

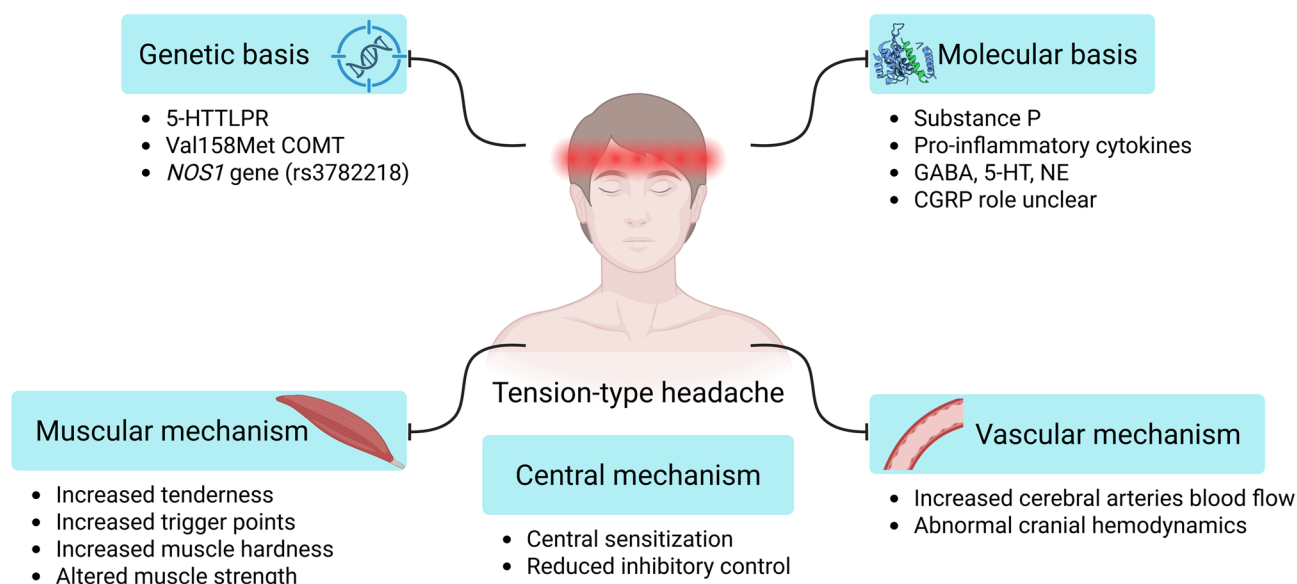


Fig. 2 Pathophysiology of tension-type headache. The pathophysiology of tension-type headache involves genetic, molecular, muscular, vascular, and central factors. Key factors include genetic polymorphisms, neuroinflammatory mediators, muscular abnormalities, altered central pain modulation, and changes in cerebral hemodynamics. Created in BioRender. Wang, S. (2025) <https://BioRender.com/fs561jc>. 5-HT: 5-hydroxytryptamine; CGRP: calcitonin gene-related peptide; NE: norepinephrine

Recent candidate gene studies continue to explore the genetic underpinnings of TTH. Yet, no genome-wide association studies (GWAS) have been conducted specifically for TTH so far. No definitive causative genes have been identified. A study investigating the *NOS1* gene (rs3782218) found that the minor allele T was significantly associated with a higher risk of developing TTH and arterial hypertension (AH) overlap syndrome, emphasizing a potential role for nitric oxide dysregulation in TTH pathophysiology [79]. Notably, GWAS focusing on the phenotype of “broadly defined headache” or “self-reported headache” from large-scale databases have identified several genomic loci [80–82]. Among these cases, TTH may account for the most common diagnosis, potentially offering insights into the genetic background of TTH.

While these studies highlight a genetic component in TTH, the high prevalence of TTH presents a challenge for genetic epidemiological research, making it difficult to distinguish genetic factors from environmental influences [23]. Some studies suggest a potential genetic overlap between TTH and migraine, with twin data indicating shared genetic factors between the two disorders [83]. Corroborated with this, many genomic loci identified from GWASs of broadly-defined headache or self-reported headache have been reported to be associated with migraine. However, specific genes contributing to TTH remain primarily unidentified, and further research is needed to clarify the genetic architecture underlying this common headache disorder.

Closing remarks

Overall, genetic influences on TTH appear to be more pronounced in cases without comorbid migraine, as well as CTTH and frequent ETTH. Current evidence suggests that the transition from ETTH to CTTH results from a cumulative interplay between genetic and environmental factors. Future research employing large-scale GWAS, twin studies, and functional genetics will be crucial in further elucidating the genetic mechanisms underlying TTH and identifying potential therapeutic targets.

Molecular basis

The molecular basis of TTH pathophysiology is characterized by a complex interplay of neurobiological processes, particularly in the realms of myofascial pain mechanisms, neuroinflammation, and neurotransmitter dysregulation. Understanding these molecular interactions provides important insights into how peripheral and central pathways contribute to the development and chronicity of TTH.

From a peripheral perspective, myofascial structures prominently contribute to the pain experienced in TTH. The activation of muscle trigger points leads to the release of several nociceptive mediators, including substance P, calcitonin gene-related peptide (CGRP), and pro-inflammatory cytokines [84]. These mediators are released from sensory nerve endings in the muscles and may induce local neurogenic inflammation, further exacerbating pain. Importantly, studies suggest that this local inflammation is characterized by the increased expression of pro-inflammatory cytokines, such as interleukin-1

beta (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α), which sensitize peripheral nociceptors and enhance pain perception [85, 86].

The central nervous system (CNS) is equally implicated in the pathophysiology of TTH through mechanisms of central sensitization. This phenomenon is often initiated by prolonged nociceptive input from peripheral structures. It is characterized by the hyperexcitability of neurons in the spinal cord and brainstem, particularly within pain pathways such as the trigeminal and cervical spinal systems [87]. Central sensitization can result in alterations in neurotransmitter release profiles, particularly with regard to glutamate and gamma-aminobutyric acid (GABA). An upregulation of excitatory neurotransmission due to increased glutamate activity has been noted, which may promote heightened sensitivity to stimuli and contribute to pain [26]. Conversely, a reduction in GABAergic signaling, which serves to inhibit neuronal excitability, may exacerbate this imbalance, fostering an environment conducive to pain perception [88].

Neurotransmitter dysregulation is further evidenced by the roles of 5-hydroxytryptamine (5-HT) and norepinephrine (NE) in TTH. Research has indicated that alterations in levels of 5-HT can influence the modulation of pain. Reduced serotonergic activity may contribute to increased pain sensitivity and the precipitation of headache episodes [89]. Furthermore, the locus coeruleus-norepinephrine system is implicated in the response to stress, which frequently correlates with TTH frequency and severity. Dysregulation of norepinephrine may not only enhance pain perception but also affect the neuroplasticity of pain pathways [90].

Additionally, the genetic and environmental factors associated with TTH may contribute to an individual's pain susceptibility through molecular mechanisms. Polymorphisms in genes encoding for receptors such as the 5-hydroxytryptamine receptor 2 A (5-HT_{2A}) have been investigated for their potential role in TTH susceptibility, suggesting a genetic basis that could predispose individuals to the disorder [91]. Environmental triggers, particularly chronic stress, can exacerbate these molecular pathways, signaling through pathways such as the hypothalamic-pituitary-adrenal (HPA) axis which can heighten inflammatory responses and influence neurotransmitter levels in a manner that predisposes individuals to TTH [92].

Lastly, the role of neuroinflammation in exacerbating TTH has become a focal point of recent research. Elevated levels of inflammatory markers in the cerebrospinal fluid of patients with CTTH indicate a possible pathophysiological link between systemic inflammation and central pain mechanisms. This suggests that neuroinflammatory processes may influence the neurotransmitter

dynamics and pain signaling pathways that underpin the headache disorder [93].

Closing remarks

In summary, the molecular basis of TTH encompasses a multitude of pathways and interactions, including myofascial nociceptive processes, central sensitization and neurotransmitter dysregulation, as well as genetic predispositions and neuroinflammatory mechanisms. Collectively, these factors contribute to a complex biological network that shapes the clinical manifestations of TTH, necessitating comprehensive strategies for management and treatment.

Central mechanisms

While peripheral mechanisms are pivotal in the generation of pain in TTH, central mechanisms are critical to its chronification [26, 94, 95]. In TTH, central mechanisms encompass both central sensitization and dysfunction in descending pain modulation [26]. Altered nociceptive input from myofascial structures leads to sensitization of central nociceptive pathways, including the dorsal horn, spinal trigeminal nucleus, and thalamus, amplifying pain perception [26]. At the same time, impairments in descending pain modulatory systems further exacerbate this sensitization by diminishing inhibitory control and facilitating pain persistence [26].

Central sensitization, defined as heightened responsiveness of central neurons to nociceptive stimuli, is a hallmark of CTTH and, to a lesser extent, frequent ETTH [19]. An association between central sensitization and attack frequency has been observed [96], with patients experiencing CTTH showing decreased pain detection thresholds, widespread hyperalgesia, and allodynia [65, 97, 98]. These features extend beyond the pericranial region to extracephalic areas, reflecting a dysregulated central pain processing system that distinguishes CTTH from its infrequent episodic counterpart [99]. The proposed cascade leading to central sensitization in CTTH begins with the sensitization of peripheral nociceptors due to abnormal input from myofascial structures. This process progresses to involve second-order neurons in the spinal trigeminal nucleus and dorsal horn, and third-order neurons in the thalamus [26].

Central sensitization in TTH involves synaptic and postsynaptic mechanisms that enhance pain perception and contribute to chronification. At the synaptic level, repeated nociceptive input strengthens connections between nociceptive afferents and second-order neurons, increasing dorsal horn sensitivity and lowering pain thresholds, a process known as homosynaptic facilitation [100]. Additionally, heterosynaptic facilitation enhances the recruitment of normally non-nociceptive mechanoreceptors into pain pathways [100]. At

the postsynaptic level, prolonged nociceptive signaling activates N-methyl-D-aspartate receptor and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, triggering intracellular cascades that enhance receptor sensitivity, promote synaptic plasticity, and facilitate central pain propagation, further exacerbating hyperalgesia and allodynia [100].

Consistent with the prolonged changes induced by central sensitization, neuroimaging studies have revealed alterations in cortical and subcortical regions involved in pain perception, such as the insula, anterior cingulate cortex, and somatosensory cortex, particularly during ictal phases of TTH [20, 29]. Structural imaging studies have identified decreased volume in limbic system regions associated with pain processing, including the insula and anterior cingulate cortex [30, 31]. These changes are more pronounced in CTTH and associated with longer disease duration, suggesting that persistent nociceptive input drives long-lasting central changes [20]. Such alterations likely represent the brain's adaptation to chronic pain and are central to the cognitive and affective modulation of pain in TTH.

Nitric oxide (NO) plays a significant role in central sensitization and nociceptive processing in TTH [101]. Elevated nitric oxide synthase (NOS) activity in CTTH suggests upregulation of NO pathways at the levels of the spinal dorsal horn, trigeminal nucleus, and supraspinal structures [102]. Provocation studies using glyceryl trinitrate (GTN), a NO donor, have demonstrated delayed-onset headaches resembling TTH attacks in CTTH patients [103]. These findings highlight the importance of NO-mediated mechanisms in central sensitization and suggest a shared pathophysiological mechanism with chronic migraine, raising the question of whether the two conditions might converge into a single chronic entity [104].

Descending pain modulatory pathways, including diffuse noxious inhibitory controls (DNICs), are essential for maintaining the balance between nociceptive input and central processing [105]. In TTH, DNICs are impaired, resulting in reduced inhibitory control and heightened pain facilitation [60, 64]. Neurophysiological studies have shown diminished inhibitory responses in CTTH patients compared to controls, which may amplify nociceptive inputs from peripheral sources and exacerbate central sensitization, thus facilitating chronic headache [21]. Key structures in descending pain modulation include the periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM) [106]. These regions interact with supraspinal areas such as the anterior cingulate cortex, insula, and thalamus to modulate the sensory and affective dimensions of pain. Dysfunction in these networks disrupts inhibitory pathways, contributing to the persistence of TTH. Additionally, disruption of

serotonergic systems, integral to descending pain modulation, has been described in CTTH patients [107].

Comorbidities and psychosomatic factors, including stress, depression, and anxiety, significantly influence central mechanisms in TTH [108]. Stress is a recognized trigger for TTH and may exacerbate central sensitization through increased sympathetic activity and cortisol release [109]. Depression and anxiety, common in patients with TTH, are associated with reduced pain thresholds and amplified central sensitization [108]. Sleep disturbances, such as insomnia, poor sleep quality, and sleep apnea, are frequently reported in patients with TTH and share common pathophysiological pathways with central pain processing [110]. Dysregulated neurotransmitter systems, particularly those involving serotonin and noradrenaline, may link sleep disorders with increased pain perception in TTH [111].

Closing remarks

Central mechanisms are integral to the pathophysiology of TTH, particularly its chronic form. Central sensitization and impaired descending pain modulation underpin the transition from ETTH to CTTH. A deeper understanding of these processes is essential for developing targeted therapeutic approaches aimed at mitigating the chronicity and impact of TTH, ultimately improving patient outcomes.

Peripheral mechanisms

Peripheral mechanisms have long been considered a key factor in the pathophysiology of TTH. This is reflected in the first classification of headache disorders, where “muscle contraction headache” was designated as a separate entity [112]. This section reviews the evidence supporting the role of peripheral structures and mechanisms in TTH, providing a balanced analysis of the available data and highlighting existing research gaps.

Pericranial muscle tenderness is a common finding in patients with TTH [62, 63]. However, it is neither a highly sensitive nor specific marker, as not all patients exhibit it, and it has also been observed in individuals with migraine or healthy controls [113]. Increased muscle tenderness appears to be more strongly associated with CTTH than with ETTH [65, 114, 115]. It has been linked to more frequent and severe TTH episodes [116, 117].

However, the relationship between muscle tenderness and headache severity is not straightforward. Some patients with significant muscle tenderness experience only mild headaches, while others with minimal tenderness report severe headaches [65, 114, 115]. A longitudinal study that followed 549 out of 740 patients for twelve years found that pressure pain thresholds decreased only in those who eventually developed CTTH. Notably, there

were no baseline differences in pressure pain thresholds between those who later developed headaches and those who remained headache-free. This finding suggests that the observed changes in pain sensitivity may be a consequence of CTTH development rather than a predisposing factor [118].

Pericranial muscle tenderness can be assessed through manual palpation [119] or experimentally. Studies using pressure pain thresholds and quantitative sensory testing have shown that patients with TTH exhibit lower pain thresholds compared to healthy controls [120]. Additionally, patients with TTH demonstrate altered pain hypersensitivity in both cephalic and extracephalic regions, particularly in the temporalis and trapezius muscles [120–122].

One specific cause of pericranial muscle tenderness is the presence of myofascial trigger points—circumscribed, palpable nodules or taut bands [123]. These can be subclassified as **active**, when they cause persistent localized pain, or **latent**, when pain is only elicited upon palpation [124].

Myofascial trigger points can be evaluated during a craniofacial examination and are commonly found in the temporalis, masseter, semispinalis capitis, scalene, and trapezius muscles. These trigger points are not only relevant to symptom generation but also carry significant weight in the clinical assessment and classification of TTH, especially in distinguishing subtypes with pericranial muscle involvement [125]. In research settings, they can also be assessed using various diagnostic techniques, including electromyography [126, 127], ultrasound [128], magnetic resonance imaging [129], microdialysis [130], sonoelastography [131], and infrared thermography [132]. However, neither complementary imaging studies nor histological examinations have consistently identified structural abnormalities in all patients. This inconsistency could be attributed to technical limitations, a transient nature of the changes, or variations in underlying pathophysiological mechanisms, which remain to be fully understood.

Another feature linked to TTH is muscle hardness or tightness. Patients with TTH exhibited higher muscle hardness values in the cranial and cervical regions, with no significant differences between ETTH and CTTH [133]. Muscle hardness correlated with muscle tenderness, and abnormal values were observed not only during TTH episodes but also interictally [40].

The role of peripheral factors has also been explored in relation to muscle strength. Studies have found weaker muscle strength in the neck extensor muscles of patients with high-frequency TTH compared to controls, along with a reduced cervical extension/flexion ratio ([134]. Reduced strength in the neck and shoulder muscles has also been observed in children with TTH [135].

When comparing TTH patients with healthy controls, no statistically significant differences in neck extensor muscle strength were found, except in patients with a higher frequency of episodes, greater headache intensity, and those reporting neck pain [136]. Additionally, some researchers have suggested that the co-activation of the sternocleidomastoid and splenius capitis muscles may be associated with the pathophysiology of CTTH [137].

Neck pain is prevalent in the general population, with an estimated one-year prevalence of 68%, and is more common in individuals with primary headache disorders (86%) compared to those without primary headaches (57%) [138]. Cervical muscles are innervated by the first cervical nerves, which are connected to the trigeminal nucleus caudalis [139]. This anatomical connection and shared neural pathways may help explain the association between neck pain and headache, as well as the potential link between cervical musculoskeletal disorders and TTH.

Hyperalgesia and allodynia have been evaluated in patients with TTH, comparing tender and non-tender muscles. TTH patients showed response to non-painful stimuli, suggesting that myofascial pain may be driven by low-threshold mechanosensitive afferents, which project to sensitized dorsal horn neurons [115].

Provocation studies are not limited to migraine or cluster headache. In 1996, a study attempted to induce headache in TTH patients and age- and sex-matched controls by sustained tooth clenching. The study found that headaches occurred more frequently in TTH patients (69% vs. 17%) and were associated with the presence of pericranial muscle tenderness, as well as an increase in the mechanical pain threshold [140]. In another study involving 60 healthy participants, headache occurred less frequently in individuals who showed a decrease in pericranial tenderness after the tooth-clenching task [141]. The reason why not all TTH patients experience headaches after these provocation studies remains unclear, suggesting a pathophysiology more complex than a purely muscular origin.

From a pathophysiological perspective, peripheral sensitization of the myofascial sensory afferents and muscle nociceptors likely contributes to the development of muscular hypersensitivity and pericranial muscle pain during TTH. Studies have demonstrated that, in healthy individuals, infusing hypertonic saline into pericranial muscles can induce head pain [142]. Furthermore, infusing a combination of bradykinin, histamine, serotonin and prostaglandin into the trapezius muscle could induce worsening pain in patients with TTH [143]. Additionally, local ischemia in muscles could activate nociceptors [42]. Muscle hyperfunction and contraction may lead to increased metabolism and the accumulation of waste products [25, 144]. The persistent activation of nerve

endings around myofascial trigger points and pericranial muscles could alter the pain thresholds of A-delta and C fibers [145]. Furthermore, repetitive activation of myofascial trigger points could contribute to central sensitization, especially in individuals with CTTH. Lower pressure pain threshold in multiple body areas, including widespread pressure pain sensitivity [99], and increased sensitivity of the cranial nerves, such as the supraorbital nerves, have been observed in patients with CTTH [146].

Various animal models have been developed to study TTH. The primary focus has been to investigate the impact of nociceptive afferent input from neck muscles on pain processing within the central nervous system [147]. For example, injecting adenosine 5'-triphosphate (ATP) into the temporal muscle of mice increased the spinal trigeminal neuron afferent input activity from the temporal muscle and dural mater [148], suggesting the interplay between peripheral myofascial activation and central sensitization. Future studies should also investigate the effect of psychological factors, including anxiety and depression, other mechanical factors, such as temporomandibular joint dysfunction, neck and shoulder pain, and other comorbidities, such as fibromyalgia on the development and progression of TTH.

A common argument against the peripheral origin of TTH is the limited efficacy of occipital nerve blockade [149] or botulinum toxin in its preventive treatment. However, a recent meta-analysis of 390 CTTH patients and 297 placebo controls found improvements in headache frequency, intensity, duration, and acute treatment usage after botulinum toxin [150]. Furthermore, therapies that primarily target the periphery, such as manual therapy [151, 152], dry needling [153] and acupuncture [154] have shown varying degrees of improvement in TTH patients.

Closing remarks

Peripheral mechanisms, including pericranial muscle tenderness, trigger points, muscle hardness, and altered muscle strength, have been proposed to contribute to TTH pathophysiology. Among these, the distinction between TTH with and without pericranial muscle tenderness, as included in the ICHD, reflects a relevant clinical observation. From a clinical perspective, TTH with or without pericranial muscle tenderness may assist in non-pharmacological interventions, particularly physical therapy and other muscle-targeted interventions. However, inconsistencies exist, and the causality remained to be elucidated. The utility of classifying TTH based on pericranial tenderness in clinical research is still under debate due to variability in assessment methods and the lack of consistent correlation with headache frequency or disability. While some studies suggest pericranial tenderness may reflect underlying sensitization, this

classification has not been widely adopted. Future studies should aim to standardize assessment methods, investigate the interplay between peripheral and central mechanisms, and improve the clinical and research utility of TTH subtypes.

Vascular factors

In contrast to theories on migraine and cluster headache pathophysiology, in which (neuro)vascular mechanisms have played a prominent role [155], their influence in TTH is less convincing, and therefore, remains a topic of ongoing debate. This section summarizes the key literature on (i) blood flow velocity and (ii) cranial hemodynamics, including the role of the neuropeptide CGRP, in relation to TTH.

Blood flow velocity

Findings on the relationship between blood flow velocity and TTH are inconsistent. Wallasch et al. investigated vascular features in patients with CTTH using transcranial Doppler ultrasound (TCD) [156]. The study compared blood flow velocities between the basal cerebral arteries and submandibular extracranial segment of the internal carotid artery in 20 CTTH patients and 20 age- and sex-matched controls. No significant differences in ultrasonic features were observed between both groups. Furthermore, a study by Karacay Ozkalayci et al. examined blood flow velocities in the anterior and posterior circulation arteries using TCD [157]. This study included 25 control subjects, 40 migraine patients, and 10 CTTH patients, all in attack-free periods and not using prophylactics for either migraine or TTH. The results did show a significant increase in basilar artery cerebral blood flow velocities in TTH patients compared to controls. In contrast, no differences were found in the other arteries (i.e., anterior cerebral artery, middle cerebral artery, posterior cerebral artery, and vertebral artery). The exact mechanism underlying this increase remains unclear but may be related to the constriction of conductance vessels or dilation of resistance vessels [157]. In another study, Khedr et al. used TCD and measured cerebrovascular reactivity in response to 14 Hz photic stimulation for 100 s in 37 migraine patients, 24 CTTH patients, and 50 age- and sex-matched healthy controls [158]. Compared with controls, higher cerebrovascular reactivity was observed in different vascular areas in migraine patients and TTH; middle cerebral artery in migraine patients, and the vertebral artery in TTH patients. Sliwka et al. used TCD and measured spontaneous oscillation in middle cerebral artery in 30 patients with migraine, 28 patients with CTTH and 30 controls. Patients with CTTH had lower values for Mayer wave activity, a sign of an impairment of sympathetic activity, in comparison with normal controls [159].

Cranial hemodynamics and calcitonin gene-related peptide

Comparable to how human provocation models have advanced our understanding of signaling pathways in migraine [160], similar approaches have been applied in TTH and helped to uncover the role of vascular mechanisms in patients with TTH.

A provocation study by Hannerz et al., using sublingual nitroglycerin besides head down tilt, indicated an association between pain intensity in patients with CTTH and cranial hemodynamics [161]. A placebo-controlled study showed that infusion of GTN, a NO donor, induces CTTH patients [103]. While some showed that GTN treatment increases the production of CGRP in the trigeminal ganglion in rodents [162], others showed no induction of headache via immediate release of CGRP in healthy participants [163], nor in patients with CTTH [164].

CGRP is a vasodilatory neuropeptide that is known to play an essential causal role in migraine physiology—being a target of the novel monoclonal antibodies and gepants [165–167]. CGRP causes relaxation of cardiovascular smooth muscle cells of all arteries studied so far, and is a rescue molecule in cerebral and cardiac ischemia, including stroke [168, 169]. While migraine— rather than TTH—is an important risk factor for stroke [170], TTH is a common type of headache seen after stroke. It has been reported that headache occurs in approximately one-quarter of patients with ischemic stroke [171].

The direct role of CGRP has been studied in only a few studies including TTH patients. One of the earliest studies on this topic was performed by Bach et al., who showed normal CGRP levels in lumbar cerebrospinal fluid obtained from 41 patients with CTTH and 7 healthy controls, unaffected by an 8-week treatment period with the atypical antipsychotic sulpiride or selective serotonin reuptake inhibitor (SSRI) paroxetine [172]. Gupta et al. investigated plasma levels of CGRP in migraine and TTH patients during the interictal period, comparing them to a control group [173]. Results indicated no significant differences in CGRP levels between the three groups, with a minimal effect of age. In addition, plasma CGRP concentration did not differ between ETTH and CTTH patients. The absence of differences was confirmed in another study, including 30 CTTH patients and 34 age- and sex-matched healthy controls [174]. CGRP levels in the peripheral and cranial circulation (the latter, by collecting blood from the external jugular vein) were compared. The study showed that CGRP levels in the peripheral circulation were slightly higher— yet non-significant— in TTH patients than in controls on days without headache. Further, no significant differences were observed in CGRP levels measured in the cranial circulation. In both, the peripheral and cranial circulation, no significant differences in CGRP levels were observed based on

the presence or absence of headache. However, a subgroup of TTH patients with usual throbbing headaches—as typically seen in migraine— had significantly higher CGRP levels than controls, both in the ictal and interictal phase. The findings indicate that while CGRP may not play a major role in CTTH overall, headaches with pulsating pain quality could share biological similarities with migraine.

Closing remarks

Unlike migraine, the role of vascular dysfunction and CGRP in TTH remains unclear. Studies on cranial hemodynamics have yielded inconsistent results. In addition, CGRP levels in TTH patients generally do not differ from controls, except in those with migrainous characteristics. These findings suggest that TTH lacks a strong vascular or CGRP-driven mechanism.

Comorbidities of TTH

Several comorbid conditions have been identified to be associated with TTH. (Fig. 3) However, few studies have focused specifically on the comorbidities of TTH and our knowledge is based also on the data from studies investigating various type of primary headaches.

The frequency of back pain was increased (2.3 fold) in patients with pure TTH and much more (3.1 fold) increased in those with both TTH and migraine. This was also found to be related to the impact of TTH on daily activities [175]. A German population-based study showed that CTTH was associated with the number of days with back pain [176]. Furthermore, a strong association has been shown between neck pain and TTH. Neck pain was reported by the 90% of the patients with TTH in Danish population, with a four-fold high risk in the coexistence of TTH. Its frequency was increased in association with the number of days with TTH [138]. Although the underlying mechanisms are not well known, central sensitization of common nociceptive pathways is suggested to underlie the comorbidity of these pain conditions [176]. Pain pressure thresholds were found to be lower in patients with comorbid neck pain and TTH in comparison to those pure TTH, supporting this theory [177].

Temporomandibular disorders (TMD) are also associated with TTH. A recent systematic review concluded that TTH was the second most common primary headache coexisting with TMD [178]. The risk of ETTH, although lower than that seen in migraine, was 1.9- and 4.4-fold increase in patients with myofascial TMD and articular TMD, respectively [179]. This relationship was higher in patients with TTH combined with migraine [180]. Moreover, frequent ETTH and comorbid TMD have been reported to be associated with awake bruxism and anxiety but not with sleep bruxism [181]. It has also

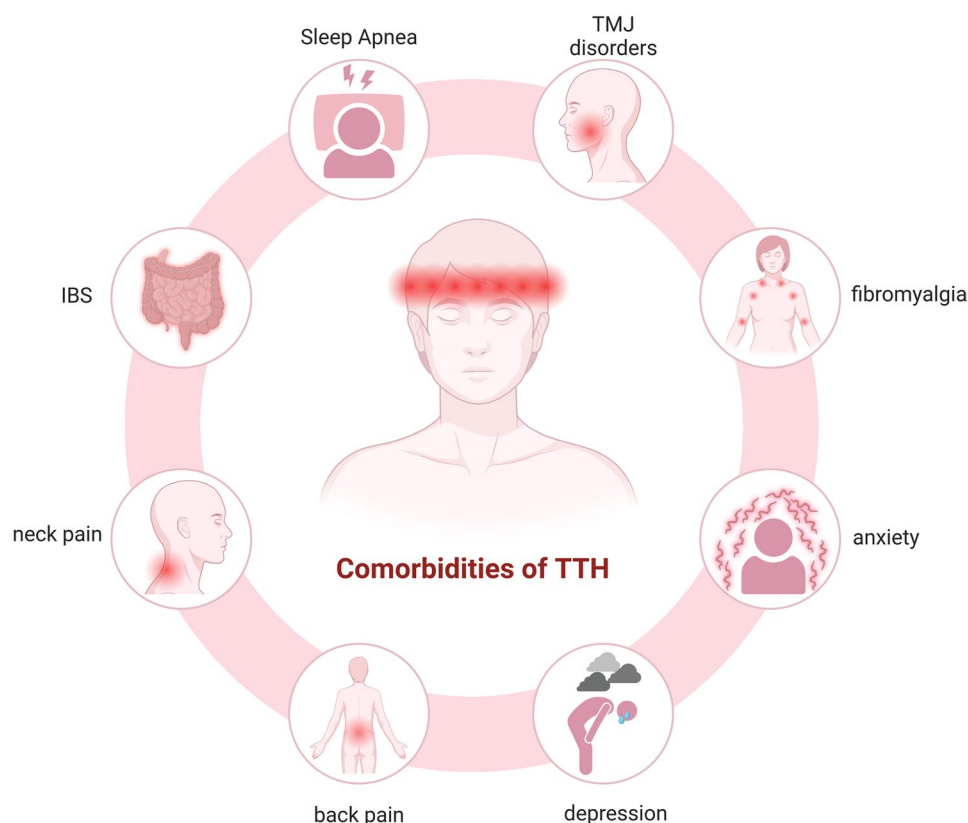


Fig. 3 Common comorbidities of tension-type headache. Tension-type headache commonly co-occurs with musculoskeletal, gastrointestinal, and psychological disorders. Created in BioRender. Wang, S. (2025) <https://BioRender.com/0lbeodj> IBS: irritable bowel syndrome; TMJ: temporomandibular joint; TTH: tension-type headache

been hypothesized that TMD causes alterations to nociceptive pathways within the brain, playing a predisposing role, in patients with ETTH. Another possible mechanism is the role of central sensitization which occurs in the context of primary headaches and may result in the development of pain in peripheral structures, such as the temporomandibular joint [178].

Fibromyalgia, characterized by diffuse musculoskeletal pain, is also reported to co-exist with TTH in several studies. This complex pain condition is present in 35–39% of the patients with TTH [182], with a higher prevalence than in the general population [183]. On the other hand, TTH is experienced by 38–70% of the patients with fibromyalgia according to several reports [184, 185]. Moreover, the association between TTH and fibromyalgia is more robust in patients with CTTH in comparison to those with ETTH [186]. The common pathophysiology underlying the comorbidity of the two conditions is thought to be central sensitization, as the coexistence of fibromyalgia is associated with chronification of TTH [187]. Combined fibromyalgia and CTTH showed also frequent association with neck and back pain [188].

TTH was also reported among the most common five comorbidities seen in patients with inflammatory bowel syndrome [189], showing association with the worsening of this gastrointestinal (GI) system disorder. Because the TTH attacks can be precipitated by the episodes of visceral pain [190]. This is hypothetically explained by a possible effect of increased nociceptive inputs from the GI system on the excitability of the central nervous system [189].

Few studies investigated comorbidity of TTH and hypothyroidism, and lower levels of thyroid hormones characterized by hypoactivity of hypothalamus-pituitary-thyroid axis has been reported in patients with CTTH [191]. A bidirectional relationship between TTH and arterial hypertension is also supported by several studies, although the pathophysiological link is poorly understood. It has been hypothesized that nitric oxide-related shared mechanisms may have a role in the development of both conditions [192].

The risk of having Parkinson's disease was found to be higher in patients with TTH in comparison to those without TTH [193]. However, this link is not well-demonstrated in the other studies [194]. Studies have also reported an increased risk of dementia in patients with

TTH, associated with old age and the presence of other comorbid diseases [195, 196].

TTH constitutes also the most common headache disorder comorbid with sleep disturbances such as insomnia, obstructive sleep apnea (OSA) and poor sleep quality reflected by excessive day time sleepiness [197, 198]. These conditions are associated with an increased risk of developing TTH or its exacerbation. The bidirectional relationship between insomnia and TTH is a well-known entity, however, data concerning the co-existence of TTH and OSA remains controversial [197]. The risk of developing restless syndrome was reported to be higher in patients with TTH in comparison to those without TTH [199]. Co-existing psychiatric diseases has also an impact on these associations.

A significant body of research supports the strong association between TTH and psychiatric comorbidities, particularly generalized anxiety disorder (GAD) and major depressive disorder (MDD). A cross-sectional study in rural India found that 70.6% of TTH patients had comorbid GAD, while 54.1% were diagnosed with MDD [200]. Similarly, psychopathological symptoms, especially internalizing disorders, were significantly more prevalent among TTH patients than controls [201]. Juang et al. [202] reported that 64% of CTTH patients had psychiatric diagnoses, with major depression (51%) and panic disorder (22%) being the most common. Additionally, a multicenter study in Italy study found CTTH was associated with higher scores for depression, state and trait anxiety, and negative state affect and further emphasized this link, revealing that 84.8% of TTH patients had at least one psychosocial stressor or psychiatric disorder, with GAD and dysthymia being the most prevalent [203].

Depression appears to be the most frequently observed psychiatric disorder among headache patients. A comparative study found that individuals with TTH experienced significant impairments in quality of life and functional ability, often due to untreated psychiatric conditions [204]. Notably, personality traits and maladaptive coping mechanisms also play a crucial role in CTTH. Patients with TTH scored higher on neuroticism and automatic thoughts while displaying lower assertiveness, indicating difficulties in emotional expression and regulation [108, 205]. Similarly, Heckman et al., highlighted the role of personality factors in the persistence of CTTH [206].

Young's concept of Early Maladaptive Schemas (EMS) provides further insight into the psychological underpinning of TTH. Dysfunctional cognitive patterns shaped by adverse experiences may contribute to both development and persistence of these headaches. Recent studies suggest that EMS influencing perception, emotions, and behaviors, potentially exacerbating various psychological disorders, such as depression, anxiety, and somatization.

Notably, patients with TTH, exhibit higher scores in emotional deprivation and vulnerability to harm, underscoring the need for targeted psychotherapeutic interventions [207].

Psychiatric comorbidities are also prevalent among children and adolescents with primary headaches. Anttila et al. [208] and Margari et al. [209] found that pediatric headache sufferers exhibit a significant burden of emotional and behavioral disturbances, including anxiety, mood disorders, and somatic complaints. Additionally, both Internalizing and externalizing problems were significantly represented among children with headaches compared to the controls [209]. These findings reinforce the necessity of early psychological screening and intervention to mitigate the long-term impact of psychiatric symptoms in young patients.

Closing remarks

TTH is highly comorbid with musculoskeletal pain, psychiatric disorders, sleep disturbances, and systemic diseases, likely linked through central sensitization mechanisms. Conditions such as fibromyalgia, TMD, and anxiety exacerbate headache burden, impacting severity and treatment response. Despite growing evidence, many underlying mechanisms remain unclear, particularly in hypertension, Parkinson's disease, and dementia. Multidisciplinary approaches integrating neurology, psychiatry, pain management among others is essential.

Management (Fig. 4)

Non-pharmacological treatments

Neuromodulation

Among TTH patients, especially CTTH patients, who do not respond adequately to conventional pharmacotherapy, neuromodulation holds potential as a non-pharmacological treatment option [210]. Neuromodulation refers to the therapeutic modulation of neuronal function or networks through electrical, magnetic, or other forms of physical stimulation to alleviate symptoms. The proposed mechanism of pain relief involves regulating or inhibiting pain signaling pathways via cortical excitability modulation and alterations in neuroplasticity [210, 211].

In migraine and cluster headache, a few noninvasive neuromodulation techniques, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and peripheral nerve stimulation (PNS), have shown efficacy in reducing pain frequency and severity or mitigating acute attacks [212, 213]. However, neuromodulation research on TTH is comparatively scarce. Several neuromodulation devices (e.g., TMS or vagus nerve stimulator) have gained Food and Drug Administration (FDA) clearance or approval, yet their indications are specifically for migraine or cluster headache, not TTH. Nevertheless, considering the shared

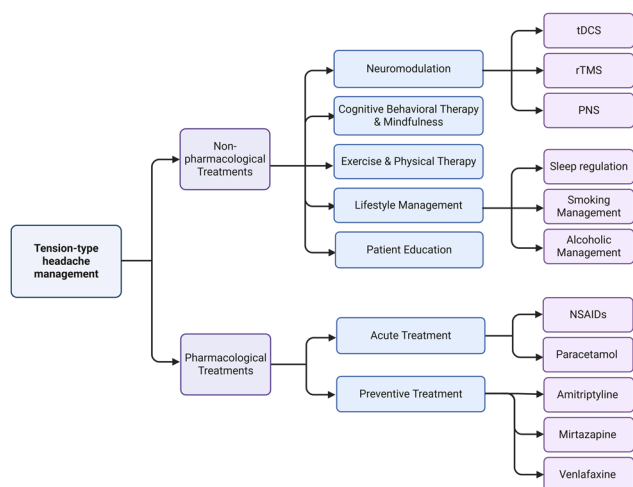


Fig. 4 Overview of tension-type headache management strategies. Tension-type headache management includes pharmacological treatments (acute and preventive) and non-pharmacological interventions such as neuromodulation, cognitive behavioral therapy, physical therapy, lifestyle modifications, and patient education. Created in BioRender. Wang, S. (2025) <https://BioRender.com/yt61fvz>. NSAIDs: non-steroidal anti-inflammatory drugs; PNS: peripheral nerve stimulation; tDCS: transcranial direct current stimulation; rTMS: repetitive transcranial magnetic stimulation

pathophysiology of migraine and TTH, neuromodulation may offer acute or preventive benefits for TTH.

TMS is a noninvasive technique that uses rapidly alternating magnetic fields to induce electric currents in the brain, leading to neuronal depolarization and modulation of cortical activity. Two trials conducted in India, involving 20 and 30 patients with CTTH, respectively, reported that repetitive TMS (rTMS) delivered to the right dorsolateral prefrontal cortex yielded greater improvements in pain intensity and HIT-6 compared with sham stimulation [214, 215]. rTMS sessions are relatively short, typically lasting 20–30 min. However, the high cost of equipment and the need for specialized personnel are significant drawbacks. Moreover, there is no standardized protocol regarding stimulation intensity, frequency, or target location. rTMS may be considered for patients with CTTH who exhibit features of central sensitization and show inadequate response to other pharmacological or physical therapies.

tDCS is a technique that employs a small device to deliver low-intensity direct current (usually 1–2 mA) through the scalp, thereby modulating the resting membrane potential and influencing cortical excitability with relatively few adverse effects. In two studies that included a small number of TTH patients within participants with headache, tDCS was associated with reductions in headache frequency, although the stimulation protocols varied [216, 217]. tDCS devices are portable and relatively inexpensive, but determining optimal electrode placement can be challenging. This modality may be considered

for TTH patients who demonstrate good adherence and motivation for home-based self-management programs.

PNS collectively refers to interventions such as transcutaneous electrical nerve stimulation (TENS), repetitive neuromuscular magnetic stimulation (rNMS), occipital nerve stimulation (ONS), and supraorbital nerve stimulation (SNS), all of which deliver localized electrical or magnetic stimuli to peripheral nerves with the goal of alleviating pain and muscle tension. A trial in Iran applied TENS to the temporal and occipital regions in CTTH patients, reporting decreased headache intensity after three months [218]. A retrospective study from Germany in pediatric headache patients, including some with TTH, applied rNMS to the upper trapezius muscles [219, 220]. A few studies also investigated ONS and SNS in TTH and other headache types, noting reductions in headache intensity and frequency [221–223]. However, none of these compared outcomes with sham stimulation, leaving the evidence relatively weak. Nonetheless, PNS may be considered for TTH patients whose pain is localized to a specific peripheral nerve distribution.

Closing Remarks While neuromodulation for TTH remains underexplored, preliminary findings suggest that rTMS, tDCS, and various forms of PNS may help reduce headache frequency and intensity in certain patients, particularly those with CTTH or refractory TTH. Further high-quality studies with standardized protocols are warranted to confirm and optimize these benefits.

Occupational medicine, cognitive behavioral therapy, and mindfulness

As outlined in the companion paper on migraine that was recently published [212], the impact of the workplace and occupational factors on the headache disorder in question needs to be considered as well as, conversely, the impact of the headache disorder on work ability and productivity. Much of the literature on work-related causes of headache is not specific to TTH, and more research is therefore needed to address this type of headache specifically. Having said that, occupational-related risk factors for TTH were considered in a number of investigations, including in a study from Denmark, which identified that among gainfully employed participants, TTH was associated with having too little time to do the current job among women and with exposure to fumes in men [224]. Research from China showed that among information technology staff use of a computer for more than 8 h per day was associated with TTH [225]. A Chinese study on medical staff showed that, among nurses, having a senior job title was identified as a risk factor for TTH [226]. That study also showed that working more than six-night shifts per month was associated with TTH in physicians [226]. A study from Saudi Arabia assessing headache risk

	Headache Diaries 	Alcoholic Management 	Smoking Cessation 	Sleep Regulation 
Impact on TTH	Improves diagnostic accuracy; supports subtype differentiation	Unclear relationship with TTH; further investigation needed	Inconsistent; higher risk in adolescents	Improves sleep quality; reduces headache frequency and severity
Evidence Strength	Observational studies show improved adherence & accuracy	No association based on systematic reviews	No association in adults; higher risk in adolescents	Multiple RCTs support CBT and sleep hygiene
Key Considerations	Low specificity requires cautious interpretation	Mechanisms unclear	Age-specific susceptibility warrants further investigation	Fixed schedules, avoid long naps; consider sleep logs

Fig. 5 Summary of lifestyle management strategies in tension-type headache. Key interventions include keeping headache diaries, alcohol and smoking management, and sleep regulation, each with varying evidence strength and clinical considerations. Created in BioRender. Wang, S. (2025)<https://BioRender.com/ueqd7ss>. CBT: cognitive behavioral therapy; RCT: randomized controlled trial; TTH: tension-type headache

factors in healthcare providers also found that TTH was more frequent in those working night shifts, and it furthermore found that TTH was associated with having an intrusive leader as well as with violence at work [227]. In a study from Brazil, TTH was linked with higher job control and lower job demand [228]. Moreover, in the COVID-19 context, headaches associated with wearing personal protective equipment (face masks, respirators, protective eyewear) have been noted in healthcare workers, and such headaches may present with tension-type features [229].

The impact of TTH on work ability and productivity is significant, especially considering the frequent nature of the condition, and this impact may manifest as absenteeism but may also occur through presenteeism. For example, a study by Simić et al. [230] showed that while 2.2% of people with TTH had lost workdays due to headache in the past month, most spent some time working while having a headache. Kim et al. [231] investigated the economic impact caused by headache among information technology workers in Korea and estimated the annual economic loss per person caused by TTH as $\$32.8 \pm 206.7$ USD due to absenteeism and $\$166.8 \pm 517.8$ USD due to presenteeism.

There is some evidence for the non-pharmacological treatment options of cognitive-behavioral therapy (CBT) and mindfulness-based approaches, although trials that specifically address people with TTH tend to be small, meaning that further investigation and confirmation of the effectiveness of these approaches are needed. For example, there appears to be incremental benefit to adding CBT to relaxation training in elderly patients with TTH, based on a small randomized controlled trial (RCT) [232]. Omid and Zargar [233] investigated the effect of mindfulness-based stress reduction in another small RCT and showed a significant improvement in pain intensity. Cathcart et al. [234] demonstrated in a further small RCT that brief mindfulness-based therapy resulted in a significant decrease in headache frequency in subjects with CTTH. However, a systematic review

on TTH in a pediatric population opined that the effect of mindfulness therapies was inconclusive - as different trials yielded contradictory results - while adding that mindfulness therapy might be useful as a coping strategy, regardless of a possible effect on headache frequency or pain intensity [235].

About half of persons suffering from TTH also display clinically significant levels of depression or anxiety [4]. Patients with TTH are 3–15 times more likely than others to be diagnosed with an anxiety or mood disorder [4]. Rigorous screening for and treatment of comorbid psychiatric conditions are likely to improve clinical outcomes. It should be noted that associated depression or anxiety may be treatable through CBT.

Closing Remarks TTH has a significant impact on workplace productivity and occupational health, contributing to both absenteeism and presenteeism. Studies highlight occupational risk factors such as high job demands, long work hours, and night shifts, emphasizing the need for workplace adaptations. While CBT and mindfulness-based interventions show some promise, further research is needed to confirm their effectiveness in TTH management. Additionally, given the strong link between TTH and anxiety or mood disorders, addressing such comorbid conditions through targeted interventions may enhance treatment outcomes. Future research should explore integrated approaches to improve both clinical and occupational well-being in patients with TTH.

Lifestyle management, diet, and nutraceuticals

To date, lifestyle modification has been widely recognized as a cornerstone of TTH management. (Fig. 5) It is essential to have a multifaceted approach to prevention and treatment of TTH which should incorporate non-pharmacological modalities and target an individual's day-to-day routine. In this context, modifications to diet with the potential introduction of nutraceuticals and lifestyle management strategies, including headache diaries, consistent sleep hygiene, avoidance or limitation

of alcohol and other psychotropic substances intake, and smoking cessation play a pivotal role in TTH management. Healthier dietary choices and normalization of eating patterns, stress reduction, and, on a larger scale, solidified social connections and support coupled with financial wellness also create a positive background and contribute substantially to overall health improvement, thus, reducing the frequency and intensity of TTH. Furthermore, mitigation of unhealthy lifestyle habits may help to reduce medication overuse commonly seen in people with CTTH. Below is a systematic synthesis of research perspectives on key intervention domains.

Headache diaries The implementation of standardized headache diaries recording coupled with comprehensive patient education constitutes a critical component of effective headache management. Systematic recording of core elements via headache diaries - particularly temporal frequency profiles, pain quantification metrics, and symptom evolution patterns- enables the formulation of evidence-based treatment algorithms and facilitates personalized therapeutic decision-making in TTH management. Two studies highlighted the potential of electronic headache diaries to improve diagnostic precision and support clinical decision-making in TTH management [236, 237]. However, their relatively low specificity—potentially related to the heterogeneity of TTH clinical manifestations—needs cautious interpretation. Electronic diaries are increasingly prioritized in clinical and research settings due to their operational convenience and superior data integration capabilities. In a comparative study spanning 504 days of headache documentation, electronic diaries (via handheld devices) demonstrated superior patient adherence and satisfaction over paper-based diaries [238]. Furthermore, headache diaries prove instrumental in TTH subtype differentiation, reducing misclassification rates [239, 240]. Future studies should prioritize refining electronic diary algorithms via multimodal data to boost specificity, while aligning diagnostic criteria with diary parameters to develop precision frameworks for TTH therapies.

Limitation or avoidance of alcohol Numerous studies have confirmed alcohol consumption as a trigger factor for headache attacks; however, the underlying mechanisms remain unclear [241, 242]. A systematic review and meta-analysis [243] encompassing 19 migraine studies and 7 TTH studies revealed a negative correlation between alcohol intake and migraine incidence, while no such association was observed for TTH. Similarly, large-scale studies involving 5,500 and 390 patients did not reveal any association between alcohol intake and risk for TTH [242, 244]. Nevertheless, some observational studies reported that up to 50% of TTH patients identified alcohol, par-

ticularly beer, spirits, and red wine (with or without concomitant cheese consumption), as potential triggers [245]. However, these findings are limited by the lack of information regarding the amount of alcohol consumed and the time interval between its intake and TTH onset. Additionally, results of multivariable logistic regression analysis confirmed consumption of light alcoholic beverages (at least 0.5 L per week) and strong alcoholic beverages (150 g per week) lost significance with TTH [246]. Taken together, current evidence remains inconclusive, and further investigation is warranted to elucidate the relationship between primary headache disorders and alcohol consumption.

Smoking cessation The relationship between smoking and TTH remains inconsistent across studies. Large-scale adult cohort studies, such as the Nord-Trøndelag and German, reported no significant association between smoking and TTH [247, 248]. However, adolescent-focused research revealed distinct patterns: The Norwegian HUNT cohort identified smoking as an independent predictor of recurrent headaches (including TTH) (odds ratio, OR = 1.5) [249], while the Dunedin cohort demonstrated elevated headache risk among adolescent smokers (OR = 2.16), though this association diminished in adulthood [250]. Methodological limitations, particularly the lack of rigorous differentiation between TTH and other headache subtypes in adolescent studies, complicate causal interpretations [249, 250]. While current evidence does not establish a definitive smoking-TTH relationship, age-specific susceptibility in adolescents warrants further investigation.

Sleep regulation Regular sleep cycles are a key intervention point that has been the focus of numerous studies [251–253]. A systematic review of 16 RCTs by Probyn et al. [252] demonstrated that CBT and progressive sleep restriction significantly improve sleep quality while reducing headache frequency and intensity of TTH. CBT components—including sleep hygiene education, cognitive restructuring (e.g., correcting misconceptions like “mandatory 8-hour sleep”), and progressive muscle relaxation—showed efficacy in improving headache-related dysfunction and improving sleep quality [252]. Progressive sleep restriction protocols involve weekly 30-minute reductions in time-in-bed, combined with stimulus control therapy (leaving bed if unable to sleep within 20 min), which improves sleep quality and reduces morning headache incidence [252]. Complementary strategies include keeping a sleep log (tracking sleep latency, awakenings, and morning headache patterns) and foundational sleep hygiene education (e.g., maintaining fixed schedules, and avoiding naps longer than 30 min) [252].

Diet With the rapidly increasing attention to the role of dietary modifications in managing various acute and chronic physical and mental health conditions, a few literature sources looked into those aspects through the lens of TTH management. Aside from aforementioned alcohol intake, the key considerations are summarized below:

Meat-based diet Saturated fatty acids, mainly found in meat, were found to be associated with more severe headache episodes in patients with TTH [254]. Evidence suggests that a plant-based diet help alleviate TTH and reduce their frequency and severity via numerous mechanisms, including but not limited to elimination of common triggers, reducing inflammation and providing larger nutrient benefits.

Missing meals Few studies reported that TTH can be triggered by skipping meals; however, the proportion of patients reporting this as a triggering agent varied substantially between studies ranging from 16% to over 50% and the estimates might be subject to bias due to the retrospective design of most of the studies [245, 255].

Various dietary triggers Up to 50% of patients reported various food items to be related to their TTH, increasing the odds as much as twice [245, 256]. Specifically, up to 20% of patients revealed that chocolate precipitates their TTH and up to 10% implicated cheese and ice cream in the onset of their TTH [245, 255]. Other foods, such as nuts and dairy products have been suspected of triggering TTH.

Additives Some studies reported on the association of TTH with aspartame (an artificial sweetener, up to 12%), monosodium glutamate (MSG, a flavor enhancer commonly added to processed foods, up to 15%), and sugar (up to 10%), but the evidence remains inconclusive [255]. The findings pertaining to the role of nitrite/nitrate and intake also remain controversial.

Caffeine and its withdrawal Earlier studies failed to show the association between coffee intake and TTH. In line with that, the findings have also been conflicting when it comes to the withdrawal of caffeine [245, 255].

Nutraceuticals The role of a few nutraceuticals has been explored mirroring an increased scientific and public interest in these remedies [257]. Below, we provide a synopsis of the nutraceuticals studied in TTH:

Niacin (nicotinic acid, vitamin B3) Niacin causes peripheral vasodilation of the intracranial and spinal vessels, increasing the rate of intracranial blood flow. Both oral and intravenous niacin formulations were shown to

provide benefits for people with TTH, specifically, for aborting acute attacks; however, the strength of evidence is limited due to the case-series design of those studies [258–261].

Cobalamin (vitamin B12) Vitamin B12 possesses antioxidant and anti-inflammatory properties and plays an important role in brain function, red cell formation and DNA synthesis. One pediatric study showed that correction of vitamin B12 deficiency resulted in complete resolution of TTH, anemia and concomitant anxiety [262].

Magnesium Magnesium contributes to proper muscle contraction-relaxation and thus may help to alleviate TTH. It has been shown that patients suffering from mild-to-moderate TTH have magnesium deficiency in up to 50% of cases and serum levels tend to be even further reduced during the attacks [263, 264]. Supplementation with magnesium pidolate was shown to be effective in reducing the number of days with TTH by 69.9% in an open-label pediatric trial [265].

5-Hydroxytryptophan (5-HTP) 5-HTP is a precursor to serotonin with potential analgesic effects mediated by plasma beta-endorphins and serotonin – estrogen interactions [257]. One double-blind RCT demonstrated a significant decrease in the consumption of analgesics and the number of days with TTH [266].

Closing remarks Current evidence consistently supports lifestyle modification as a cornerstone of TTH management. Future research should prioritize long-term intervention outcomes for personalized care. Integrating multidisciplinary collaboration (e.g., psychological support, physical therapy) with patient-led self-management strategies holds promise for optimizing long-term TTH prognosis. Dietary factors such as meat consumption, missing meals, and certain additives have been linked to TTH as well as alcohol consumption and smoking. Nutraceuticals like niacin, vitamin B12, magnesium, and 5-HTP also show potential benefits. Despite promising insights, further high-quality trials are needed to validate these interventions and establish evidence-based guidelines for TTH prevention and treatment with lifestyle modifications, diet and nutraceuticals.

Exercise, physical therapy, and patient education

In treating TTH, physiotherapy interventions, exercises, manual therapy, soft tissue release (STR), and patient education, can be used as a complement or alternative to pharmacological treatments. These interventions are beneficial for patients who experience drug side effects, wish to prevent excessive medication use, or prefer non-drug options.

Patient education Patients who experience recurrent and chronic symptoms often have comorbid psychiatric conditions that contribute to headache persistence. Anxiety and depression reinforce the chronicity of TTH and complicate treatment. Educating patients about the benign nature of TTH can alleviate anxiety and enhance adherence to management strategies. Addressing patient concerns through structured education fosters adherence to behavioral and physical interventions. Identifying headache triggers such as poor posture, sleep disturbances, myofascial pain, and mental health allows for personalized interventions [267]. Patients should understand that untreated myofascial trigger points can sustain chronic headaches and contribute to central sensitization. Structured education techniques, including self-applied trigger point release, therapeutic stretching, and heat therapy, helps patients take an active role in alleviating pain. Studies support that patient awareness and engagement in myofascial pain management improve adherence to treatment plans and reduce headache recurrence [123].

Research by Mesa-Jiménez et al. (2015) highlights that a combination of manual therapy and pharmacological care provides short-term relief by significantly reducing headache frequency, intensity, and duration [151]. However, patient education is key to sustaining long-term benefits and adherence to treatment plans.

Physiotherapy treatment Physiotherapy treatment is recommended treatments in the management of symptoms such as pericranial muscle tenderness-tension in TTH treatment [153]. The aim is to reduce hypersensitivity by reducing muscle tension and increasing oxygenation and blood flow [268]. The focus of most of these interventions on the head and neck shows that they target the effects of excessive tension and trigger points in these muscles around the head and neck, prolonged abnormal posture and exposure to mechanical load, trigeminocervical junction effects, and general stress. In general, there is no significant side effect other than minor musculoskeletal pain for physiotherapy treatments and they are safe approaches [269].

Exercise In literature studies, 6 weeks of craniocervical strengthening exercises provide significant improvements in HRQoL, medication use, headache frequency, headache impact, craniocervical-rotational angle, and TTH duration [269–274]. Three to four weeks of strengthening exercises significantly improve in disability compared to the no intervention group [275] and the physical agents group, including thermotherapy and transcutaneous electrical stimulation [273]. Postural correction exercises also show a significant effect in reducing headache frequencies (–24%) [272]. According to a meta-analysis, aerobic exercise performed 3 days a week for 3–6 months was asso-

ciated with a reduction in headache duration (weighted mean difference: –5.1, 95% confidence interval (CI): –8.97–1.22) [276]. In the meta-analysis results of Varangot-Reille et al., neck, upper extremity and craniocervical strengthening exercises provided a significant moderate clinical effect on headache intensity (standardized mean difference (SMD): –0.84, 95% CI: –1.68– –0.01, very low evidence) [269]. In an umbrella and mapping review, the applicability of strengthening exercises was moderate but had a limited certainty in evidence [277].

Yoga may regulate nociceptor sensitivity by targeting the symptoms that develop upon stress in TTH [278]. According a meta-analysis, yoga was significantly effective in the short term in improving headache intensity (SMD: –3.43, 95% CI: –6.08– –0.70), headache frequency (SMD: –1.97; 95% CI: –2.75– –1.20), and headache duration (SMD: –1.45, 95% CI: –2.54– –0.37). These significant improvement results were from TTH patients and no significant effect was found in migraine patients [279]. There is a lack of evidence on long-term effects due to a lack of long-term follow-up. In addition, the heterogeneity of the studies, not considering ETTH or CTTH, small sample size, lack of randomization, and the small number of sample groups for pure TTH keep the level of evidence weak [279].

Manual therapy Within the scope of manual therapy, mobilizations, manipulations or osteopathy approaches can be addressed. Different manual therapy interventions are applied in different dosages (10–30 min session times for 4–6 weeks) in treatments [152]. Manual therapies provide improvements in headache intensity, frequency, headache effect, HRQoL, disability and craniocervical joint range of motion, but these heterogeneous treatments are not superior to each other [152, 280]. According to a meta-analysis results, although manual therapy may have positive effects on improving the intensity and frequency of pain, high-speed and low-amplitude techniques are not superior to no treatment in reducing the intensity of pain (SMD: 0.01, low evidence) and frequency (SMD: –0.27, moderate evidence) [153]. The role of central sensitization in TTH is partially addressed and it has been stated that manual therapy applied at high speed may not have a positive effect on healing in patients with central sensitization [19, 153, 281, 282]. However, data that can confirm the effect of this judgment are lacking in the current literature [153]. In the results of an umbrella and mapping review, spinal manipulation is effective with limited evidence and strong applicability in reducing headache frequency and pain intensity [277]. The level of evidence is low due to high heterogeneity, small sample size, and few RCTs in manual therapy interventions [153, 280]. On the other hand, data on the short-term and long-term effects

of manual therapy in ETTH or CTTH are also lacking in the literature [153].

Massage therapy and soft tissue techniques The mechanisms of massage therapy in TTH treatment include reducing muscle tension (especially in pericranial and cervical areas), stimulating mechanoreceptors to inhibit pain signals (gate control theory), increasing PPT by desensitizing myofascial trigger points, enhancing blood flow to clear inflammatory mediators, and lowering stress hormones. Several studies support these effects: Moraska et al. found that after 12 massage sessions over six weeks, participants had a 30% reduction in headache intensity and decreased frequency from 4.7 to 3.2 episodes per week [283]. Chatchawan et al. reported sustained PPT increases and reduced headache intensity after Thai traditional massage [284]; and Quinn et al. observed rapid decreases in headache frequency and duration after eight massage sessions, though intensity changes were less pronounced [285]. Techniques targeting myofascial trigger points and pressure pain thresholds, such as myofascial release and Thai traditional massage, demonstrate significant benefits, with some effects sustained over follow-up periods. While promising, further large-scale, high-quality RCTs are needed to standardize protocols and confirm these findings.

Soft tissue technique is a manual therapy approach that targets myofascial pain in the cranio-cervical region. By applying gentle pressure, stretching, and mobilization to muscles such as the sternocleidomastoid, temporal, suboccipital, masseter, and upper trapezius. In a randomized trial of 97 participants, Ferragut-Garcías et al. showed that combining soft tissue therapy and neural mobilization led to a 57% reduction in headache frequency—better than either treatment alone or placebo [286]. Similarly, Ramadan et al. randomized 72 patients to receive instrument-assisted soft tissue mobilization (IASTM), pressure algometry, or sham: the IASTM group reported a drop on headache days from 15 to 2 and an improvement in cervical curvature from 17.5° to 31.4°. Both studies highlight how deeper mechanical stimulation can significantly enhance clinical outcomes in TTH [287].

Combined treatment When literature evidence is examined, combined interventions of physiotherapy treatments (MT, STR, exercises, or electrical currents such as TENS) are more effective in the short term than their application alone in reducing symptoms such as headache and frequency [288]. According to a network meta-analysis, the combined application of physiotherapy and TENS was the most effective approach in reducing headache intensity compared to control (mean difference (MD): −4.18, moderate confidence (MC)) and usual care (MD: −3.8,

MC) [288]. Among MT, mobilization and exercises were reported to be the most effective approaches in reducing headache frequency compared to controls (MD: −13.03, low confidence) and usual care (MD: −13.95, MC) [288]. Suboccipital inhibition, trigger point therapy, craniocervical region STR, nerve mobilizations, electroacupuncture, microwave, deep breathing exercises, and neck muscle relaxation were reported to be effective in the short term [289]. Meta-analysis results are insufficient for medium and long-term effectiveness, but in a systematic review, mobilizations and posture training, myofascial release techniques, trigger point therapy, suboccipital inhibition, manipulation of the upper cervical spine alone or with neck massage, and neck muscle relaxation applied together with deep breathing exercises were reported to be effective in the medium term between 8 weeks and 3 months. In the long term, 36 weeks of mobilization and posture training were reported to be effective [289]. In general, the combined application of different physiotherapy approaches seems to be effective in the treatment of TTH, especially in the short and medium term, while regular mobilization and posture exercises can provide permanent benefits in the long term.

Closing remarks Treatments targeting the craniocervical and mandibular regions for TTH provide improvements in headache frequency and intensity in the short and partly medium term. However, for other headache symptoms, evidence for the improvement effects in the distinction between ETTH and CTTH and long-term effects is limited and there is no standard physiotherapy protocol due to the heterogeneity of the studies [289].

Pharmacological treatments

Acute treatment

Most individuals affected by ETTH treat their headaches with over-the-counter simple analgesics, owing to their availability and absence of disease-specific treatments [26, 290, 291]. Current clinical guidelines from different countries recommend monotherapy for ETTH in adults, with either nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol as first-line treatment [292–294]. Non-selective NSAIDs exert their analgesic effects primarily through the peripheral inhibition of the cyclooxygenase (COX-1 and COX-2) pathway, whereas paracetamol analgesic effects are more complex and involve inhibition of COX-2 and other central pathways, such as the endocannabinoid and serotonergic pathways (reviewed in [295, 296]).

Recently, two network meta-analysis compared the efficacy and safety of simple analgesics for the treatment of ETTH in adults. Both studies demonstrated that NSAIDs and paracetamol are more effective and as safe as placebo, with NSAIDs being more effective overall [292, 293]. The

meta-analysis done by Xie et al. revealed that among NSAIDs, ibuprofen showed the best efficacy for pain-free status at 2 h followed by diclofenac (not statistically different), with a surface under the cumulative ranking curve (SUCRA)-ranking of 91.7% and 83.3% respectively [293]. Paracetamol was less effective than most NSAIDs with a SUCRA-ranking of 37.1% [293], however, another meta-analysis from Alnasser et al. found no statistically significant difference in efficacy between ibuprofen and paracetamol [292]. As there are very few direct head-to-head trials of ibuprofen and paracetamol, both medications remain recommended as first-line therapy for ETTH in adults.

The adverse events rates of all simple analgesics were no higher than those of placebo in both meta-analyses, with neither severe adverse events nor death events reported [292, 293]. The most reported mild adverse events for ibuprofen were nausea and dizziness, while the most adverse events related to paracetamol were stomach discomfort and dizziness [292, 293]. Thus, monotherapy with simple analgesics for ETTH has a favorable safety profile; however, as NSAIDs may be associated with renal insufficiency or GI bleeding, paracetamol may be considered as preferred option for patients with higher risk of those adverse effects [26, 292]. Unfortunately, some patients with ETTH do not obtain adequate pain relief and often require combination analgesics or analgesic plus adjuvants, notably caffeine.

Caffeine may increase the antinociceptive effects of analgesics by promoting their gastric absorption [297]. Clinical trial evidence suggests that combining caffeine with over-the-counter analgesics, such as paracetamol, aspirin, and ibuprofen, significantly enhances efficacy compared to using the analgesic alone in TTH treatment [298, 299]. The European Federation of Neurological Societies (EFNS) guideline also recommends the oral use of caffeine combinations for the acute treatment of TTH with level B recommendation [300]. As is typical with over-the-counter preparations, tolerability is generally good for most patients, with adverse events (e.g. nervousness, nausea, abdominal discomfort, dizziness etc.) being predictable, mild, and transient [297]. However, the frequency of using these combination analgesics should be carefully monitored and limited to less than 10 days per month to avoid the risk of developing MOH [301]. Further studies are needed to explore the relationship between caffeine dosing and clinical outcomes in patients with TTH.

Triptans (e.g., sumatriptan, rizatriptan) and ergots (e.g., ergotamine, dihydroergotamine) are migraine-specific acute treatments designed to target serotonin receptors. They are not typically considered first-line treatments for TTH. Gepants (e.g. rimegepant, atogepant), a new generation of migraine treatment that works by blocking

CGRP, have not shown efficacy for TTH relief in randomized trials, either [301].

Closing remarks For most individuals with ETTH, over-the-counter NSAIDs and paracetamol remain the first-line treatments, with NSAIDs generally being more effective. Recent network meta-analyses confirm their efficacy and safety, although paracetamol may be preferable for patients at higher risk of NSAID-related adverse effects. Combination of analgesics with caffeine offers additional benefits but should be used cautiously to prevent medication overuse. Migraine-specific treatments, including triptans, ergots, and gepants, have not demonstrated efficacy for TTH but may be considered in patients with comorbid migraine.

Preventive treatment

Preventive treatments are essential for reducing the frequency, intensity, and duration of headaches in individuals with frequent ETTH or CTTH [26]. Preventive measures may be indicated when simple analgesics prove ineffective, are poorly tolerated, or contraindicated. The primary objective of preventive therapy is to decrease headache frequency and severity while improving the response to acute treatments [302]. A patient-centered approach is crucial when selecting a preventive strategy, considering individual expectations and preferences. If patients experience substantial improvement, such as a reduction of more than 30–50% in monthly headache days, treatment tapering or discontinuation may be considered after 3 to 6 months, provided comorbidities such as anxiety or depression are absent [240]. Regular monitoring is recommended to identify any recurrence of symptoms.

Amitriptyline, a tricyclic antidepressant, is highly effective for TTH management and holds a level A recommendation by the EFNS Task Force [300]. Its mechanism of action includes inhibiting serotonin and norepinephrine reuptake, reducing pericranial muscle tenderness, and attenuating central sensitization through peripheral antinociceptive effects [141, 303]. The standard treatment regimen begins with a dose of 10 mg at bedtime, with gradual weekly increases of 5–10 mg in cases of insufficient efficacy. Based on clinical trials that utilized doses ranging from 50 to 150 mg, the recommended maximum dose is set at 75–100 mg [303, 304].

Amitriptyline is the first-choice prophylactic treatment across age groups and was reported to be superior to placebo in reducing headache frequency (weighted mean difference: –4.8 headaches/month) and number of analgesic medications consumed (weighted mean difference: –21.0 doses/month) after 4 to 24 weeks of treatment [304]. Reduced efficacy has been observed in patients with widespread pain hyperalgesia [305]. Common side

effects include drowsiness, weight gain, dry mouth, and constipation. Special care should be taken to avoid aggravation of glaucoma, urinary retention, and cardiac arrhythmias in vulnerable patients.

Mirtazapine, a noradrenergic and specific serotonergic antidepressant, has shown efficacy supported by a level B recommendation [306, 307]. Although mirtazapine has not been specifically tested in elderly individuals for the prevention of TTH, it is widely prescribed as a first-line treatment for depression in older adults, suggesting it may be particularly suitable for elderly patients with TTH [308]. Side effects of mirtazapine include drowsiness, somnolence, and weight gain. Venlafaxine, a SSRI, has demonstrated effectiveness for TTH prevention in a single trial [309]. While better tolerated than amitriptyline, venlafaxine may cause side effects such as dizziness, nausea, abdominal pain, and vomiting. Additional antidepressants with level B recommendations include clomipramine, maprotiline, and mianserin [300].

Tizanidine, a muscle relaxant, has been evaluated for CTTH prevention in two placebo-controlled studies, but findings were inconclusive [310, 311]. One trial investigating the combination of a β -blocker (pindolol) and amitriptyline found this combination to be more effective than placebo but not superior to amitriptyline monotherapy [312]. Open-label studies have highlighted the potential efficacy of topiramate, valproate, and buspirone in CTTH prevention [313–315]. These treatments may be considered for patients who do not respond to or cannot tolerate standard therapies. Memantine has been shown to reduce pain intensity in patients with CTTH, although the effect appears to be modest [316]. Currently, there is limited evidence supporting the use of SSRIs for the prevention of TTH [317].

Botulinum toxin A is currently being investigated as a potential treatment for frequent and CTTH in individuals experiencing 10 or more headache days per month (NCT04857671). Additionally, vitamin D supplementation is under study in patients with ETTH and CTTH who are undergoing treatment with amitriptyline or topiramate (NCT05860062).

Closing remarks Amitriptyline remains the first-line prophylactic option, demonstrating significant efficacy, though side effects should be carefully monitored. Mirtazapine and venlafaxine offer alternative options, particularly for patients who cannot tolerate amitriptyline. Topiramate, valproate and buspirone showed potential efficacy. These medications may be considered when the first-line treatments fail. Botulinum toxin A and vitamin D supplementation are under investigation. A patient-centered approach is crucial in selecting the most suitable preventive treatment, with regular monitoring to assess treatment response and adjust strategies accordingly.

Prognosis

Research on the prognosis of TTH is limited compared to that on migraine. The most insightful data on the natural history of TTH are derived from studies that offer cross-sectional prevalence information across different age groups or from longitudinal follow-up research.

However, such prevalence data do not effectively capture long-term prognosis because they do not track individual patients over extended periods. Additionally, the variability in TTH prevalence is generally greater across studies compared to migraine. This variability often results from differences in methodology, such as how cases are defined, and potential variations among ethnic groups [2]. Another contributing factor may be that the characteristics of headaches in some patients evolve over time, necessitating adjustments to the TTH diagnosis. The issue of differential diagnosis between TTH and migraine can also be problematic, as they share common features such as cranial autonomic symptoms and the overlap of TTH with orofacial pain [318–320].

Stovner et al. reported a global average lifetime prevalence of TTH across all ages at about 46%, with a lower prevalence in children – 31% [321]. CTTH is rare in those under 15 years old [322]. However, the latest data extracted from 31 studies, including 13,105 children and adolescents with TTH showed that the prevalence was 17%, of the 23 studies reported difference prevalence by sex, the prevalence was 11% in females and 9% in males. The prevalence of ETTH was 4–29% and CTTH was 0.2–12.9% [323].

The most comprehensive epidemiological study to date by Schwartz et al. involved 13,345 individuals aged 18 to 65, revealing that 30–40% of younger adults and 25–30% of those over 60 experience ETTH. The incidence does not change much, although there is a slight peak in patients aged between 35 and 55 years. For CTTH, the overall prevalence was 2.2%, with similar prevalence across all age groups from 18 to 65 years, showing that CTTH is a problem throughout life [324]. However, in the very old (> 70 years) the prevalence of CTTH seems to decrease [325].

Population-based follow-up studies assessing the long-term prognosis of TTH are relatively scarce. Generally, the prognosis in these studies is favorable. For example, a 12-year Danish population-based study found that 45% of adults with frequent ETTH or CTTH at baseline were in remission, though 39% still experienced frequent ETTH and 16% continued to have CTTH. Factors associated with poor outcomes included the presence of CTTH at baseline, co-existing migraine, unmarried status, and sleep disturbances. Conversely, factors predicting remission included older age and the absence of CTTH [326].

In a 30-year prospective study from Switzerland, 7% continued to have TTH for more than half of the

follow-up period. This study showed that there is the considerable overlap between different types of headache over time. These findings suggest that headache research based on strict diagnostic classifications may not fully reflect the true complexity of headaches in the general population [327].

In a population-based study from Norway comparing cross-sectional one-year prevalence of major headache types in two surveys performed with a 11-year interval, all headache types markedly decreased during the 22-year follow-up period. In this study, they also found that occurrence of chronic musculoskeletal complaints and high score of depression or anxiety at baseline increased the risk of having persistent headache [328]. In a 5-year population-based survey from Turkey, remission occurred in 29% of individuals with TTH. They found no predictive factor for persistent TTH [329].

The prevalence of CTTH in the general population is unknown - epidemiological studies suggests that it may be around 3–16%, but this seems to be an underestimation [251, 323]. The prognosis for this type of headache is uncertain, especially considering the fact that this type is more common in patients with longer durations of illness and current therapeutic strategies are limited. Risk factors for the development of chronic daily headache on the basis of TTH in elderly adults are similar to those observed in the general adult population. These include overuse of analgesics, depression, a history of migraine and various other pain syndromes but also limited access to healthcare resources [291, 330]. Other potential risk factors for the chronification of TTH, such as the coexistence of facial pain, bruxism or musculoskeletal disorders, are still being discussed, but the results are inconclusive [123, 319, 331].

Closing remarks

While TTH generally has a favorable prognosis, with many individuals experiencing remission or reduced headache frequency over time, various factors can influence poor outcomes, including co-morbid migraine. However, whether TTH is a risk factor for developing migraines remains a subject of debate since it is common to encounter patients who have coexisting conditions of migraine, TTH, and MOH in clinical practice. Other important factors associated with the chronification of TTH are psychiatric illness and overuse of analgesics.

Psychosocial impact of TTH

The psychosocial impact of TTH includes several domains, such as the impact on time with disability, HRQoL, and the relations with others [332].

Compared to migraine, TTH is much more prevalent: according to the latest estimates of the Global Burden of Diseases, Injuries, and Risk Factors (GBD) study, TTH is

the second most prevalent condition affecting 2.01 billion people worldwide (26.4% of the population), and 1.27 of those aged 15–49 (32.7% of the population) [333]. However, in terms of health loss, as expressed by the years lived with disability (YLDs) metric, TTH holds the 20th position in all-age ranking (0.5% of all-cause YLDs), and the 12th position among those aged 15–49 (0.7% of all-cause YLDs). The main reason for the scarce recognition of health loss due to TTH, compared to migraine which is a leading cause of health loss, is grounded on the disability weights, which are 0.434 and 0.036 respectively for migraine and TTH (i.e. patients with migraine and TTH respectively experience a 43.4% and 3.6% health loss during an attack compared with a person in full health). However, the difference in impact might not be so wide: as shown in a recent meta-analysis addressing disability across primary headaches, the impact is mostly connected to age and medication intake, rather than diagnosis [334].

TTH extends beyond the headache attacks, affecting psychological well-being, social interactions, and lifestyle. A cross-sectional survey using modified cluster sampling from the adult population (18–65 years) in the European Union revealed that interictal symptoms were reported by 18.9% with TTH [335], e.g. as avoidance behaviors due to fear of pain. TTH is a disabling disorder along with migraine, and the two conditions often present together. Patients with CTTH have similar SF-36 profiles to those with chronic migraine [336]. A nationwide survey in Korea revealed that 4.8% of patients with TTH experienced at least one day with activity restriction due to headache in the last 3 months and approximately one-fifth had a significant headache impact [337].

There are various reports on the impact of TTH in comparison with migraine. Using a metric of burden defined by intensity as a proxy for disability multiplied by the headache frequency, global mean disabilities of TTH resulted higher than that of migraine [321]. One study from the USA demonstrated that both CTTH and ETTH cause a high number of workdays lost [324]. As shown by a European study, the percentage of people who lost at least one workday was four-time higher among those with migraine than those with TTH, but the total amount of lost workdays was three-time higher among those with TTH due to higher prevalence [338].

The HRQoL of persons with TTH is lower than that of the general population, as shown in a recent population study [339], and such impaired HRQoL is a driver for seeking care [340]. A study from Spain among patients with CTTH showed that headache frequency has a greater impact than headache intensity on HRQoL [336]. Fewer articles have studied the impact of TTH on HRQoL compared to migraine [341]. Patients with CTTH report limitations in physical functioning, fatigue,

and difficulty concentrating. Emotional well-being is also compromised, with patients experiencing frustration, helplessness, and irritability due to the ongoing discomfort and headaches' unpredictability. Comparative HRQoL studies showed that patients with migraine and with TTH, especially with CTTH [342], had comparable results in most of 36-Item Short Form Survey (SF-36) scales, with the exclusion of social functioning and bodily pain, where patients with migraine had worse scores [343].

TTH can significantly impact family or others' relations. About 10% of persons with TTH felt their families and friends do not understand or accept their disease, and 26.7% were reluctant to tell others of having headache [335]. There are reports on TTH impact on family relations [344, 345]. Adolescents with TTH had a significantly lower family-related wellbeing than those without headache [344]. Parental separation might contribute to or exacerbate the experience of TTH, potentially leading to strained family relations: in fact, individuals with TTH are more likely to experience parental separation or divorce compared to those without headaches, suggesting that family structure may play a role in TTH development [345]. Moreover, TTH sufferers often report fewer peer relations compared to those with migraine or no headaches [345]. This lack of social interaction can further isolate individuals, potentially leading to increased reliance on family members for social support, which can strain family relationships. The emotional burden of TTH can manifest as anger and general distress, rather than specific symptoms of anxiety or depression [346]. This general distress can lead to misunderstandings and conflicts in relationships, as individuals may struggle in managing their emotions [347].

The psychosocial impact of TTH is mostly measured with disease-specific or generic questionnaires. A recent review showed that different instruments are used to track disability, HRQoL and work-related impact [347].

Examples of headache-specific disability measures such as the 6-item Headache Impact Test (HIT-6) [348], the Headache Disability Inventory (HDI) [349] and the Migraine Disability Assessment Scale (MIDAS) [350]. The HIT-6 measures the impact of headaches on a person's life over a one-month period and is useful in both clinical research and practice for screening and monitoring patient outcomes. The HDI address headache's impact with two domains, physical and emotional components (HDI-P and HDI-E), which help quantify the burden of headaches on individuals' lives. The MIDAS addresses days' loss due to headache in work, household and leisure time over the preceding three months. An example of generic disability measure is the World Health Organization Disability Assessment Schedule (WHODAS), which evaluates difficulties in undertaking

daily activities connected to cognition, mobility, self-care, relationships, life activities, and participation [351].

HRQoL is often measures with the SF-36, the most widely used generic HRQoL measure, which address multiple health domains, such as physical functioning, bodily pain, and mental health, which are significantly affected in TTH patients [342]. In addition to this, the World Health Organization Quality of Life 8-question scale (WHOQOL-8) has been used in few studies, such as in population surveys, in reason of its brevity [352]. In some occasion, a migraine-specific QoL measure (the Migraine-Specific Quality of Life) has also been employed in patients with TTH: it is composed of three scales addressing restrictions in undertaking activities, prevention from undertaking activities and the emotional component connected to headaches [353].

Finally, the Work Productivity and Activity Impairment (WPAI) questionnaire is a generic instrument used to assess the impact of a disease on work productivity and daily activities past 7 days. It measures several dimensions of productivity loss, including absenteeism, presenteeism, overall work productivity loss, and activity impairment outside of work [354].

Closing remarks

TTH is indeed less severe than other primary headaches. However, its impact is noteworthy because of its high prevalence, which is likely underestimated compared to migraine. In fact, the difference in impact between the two conditions is not as broad as generally perceived. TTH has significant psychosocial consequences, especially in CTTH; it affects HRQoL, mental health, social functioning, and occupational productivity. What has to be noted is that no specific instrument exists that addresses disability and HRQoL in patients with TTH: all those addressed as "disease-specific" are specific for migraine. TTH-specific instruments are needed to recognize the broad impact of TTH so that healthcare providers can improve patient outcomes and reduce the burden of this pervasive disease.

Economic impact of TTH

TTH is the most prevalent primary headache disorder globally, imposing significant economic and personal burdens [333, 355, 356]. This review provides an overview of TTH, focusing on its economic impact and societal burden. It synthesizes global and regional epidemiological data, highlights direct and indirect economic costs, and explores psychosocial and functional impairments. Additionally, it offers insights into public health and policy interventions to mitigate this highly prevalent condition.

TTH imposes significant direct costs on healthcare systems, mainly through outpatient care and medications.

Consultation rates for TTH vary between 16% and 71% [357]. Outpatient care is the largest contributor to these costs, followed by diagnostic investigations. Medications, including acute and prophylactic treatments, are also significant contributors. Hospitalizations and specialist referrals, though less common than for migraine, can occur, particularly in chronic cases. While less frequent, emergency department (ED) visits for TTH still add to healthcare expenses. Specialist referrals, especially to neurologists, are sometimes necessary for managing chronic or refractory TTH cases [357, 358]. Advanced diagnostic tests like MRI or computed tomography (CT) scans, often used to exclude secondary headache causes, further escalate costs. Although the per-person costs of TTH are lower than migraine, the high prevalence of TTH results in substantial total healthcare expenses [358].

TTH significantly affects workplace productivity through both absenteeism and presenteeism. 2.2% of TTH sufferers reported monthly work absences, compared to 7.1% for migraine sufferers. Many TTH patients (39.7%) reported working with headaches for 9–24 h per month [230]. Presenteeism, where employees work despite reduced efficiency, is a major indirect cost contributor. In Korea, Kim et al. [231] estimated the annual economic loss per person due to TTH as $\$32.8 \pm 206.7$ USD from absenteeism and $\$166.8 \pm 517.8$ USD from presenteeism among information technology professional. Similarly, in Europe, the annual cost of presenteeism in Europe for TTH sufferers is estimated at €173 per person [359]. Indirect costs represent a staggering 92% of Europe's total economic burden of TTH. The mean per-person annual cost is €303, with €278 attributed to indirect costs. Total annual indirect costs in the European Union are estimated at €19.32 billion among adults aged 18–65, representing 92% of the €21 billion total TTH costs [359].

The economic burden of TTH is substantial, though generally lower than that of migraine on a per-person basis. However, due to its higher prevalence, the overall economic impact of TTH is significant. The total all-cause annual direct medical costs for patients with chronic migraine (\$17,878) were 2.26 times higher than those with TTH (\$7,902). Annual migraine/TTH-related costs for patients with chronic migraine (\$1,869) were 11.90 times higher than those with TTH (\$157). For all service categories (ED, inpatient, outpatient, and prescriptions), the expected costs in the migraine groups were higher than in the TTH group [360].

The indirect costs of TTH, while lower per person, are substantial due to its high prevalence. TTH accounts for 6.5% of all YLDs globally (7.7% in females and 5.1% in males) [361]. The absenteeism from TTH is considerable and almost three times more than that seen in migraine.

At least one day's absence from work per year was observed in 47.4% of TTH cases in one study, with the number of days off work ranging from 0 to 14 days annually [362]. In the European Union, the total annual cost of TTH amongst adults aged 18–65 years was estimated at €21 billion, accounting for 12% of all headache-related costs. The prevalence of TTH is greater than migraine, and the overall economic cost of TTH is higher due to its higher prevalence [363].

Both TTH and migraine significantly affect workplace productivity but in different ways. TTH tends to cause more presenteeism (reduced productivity at work), while migraine causes more absenteeism [362]. While the per-person economic burden of TTH is generally lower than that of migraine, its higher prevalence results in a substantial overall economic impact. Both conditions significantly affect workplace productivity and impose considerable costs on healthcare systems and employers.

Burden of TTH

TTH significantly reduces HRQoL, particularly in chronic cases. The SF-12 Health Survey shows lower physical and mental scores for TTH sufferers, with CTTH showing the greatest reductions [4]. Anxiety and depression are notably more prevalent among TTH patients, with chronic sufferers being 3–15 times more likely to receive a diagnosis of a mood or anxiety disorder [4]. Please also refer to the section “Psychosocial Impact of TTH” for more detailed discussion on psychosocial burden of TTH.

Over 70% of TTH patients report impaired interpersonal relationships. Regular activities are disrupted in 38% of headache episodes [364]. Sleep and energy impairments affect about one-third of patients on 10 or more days per month [4]. Repeated headache episodes and the anticipation of future headaches adversely affect family life, social interactions, and employment opportunities.

TTH impacts both physical and cognitive functioning. Cognitive impairments include slower reasoning, reduced memory retrieval, and increased distractibility [365]. Sleep disturbances and energy deficits further exacerbate the burden. In workplaces, 74% of CTTH patients experience disability days, averaging seven days in six months [4]. Reduced workability is particularly evident among women.

Public health implications

Despite its high prevalence, TTH is often underdiagnosed and undertreated. Only a minority of patients receive appropriate diagnosis and treatment [251]. Misdiagnosis is common in emergency settings; one study found that only 9.9% of TTH diagnoses met the International Classification of Headache Disorders (ICHD)

criteria [366]. Furthermore, up to one-third of TTH diagnoses may be cases of migraine [251].

Healthcare systems face numerous challenges in addressing TTHs (TTH), including limited access to headache specialists, which hampers effective management [367]. Diagnostic accuracy is compromised by inconsistent application of the ICHD-3 criteria, often resulting in misdiagnosis [366]. Despite its high prevalence, TTH research and funding remain disproportionately low compared to other headache disorders like migraine [251]. Additionally, inadequate training among healthcare providers contributes to suboptimal TTH management [366]. Finally, the lack of effective prevention strategies to halt the progression from ETTH to CTTH further exacerbates the burden of this common but underappreciated condition [251].

The global prevalence and socioeconomic burden of TTH highlight the urgent need for targeted interventions. Research should prioritize identifying modifiable risk factors, such as stress and muscle tension, and elucidating mechanisms driving the transition from ETTH to CTTH. Diagnostic tools and biomarkers can enhance accuracy and reduce underdiagnosis, particularly in emergency and primary care settings. Innovative treatment strategies, including digital tools for stress management and pharmacological agents targeting central sensitization, are promising. Public health initiatives should focus on reducing barriers to care and raising awareness about TTH's societal and economic impacts. Policymakers must allocate resources toward prevention and integrate headache management into healthcare systems.

TTH are widespread yet often underestimated conditions that impose substantial economic and psychosocial burdens. Despite lower costs than migraine, TTH's high prevalence drives its significant cumulative impact. Effective management strategies and public health interventions are essential to mitigate this burden. By prioritizing research, enhancing access to care, and addressing prevention gaps, we can reduce TTH's global impact and improve the HRQoL for those affected.

Closing remarks

TTH imposes a significant economic and societal burden, primarily through healthcare costs, workplace productivity loss, and reduced HRQoL. Although per-person costs are lower than migraine, the high prevalence of TTH results in substantial cumulative costs. Presenteeism is a major contributor to economic losses, with indirect costs accounting for over 90% of TTH's financial impact in some regions. Despite its burden, TTH remains underdiagnosed and undertreated, necessitating improved diagnostic accuracy, preventive strategies, and public health interventions. Enhancing awareness, increasing research

funding, and integrating headache care into healthcare systems can reduce the global impact of TTH.

TTH in population throughout life span

Prevalence across different age groups and genders

TTH is the most common neurological disorder worldwide, with a lifetime prevalence ranging from 30 to 78%, making it a significant public health concern [26, 361]. In 2019, the Global Burden of Disease study estimated 964.8 million cases of TTH, representing a 37% increase since 1990, with the highest burden observed in the 30–39 age group and a rising incidence among adolescents [368]. Among children and adolescents, the prevalence is approximately 17%, with minimal sex differences before puberty but a growing female preponderance after 11–12 years of age [323, 369, 370]. CTTH remains rare in adolescents (1%), peaks by age 39, and declines thereafter [330, 371]. Women bear a higher burden of both TTH and CTTH, with adult sex prevalence ratios of 1.2:1 and higher CTTH prevalence in females across all age groups [26, 372].

Importance of understanding TTH across the lifespan

Understanding TTH across the lifespan is crucial due to its high prevalence, impact on HRQoL, and potential for mismanagement. The clinical presentations of TTH can vary depending on the age group. The ICHD-3 is the diagnostic criteria for TTH, but it may have limitations when applied to children [3, 373]. TTH has risk factors and trends that differ depending on the age of patients. In addition, age can affect the type of treatment and outcome because management resources can vary greatly.

TTH in children and adolescents

Epidemiology: Prevalence and gender differences in early life

TTH is the most common primary headache disorder in children and adolescents, with prevalence, clinical features, and triggers varying by age and sex [374]. Epidemiological studies report a lifetime prevalence of 15–25% globally in this age group [375]. A meta-analysis of 31 studies involving 13,105 children and adolescents with TTH estimated a weighted pooled prevalence of 17%. However, TTH diagnosis in pediatric cases may sometimes overestimate its prevalence while underestimating migraine cases [323]. CTTH remains rare, affecting less than 1% of children and adolescents [375, 376]. Before puberty, TTH prevalence is similar in males and females (11% vs. 9%), but in adolescents, a higher frequency in females emerges, likely influenced by hormonal and psychological factors [323, 375].

Clinical features and diagnostic challenges in younger populations

Specific patterns of head pain and symptoms characterize TTH in children and adolescents, with presentations differing slightly from adults. The ICHD-3 criteria, primarily developed for adults, have limitations in younger populations [3, 373]. Preschool children may experience shorter and less frequent attacks resembling TTH [377]. Differentiating TTH from migraine in children is challenging due to overlapping symptoms, variations in presentation, and limited communication abilities. For instance, migraines in children may present as bilateral, non-throbbing pain, leading to potential misdiagnosis as TTH [375]. Both conditions can involve photophobia or phonophobia, further complicating diagnosis. Additionally, many children with TTH report migraine-like symptoms, such as unilateral pain, photophobia, phonophobia, and pain worsening with physical activity [374]. Headache types can also evolve. Studies indicate that around one-fourth of migraines transition to TTH over 8–10 years, while others may resolve [378]. Given headaches' symptom overlap and dynamic nature during developmental transitions, the continuum model suggests that TTH and migraine may represent a spectrum of the same physiological processes [379].

Impact on academic performance and social activities

TTH, though perceived as less severe than migraine, can profoundly impact the academic and social lives of children and adolescents, especially when frequent or chronic, with consequences for overall development and well-being [374, 375]. TTH can impair concentration, memory, and problem-solving skills, reducing productivity in school [380]. Chronic headache may lead to absenteeism, missed lessons, and anxiety about school, further hindering academic engagement and confidence and creating a cycle of poor performance and stress [381, 382]. Socially, TTH can limit activity participation, leading to isolation and weakened peer relationships. Fear of headaches during outings may discourage participation, causing exclusion and impairing emotional development [380, 382]. TTH-related stress, sleep disruption, and frustration from chronic pain can result in behavioral issues and further complicate interactions, highlighting its broader psychological impact [375, 381, 383].

Role of lifestyle factors, such as screen time, diet, and sleep patterns

Lifestyle factors play a significant role in triggering or exacerbating TTH. Excessive screen time on devices such as smartphones and tablets can lead to physical strain (e.g., poor posture, eye strain) and mental fatigue, which are common triggers for TTH [384]. Prolonged exposure to blue light from screens and overstimulation from

activities like gaming or social media further increase headache risk [385]. Dietary habits also influence TTH. Skipping meals or long intervals between meals can cause blood sugar fluctuations, a known headache trigger [386]. Dehydration due to inadequate water intake and consuming processed snacks, caffeine, or high-sugar items can also exacerbate TTH, particularly in susceptible children [374, 376, 387]. Nutritional deficiencies, such as low magnesium or vitamin D levels, may further contribute to headache onset [388, 389]. Sleep patterns strongly affect TTH. Poor sleep quality, irregular schedules, or excessive sleep can disrupt the circadian rhythm, intensifying headache frequency and severity. Additionally, conditions like obstructive sleep apnea or insomnia are associated with worse TTH outcomes [374].

TTH in Adults

TTH is the most common primary headache disorder, with prevalence peaking in the fourth and fifth decades of life. In early adulthood (20–39 years), prevalence reaches 42.3% in males and 46.9% in females, remaining around 42% in middle adulthood (40–59 years) [361, 371]. TTH is more common in women, who report higher pain intensity, longer-lasting episodes, and a greater likelihood of transitioning from ETTH to CTTH compared to men [26, 390]. Women also experience more trigger points, with stronger associations between anxiety, sensitivity to pressure pain, and TTH, highlighting the role of emotional factors in increasing muscle responses [391]. Females with CTTH are at higher risk of mood disorders such as depression, which, alongside stress and anxiety, exacerbates headache frequency and severity [104, 392]. Hormonal changes during the menstrual cycle, pregnancy, or menopause are additional triggers for women, who also report greater sensitivity to stress, fatigue, and emotional factors than men [390, 391]. In contrast, men are more commonly affected by triggers such as sleep disorders, poor posture, prolonged exertion, alcohol, and dehydration [26]. Sleep quality is a key factor in men, while depression and pain intensity play more prominent roles in women [392]. Gender differences in TTH are minimal before puberty but similar to adult patterns in post-pubertal age [374]. Understanding these differences is essential for developing tailored treatment approaches that address hormonal and psychological influences, improving outcomes for patients with TTH [392].

Occupational and lifestyle contributors to TTH

Occupational and lifestyle factors significantly influence the development and exacerbation of TTH within this age group, often through stress, physical strain, and unhealthy habits. Workplace stress, including high job demands, tight deadlines, and lack of control, increases TTH risk [393]. Please also refer to sections “6-a-ii.

Occupational Medicine, Cognitive Behavioral Therapy, and Mindfulness “and “6-a-iii. Lifestyle Management, Diet, and Nutraceuticals” for detailed discussion on occupational and lifestyle contributors to TTH.

Comorbidities, such as anxiety and depression

TTH is closely linked to psychiatric comorbidities, particularly anxiety and depression, with individuals suffering from TTH showing a significantly higher prevalence of these conditions compared to those without headaches [391]. Please also refer to sections “5. Comorbidities of TTH” and “8. Psychosocial Impact of TTH” for detailed discussion on these topics.

TTH in Older Adults

Changes in prevalence and clinical characteristics with aging

An older adult, TTH shows a decline in prevalence, attributed to neurobiological changes, lifestyle adjustments, and reduced stress exposure compared to younger populations. However, when TTH occurs, it often presents with atypical features, such as lower intensity and a progression from episodic to chronic patterns. These changes are linked to age-related factors, including musculoskeletal degeneration, decreased physical activity, and comorbidities like depression and anxiety [138]. Older adults also tend to underreport headache symptoms, complicating diagnosis and management. This underscores the importance of clinical vigilance and tailored treatment strategies to address their specific needs [394]. These findings highlight the need for better age-focused research and interventions to manage TTH in this population.

Influence of comorbidities (e.g., musculoskeletal disorders, cognitive decline) on TTH

Comorbidities significantly influence TTH in older adults, often altering its clinical presentation and increasing its burden. Musculoskeletal disorders, such as cervical spondylosis and temporomandibular joint dysfunction, are common in this age group and can exacerbate TTH by increasing peripheral nociceptive input and sustaining muscle tension [138, 392]. Cognitive decline, frequently seen in older adults, may further impact pain perception, symptom reporting, and treatment adherence, complicating diagnosis and management [104]. The interaction between TTH and these comorbidities highlights the need for a multidisciplinary approach to effectively address the broader health challenges older patients face. This strategy ensures comprehensive care tailored to their unique needs.

Impact of polypharmacy and age-related physiological changes on TTH management

Polypharmacy and age-related physiological changes often complicate TTH in older adults. Polypharmacy, shared in this age group due to multimorbidity, increases the risk of adverse drug interactions and medication overuse, which can worsen headache symptoms or lead to CTTH. Additionally, aging-related changes in drug metabolism and reduced renal or hepatic clearance necessitate careful adjustment of medication dosages to minimize toxicity and improve efficacy [395]. These challenges underscore the importance of individualized treatment strategies that consider the pharmacokinetic and pharmacodynamic changes of aging. Regular medication reviews are essential to mitigate the risks associated with polypharmacy and ensure safe and effective headache management in older adults.

Role of social isolation and reduced physical activity

Social isolation and reduced physical activity significantly worsen TTH in older adults. Social isolation, common in aging populations, is linked to increased stress, depression, and limited access to healthcare, all of which can amplify headache frequency and severity [396]. Reduced physical activity, often due to musculoskeletal conditions or chronic illnesses, further contributes to poor health, increased muscle tension, and impaired pain modulation, exacerbating TTH [392]. Addressing these factors through community engagement and tailored physical activity programs for the elderly can help alleviate headache symptoms and improve overall HRQoL.

Longitudinal trends and evolution

Patterns of TTH progression or resolution across life stages

Longitudinal trends in TTH show distinct patterns of progression and resolution throughout life. ETTH in early adulthood often progresses to CTTH, influenced by psychosocial stress, comorbidities, or inadequate treatment [138]. Conversely, some individuals experience symptom resolution later in life, likely due to reduced stress and age-related changes in nociceptive processing [394]. These patterns highlight the importance of early and sustained interventions to prevent chronicity. Effective management should address the dynamic interaction of biological, psychological, and social factors across the lifespan.

Factors influencing chronicity versus ETTH

The chronicity or episodic nature of TTH is influenced by various interconnected factors. CTTH is more likely to develop in individuals with high psychosocial stress, poor coping skills, and comorbidities such as anxiety, depression, or musculoskeletal disorders [397]. Frequent use of analgesics for acute pain relief can also lead to

medication overuse, a significant risk factor for CTTH [395]. In contrast, ETTH is typically associated with less severe triggers and fewer perpetuating factors, contributing to its transient nature. Recognizing these factors is essential for implementing targeted prevention strategies to reduce the progression to CTTH.

Impact of hormonal changes on TTH trajectory

Hormonal changes, particularly during menopause, significantly affect the trajectory of TTH. Declining estrogen levels during menopause can alter pain modulation mechanisms, potentially increasing headache frequency and intensity in some individuals [390]. Conversely, hormonal stabilization post-menopause may reduce TTH symptoms, highlighting the complex and individualized nature of hormonal influences [392]. These variations emphasize the importance of considering hormonal status in managing TTH in middle-aged and older women and exploring hormone replacement therapy as a potential strategy to alleviate headache burden.

Management Strategies Across the Life Span

Adaptations in pharmacological and non-pharmacological treatments for different age groups

Management strategies for TTH require age-specific adaptations in pharmacological and non-pharmacological approaches. In younger populations, emphasis is placed on lifestyle modifications, stress management, and behavioral therapies to minimize medication use, especially in adolescents where overuse is a concern [26]. Adults benefit from a combination of pharmacological options, such as NSAIDs or tricyclic antidepressants, and non-pharmacological interventions like physical therapy and mindfulness-based therapies [392, 394]. For older adults, management must address comorbidities, polypharmacy risks, and age-related changes in drug metabolism. Low-dose, well-tolerated medications, alongside interventions such as gentle exercise programs and biofeedback, are preferred [394]. These tailored approaches ensure effective and safe TTH management across all age groups.

Emphasis on lifestyle modifications, education, and preventive strategies

Lifestyle modifications, education, and preventive strategies are essential in managing TTH across all age groups. Regular physical activity, adequate hydration, and healthy sleep hygiene reduce TTH frequency and severity [138]. Education on identifying triggers and stress management techniques, such as relaxation therapy and mindfulness, empowers patients to manage their headaches [398] actively. Preventive strategies, including ergonomic adjustments to minimize musculoskeletal strain and CBT to address psychosocial stressors, are particularly

effective in preventing TTH chronicity [399]. These individualized interventions complement pharmacological treatments, enhancing overall management outcomes.

Role of multidisciplinary approaches and individualized care plans

Lifestyle modifications, education, and preventive strategies are crucial for managing TTH across all age groups. Regular physical activity, proper hydration, and healthy sleep hygiene significantly reduce TTH frequency and severity [26]. Educating patients about trigger identification and stress management techniques, such as relaxation therapy and mindfulness, empowers them to actively manage their headaches [323]. Preventive strategies, including ergonomic adjustments to minimize musculoskeletal strain and cognitive behavioral therapy to address psychosocial stressors, effectively reduce the risk of CTTH [26]. These approaches complement other treatments and enhance patient outcomes.

Closing remarks

TTH is the most prevalent primary headache disorder, affecting individuals across all life stages with varying clinical characteristics and impacts. While often underestimated, TTH significantly affects HRQoL, productivity, and psychosocial well-being. Age-appropriate management is essential, from tailored diagnostic and lifestyle interventions in children to addressing polypharmacy and comorbidities in older adults. Gender/sex differences and lifestyle factors highlight the need for personalized, preventive approaches and patient education. Future research should focus on bridging knowledge gaps, understanding hormonal and psychosocial influences, and refining management strategies. A multidisciplinary, lifespan-focused approach can reduce the burden of TTH and improve HRQoL.

Underserved populations

Medically underserved populations (MUPs) are defined by the Health Resources and Services Administration (HRSA) as groups that lack sufficient primary care health services in specific geographic areas. Underserved populations may include various racial and ethnic groups, such as Latino, African American and Native American communities. This category also encompasses immigrants, refugees and migrants. Additionally, individuals with limited English proficiency, those with disabilities, as well as homeless and low-income individuals, are also considered part of these populations [400–402]. MUPs frequently encounter significant barriers to accessing essential healthcare services, which prevent them from obtaining the medical attention they require [401].

Individuals in underserved populations who experience headache disorders face significant barriers to accessing

healthcare [291]. Health disparities in headache medicine, particularly for patients with TTH, are influenced by various factors, including socioeconomic, limited access to qualified healthcare providers, cultural stigma, insufficient knowledge about headache management, geographic location of residence, lack of health insurance (underinsured or uninsured), as well as gender identity, sexual orientation considerations [403, 404]. These factors can significantly affect HRQoL by delaying diagnosis and treatment, resulting in CTTH and reduced productivity. Frequent ETTH and CTTH lead to substantial disability and negatively impact both individuals and society [405–407].

TTH frequently occurs alongside psychological conditions such as anxiety and depression, which can worsen the effects of the headache [408–410]. Despite its high prevalence, TTH is often underdiagnosed and poorly managed, particularly in underserved populations, who are at greater risk for chronicity and disability [411].

Socioeconomic and Insurance Status

In low- and middle-income countries, limited resources create significant challenges for both healthcare professionals and patients. Key issues include inadequate access to care, a lack of education and awareness about headache disorders, economic barriers to diagnosis and treatment, and insufficient health policies [291]. Patients from low socioeconomic backgrounds often lack proper education about primary headache disorders, resulting in ignorance or confusion regarding this common and debilitating condition [412, 413]. Low socioeconomic status is a recognized independent risk factor for poor health outcomes [414–416].

Several researches have shown that individuals with low socioeconomic status tend to suffer from more frequent headache attacks, have a greater risk of developing chronic headaches and experience a more significant impact from their headaches compared to those with higher socioeconomic status [417–419]. Psychological stress is often associated with low socioeconomic status and can both trigger and sustain TTH [420–422]. High levels of chronic stress are associated with more frequent and intense TTH attacks [423, 424]. Stress may exacerbate TTH by disrupting normal pain processing in individuals who experience these headaches [86, 425]. Both mental and cognitive stress, as well as daily stress, are associated with increased pain perception and can contribute to the development of headaches or intensify transient pain in TTH patients [426].

Uninsured and underinsured patients suffering from headaches encounter significant barriers in accessing appropriate treatment. This often results in delayed diagnoses, insufficient pain management and a reduced HRQoL due to the limitations imposed by their insurance

coverage [427]. Delays or ineffectiveness in treating TTH are linked to more frequent and severe headaches, as well as increased emotional burden [428].

Race and ethnicity

Race and ethnicity are closely linked to socioeconomic inequality [429]. For example, Black or African American, Hispanic or Latino and Native American individuals tend to have lower income and education levels, as well as higher rates of poverty and unemployment compared to White individuals [430].

African American and Hispanic populations have significantly lower rates of outpatient neurology visits and are less likely to have access to specialized care for headache management [431]. Additionally, African American individuals experience higher rates of neurology-related emergency department visits, inpatient hospitalizations, and hospitalization costs compared to White participants [432].

African American patients experience a higher frequency of headache days per month, greater headache intensity and lower HRQoL specifically related to headaches compared to White patients [433]. They also report more severe and disabling headaches. Despite facing more severe conditions in specialized care settings, African American patients are twice as likely to discontinue headache treatment at specialty clinics compared to their White counterparts, even after accounting for socioeconomic status [434]. Unfortunately, there is currently no data available on racial disparities in TTH.

Geographic barriers

Populations in rural and remote areas face significant barriers to accessing healthcare [186, 406]. These barriers include long distances to healthcare facilities, transportation difficulties, a lack of healthcare providers and limited healthcare services overall [435, 436]. Access to specialized healthcare is more limited in rural areas compared to urban regions [437]. Residents in rural areas often have limited access to headache specialists, resulting in longer wait times for appointments. Consequently, they may face a more significant loss of income due to the time taken off work to attend these visits [438]. Many healthcare providers lack adequate training in diagnosing or treating TTH [439]. This is especially true in underserved areas where TTH may go undiagnosed, resulting in suboptimal care that prolongs the burden on patients [406].

Closing remarks

Disparities in TTH management among underserved populations remain a significant public health concern. Socioeconomic disadvantage, limited healthcare access and cultural barriers exacerbate health inequities,

contributing to delayed diagnoses and suboptimal treatment outcomes. Community-driven healthcare models, such as telehealth systems, mobile clinics and culturally tailored intervention programs, may help address these challenges by directly meeting the specific needs of these populations [400, 401].

Integrating headache management into primary healthcare settings represents another crucial strategy for reducing disease burden. Given that primary care services are often the first point of contact for many individuals, including those in underserved populations, embedding standardized headache assessment protocols in these settings could facilitate early diagnosis and intervention, thereby reducing the risk of chronification [291].

Additionally, increased funding for headache research in underrepresented populations, equitable distribution of healthcare resources and greater representation of diverse populations in clinical trials should be prioritized [431, 432]. Future research should further examine the role of social determinants of health in the TTH burden, emphasizing interdisciplinary approaches that integrate neurological, psychological and public health perspectives. By addressing these critical factors, healthcare systems can move toward a more equitable and effective framework for managing TTH in underserved populations, ultimately reducing the long-term burden on both healthcare systems and affected individuals.

Conclusion

TTH is the most prevalent primary headache disorder, affecting approximately 2.1 billion people worldwide. However, it remains under-recognized and insufficiently studied compared to migraine. This review underscores the multifactorial pathophysiology of TTH. Evidence from neuroimaging and neurophysiology consistently points to alterations in brain regions involved in pain modulation, particularly the ACC and insula, which may underlie the transition from episodic to chronic subtypes. Central sensitization and impaired descending pain inhibition are core mechanisms, while peripheral factors such as myofascial pain and muscle tenderness contribute to symptom persistence. Electrophysiological data further support that sensitization may be confined to the brainstem rather than involving cortical structures. Unlike migraine, TTH appears to have limited involvement of CGRP and vascular mechanisms, except in subgroups with overlapping features.

The frequent coexistence of psychiatric, musculoskeletal, and sleep-related comorbidities further complicates disease expression and underscores the need for an integrated, multidisciplinary management approach. Although non-pharmacological strategies, including neuromodulation, CBT, and lifestyle interventions, show promising outcomes, the current evidence base remains

limited, with few high-quality studies focusing specifically on TTH. These findings highlight the importance of age-specific tailoring of both pharmacological and non-pharmacological interventions in the management of TTH.

Critically, the diagnostic boundaries of TTH remain a major obstacle to both clinical practice and research. The current ICHD-3 criteria may fail to distinguish TTH from mild migraine or overlapping headache phenotypes, particularly in individuals with fluctuating or mixed features. The strict diagnostic criteria, while enhancing specificity, resulted in limited sensitivity and may inadvertently exclude large subsets of patients with clinically meaningful headache burden. Future editions of the International Classification of Headache Disorders (ICHD-4) must address these shortcomings by incorporating a more flexible diagnostic hierarchy that reflects real-world clinical presentations. Beyond improving clinical practice, an optimized diagnostic framework would also facilitate the standardization of research protocols, enabling more meaningful comparisons across studies. With more precise diagnostic boundaries, it will become feasible to conduct large-scale, longitudinal investigations to clarify disease trajectories, identify biologically distinct endophenotypes, and delineate treatment-responsive subgroups. Ultimately, a more precise and operationalized classification system will pave the way for developing objective biomarkers and support the broader goal of enhancing diagnostic accuracy and personalizing treatment strategies in TTH.

In conclusion, TTH is a heterogeneous and under-prioritized condition that significantly burdens individuals and healthcare systems. Refined diagnostic criteria, expanding mechanistic research, and developing evidence-based, individualized interventions are essential to advance the science and care of TTH.

The Hallmarks of Primary Headache trilogy thus completes the second stage of its journey with Tension-Type Headache. Let's keep moving forward in this direction.

Abbreviations

5-HT	5-hydroxytryptamine
5-HT _{2A}	5-hydroxytryptamine receptor 2 A
5-HTP	5-Hydroxytryptophan
5-HTTLPR	5-HTT-gene-linked polymorphic region
ACC	anterior cingulate cortex
AD	axonal diffusivity
AH	arterial hypertension
ALFF	amplitude of low-frequency fluctuations
ATP	adenosine 5'-triphosphate
CBT	cognitive-behavioral therapy
CGRP	calcitonin gene-related peptide
CI	confidence interval
CNS	central nervous system
COMT	encoding catechol-O-methyltransferase
COX-1	cyclooxygenase 1
COX-2	cyclooxygenase 2
CT	computed tomography scan
CTTH	chronic tension-type headache

DNIC	diffuse noxious inhibitory control
DTI	diffusion tensor imaging
ED	emergency department
EFNS	European Federation of Neurological Societies
EMG	electromyographic/electromyography/electromyogram
ES	exteroceptive suppression
ETTH	episodic tension-type headache
fALFF	fractional amplitude of low-frequency fluctuations
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GABA	glutamate and gamma-aminobutyric acid
GMD	gray matter density
GMV	gray matter volume
GTN	glyceryl trinitrate
GWAS	genome-wide association study
HADS	Hospital Anxiety and Depression Scale
HDI	Headache Disability Inventory
HIT-6	6-item Headache Impact Test
HNCS	heterotopic noxious conditioning stimulation
HPA	hypothalamic-pituitary-adrenal
HRQoL	health-related quality of life
HRSA	Health Resources and Services Administration
IASTM	instrument-assisted soft tissue mobilization
ICHD-3	The International Classification of Headache Disorders, 3rd edition
IL-1β	interleukin-1 beta
IL-6	interleukin-6
LEP	laser-evoked potential
MC	moderate confidence
MD	mean difference
MIDAS	Migraine Disability Assessment Scale
MOH	medication-overuse headache
MSG	monosodium glutamate
MUP	Medically underserved population
NE	norepinephrine
NO	nitric oxide
NOS	nitric oxide synthase
NSAID	nonsteroidal anti-inflammatory drug
ONS	occipital nerve stimulation
OR	odds ratio
PAG	periaqueductal gray
PCC	posterior cingulate cortex
PNS	peripheral nerve stimulation
PPT	pain pressure threshold
QoL	quality of life
RCT	randomized controlled trial
ReHo	regional homogeneity
rNMS	repetitive neuromuscular magnetic stimulation
ROC	receiver operating characteristic
rsFC	resting-state functional connectivity
rTMS	repetitive transcranial magnetic stimulation
RVM	rostral ventromedial medulla
SF-36	36-Item Short Form Survey
SMD	standardized mean difference
SNS	supraorbital nerve stimulation
SSRI	selective serotonin reuptake inhibitor
STR	soft tissue release
SUCRA	surface under the cumulative ranking curve
TCD	transcranial Doppler ultrasound
tDCS	transcranial direct current stimulation
TENS	transcutaneous electrical nerve stimulation
TMS	transcranial magnetic stimulation
TNF-α	necrosis factor-alpha
TTH	tension-type headache
TTS	total tenderness score
WHODAS	World Health Organization Disability Assessment Schedule
WHOQOL-8	World Health Organization Quality of Life 8-question scale
WMH	white matter hyperintensity
WPAI	Work Productivity and Activity Impairment
YLDs	years lived with disability

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Shuu-Jiun Wang planned the study and drafted Discussion section. Paolo Martelletti planned the study, drafted discussion section, and supervised the whole manuscript. Li-Ling Hope Pan and Yu-Hsiang Ling collected the entire body of the manuscript and drafted Introduction and Genetic Basis sections. The remaining authors drafted sections of the manuscript, in detail: Jr-Wei Wu and Yonggang Wang (Neuroimaging in TTH), Fu-Jung Hsiao and Gianluca Coppola (Neurophysiological Aspects of TTH), Adriana Della Pietra and Tissa Wijeratne (Molecular Basis), Kristin Sophie Lange and Bianca Raffaelli (Central Mechanisms), David Garcia Azorin and Chia-Chun Chiang (Peripheral Mechanisms), Linda Al-Hassany and Tsubasa Takizawa (Vascular Factors), Fatemeh Farham and Esme Ekizoglu (Comorbidities of TTH), Min Kyung Chu and Woo-Seok Ha (Neuromodulation), Charl Els and Sebastian Straube (Occupational Medicine, Cognitive Behavioral Therapy, and Mindfulness), Ellina Lytvyak and Zhao Dong (Lifestyle Management, Diet, and Nutraceuticals), Surat Tanprawate and Dilara Onan (Exercise, Physical Therapy, and Patient Education), Alejandro Labastida-Ramirez and Wei-Ta Chen (Acute Treatment), Lanfranco Pellesi and Soo-Jin Cho (Preventive Treatment), Marta Waliszewska and Byung-Kun Kim (Prognosis), Alberto Raggi and Ryotaro Ishii (Psychosocial Impact of TTH), Derya Uğurlu Uludüz and Najib Kissani (Economic Impact of TTH), Laura Papetti and Aynur Ozge (TTH in Population Throughout Life Span), Sophie Merve Onerli Yener and Kiratikorn Vongvaivanich (Underserved Populations).

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