Tension-type headache: current research and clinical management

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Tension-type headache (TTH) is the most common form of headache, and chronic tension-type headache (CTTH) is one of the most neglected and difficult types of headache to treat. The pathogenesis of TTH is multifactorial and varies between forms and individuals. Peripheral mechanisms (myofascial nociception) and central mechanisms (sensitisation and inadequate endogenous pain control) are intermingled: the former predominate in infrequent and frequent TTH, whereas the latter predominate in CTTH. Acute therapy is effective for episodes of TTH, whereas preventive treatment—which is indicated for frequent and chronic TTH—is, on average, not effective. For most patients with CTTH, the combination of drug therapies and non-drug therapies (such as relaxation and stress management techniques or physical therapies) is recommended. There is clearly an urgent need to improve the management of patients who are disabled by headache. This Review summarises the present knowledge on TTH and discusses some of its more problematic features.

Introduction

Tension-type headache (TTH) is an ill-defined and heterogeneous syndrome, which is diagnosed mainly by the absence of features found in other headache types, such as migraine. TTH is, thus, a featureless headache that is characterised by nothing more than a pain in the head. The term tension-type was coined by the first Classification Committee of the International Headache Society[1] to provide a new heading that underlines the uncertain pathogenesis but, nevertheless, indicates that some kind of mental or muscular tension might have a causative role. Because the exact pathogenesis is unknown, the term tension-type has been maintained in the 2nd edition of the International Classification of Headache Disorders (ICHD-II),[2] although it is commonly called "tension headache".

TTH is the most common form of headache but receives much less attention from health authorities, clinical researchers, or industrial pharmacologists than migraine does, owing to the fact that most people with infrequent or frequent TTH do not consult a doctor but treat themselves, if necessary, with over-the-counter analgesics. However, chronic TTH, defined as headache that occurs on 15 days or more per month, is a major health problem with enormous socioeconomic effects.

The exact causes of TTH are still unknown; peripheral myofascial mechanisms and central dysregulation of pain processing structures are implicated but their relative weight in the pathogenesis of TTH varies with the frequency of headache and among patients. There are no helpful investigations that diagnose TTH; therefore, the definition relies exclusively on clinical symptoms, which are less distinct than the symptoms of migraine. Because of the lack of disease-specific features, several secondary headaches—headaches known to be caused by another disorder—can present as TTH.

Despite the meagre scientific foundations with regard to the mechanisms of and treatments for TTH, patients can be managed with some success, although there have been no recent major therapeutic breakthroughs.

***Panel 1:* Tension-type headache (episodic form)—general diagnostic criteria (B–E)**

B Headache lasting from 30 min to 7 days

C At least two of the following pain characteristics:
1 Bilateral location
2 Pressing or tightening (non-pulsating) quality
3 Mild or moderate intensity
4 Not aggravated by routine physical activity, such as walking or climbing stairs

D Both of the following:
1 No nausea, vomiting (anorexia can occur)
2 No more than one of photophobia or phonophobia

E Not attributed to another disorder

From the 2nd edition of the International Classification of Headache Disorders (ICHD-II).[2]

Classification and diagnostic features

Compared with the first International Headache Society classification, the general diagnostic criteria for TTH in ICHD-II are almost the same (panel 1); the only change is the subdivision of TTH into three groups that differ by frequency of headache, with the division into episodic and chronic subtypes being useful. The chronic subtype causes greatly decreased quality of life, high disability, and substantial socioeconomic costs; however, within this subgroup, disability and, probably, pathophysiology differ between people who have occasional episodes and people who have frequent episodes of TTH. In ICHD-II, episodic tension-type headache was subdivided further into an infrequent subtype—less than one headache per month—and a frequent subtype (panel 2). The infrequent subtype has little effect on the patient, whereas patients with frequent headaches can have considerable disability that sometimes requires expensive drug or non-drug treatments.

Under the diagnostic criteria for TTH, patients coded for episodic TTH might include some patients who have a mild form of migraine without aura. Clinical

experience favours this suspicion, particularly in patients who also have migraine attacks. Some patients who present with TTH can have the pathophysiological features that are usually seen in migraine.[3] Moreover, people in the general population who are classified as having TTH can have clinical features that suggest migraine of substantial proportions.[4] In children more so than adults, the symptoms of migraine and TTH occur simultaneously.[5] In the Spectrum study, which investigated the efficacy of sumatriptan—a 5-$HT_{1B/D}$ receptor agonist—for the whole range of headaches in patients with migraine, 71% of patients who were initially diagnosed with episodic tension-type headache (ETTH) had their diagnosis changed to migraine or migrainous headache after review of their diary by the investigators.[6] Because a substantial proportion of patients with TTH present with atypical symptoms, ETTH can be difficult to distinguish from migraine without aura (ICHD-II, code 1·1) or structural brain disease.[7,8] The diagnosis of chronic tension-type headache (CTTH) is straightforward in most cases if the patient has the headache for long enough, although some patients can have migrainous features.[3–9]

A proposal for new, stricter diagnostic criteria is published in the appendix of ICHD-II (panel 3). The new criteria recommends, for future studies, the comparison of patients diagnosed in accordance with the standard criteria with others diagnosed in accordance with the criteria in the appendix for the clinical features and also the pathophysiological mechanisms and responses to treatments.

Many patients with CTTH overuse acute medication, such as combination analgesics. When this fulfils criterion B (dose and duration of substance intake) for any of the subforms in ICHD-II, the default rule is to code for probable CTTH and medication-overuse headache. When these criteria are still fulfilled after medication overuse has ceased, chronic TTH should be diagnosed and the diagnosis of medication-overuse headache discarded;[10] however, if the criteria are no longer fulfilled because the patient improves, medication-overuse headache should be diagnosed and the diagnosis of CTTH discarded.

In most patients, TTH develops from the episodic form to the chronic form.[10] However, if the headache unambiguously fulfils the CTTH criteria A–E, occurs daily, and is unremitting after 3 days from first onset, the patient can be diagnosed, according to ICHD-II criteria, with daily-persistent headache, which is another heterogeneous entity.

Epidemiology

In a population-based study, the lifetime prevalence of TTH was 79%, with 3% of patients experiencing CTTH (ie, headache on ≥15 days per month).[11] The prevalence of TTH seems to be higher in women, and declines with age in both sexes.[12] In a recent epidemiological study with a mailed questionnaire,[13] the 1-year prevalence of TTH in a 40 year old in the general population was 48·2% for infrequent ETTH, 33·8% for frequent ETTH, and 2·3% for chronic TTH.

In a longitudinal study from birth to age 26, the 1-year prevalence at age 26 was 11·1% for TTH compared with 3·2% for migraine and 4·3% for combined headache.[14]

In specialised headache clinics, the proportion of patients diagnosed with TTH varies but can reach 25%.[15]

Panel 2: Tension-type headache—specific diagnostic criteria

2·1 Infrequent episodic tension-type headache

A At least 10 episodes that occur on less than 1 day per month (less than 12 days per year) that fulfil criteria B–D

2·2 Frequent episodic tension-type headache

A At least 10 episodes that occur on one or more days per month but less than 15 days per month for at least 3 months (12 or more days and less than 180 days per year) that fulfil criteria B–D

2·3 Chronic tension-type headache

A Headache that occurs on 15 or more days per month, on average for more than 3 months (180 or more days per year) that fulfils criteria B–D

B Headache that lasts hours or may be continuous

C Both of the following:

1 No more than one of photophobia, phonophobia, or mild nausea

2 Neither moderate or severe nausea nor vomiting

2·4 Probable tension-type headache

A Episodes that fulfil all but one of criteria A–D for 2·1, 2·2, or 2·3

B Episodes that do not fulfil criteria for 1·1 (migraine without aura)

C Not attributed to another disorder

From the 2nd edition of the International Classification of Headache Disorders (ICHD-II).[2]

Panel 3: Proposal for stricter diagnostic criteria for TTH

B Headache lasting from 30 min to 7 days

C At least three of the following pain characteristics:

1 Bilateral location

2 Pressing or tightening (non-pulsating) quality

3 Mild or moderate intensity

4 Not aggravated by routine physical activity such as walking or climbing stairs

D No nausea, vomiting (anorexia can occur), photopobia, or phonophobia

E Not attributed to another disorder

From the 2nd edition of the International Classification of Headache Disorders (ICHD-II) appendix A2.[2]

Pathophysiology

Whether the pain in TTH originates from myofascial tissues or from central mechanisms in the brain is still a matter for debate. Research progress is hampered by the difficulty in obtaining a homogeneous population of patients, owing to the lack of specificity of clinical features and diagnostic criteria. Nonetheless, the present consensus is that peripheral pain mechanisms most

probably have a role in infrequent ETTH and frequent ETTH, whereas central dysnociception is predominant in chronic TTH.

Myofascial factors

Muscle activity and metabolism

The level of electromyograph activity in the pericranial muscle is, on average, higher in patients with CTTH than in healthy controls.[16] However, the difference is rarely observed if only a few muscles are investigated, and there is no association between electromyograph readings and the presence or intensity of headache.[3] As a corollary, increased hardness of the pericranial muscles has been observed in patients with CTTH but there is little asssociation between hardness and intensity of headache.[17] In one study, injections of botulinum toxin led to decreased temporalis electromyography readings in patients with CTTH after 12 weeks but no decrease in the headache.[18] During rest or exercise, the concentrations of lactate in the trapezius muscle did not differ between patients with CTTH and healthy volunteers;[19] however, the exercise-induced increase in blood flow to the trapezius muscle was blunted in patients with CTTH, which was interpreted as increased sympathetic vasoconstriction due to hyperexcitability of the CNS neurons.[20] Also, there was no increase in inflammatory mediators at tender points in the trapezius muscle in patients with CTTH.[21]

As seen in a recent MRI study,[20] the relative cross-sectional area (rCSA) of the minor and major rectus capitis posterior muscles was reduced in patients with CTTH, whereas the rCSA of the semispinalis and splenius capitis muscles was normal. The reduction in rCSA was negatively associated with the intensity, duration, and frequency of headache. Whether the atrophy of deep neck muscles that is seen in patients with CTTH is primary or secondary to the headache remains to be determined.

Taken together, these studies do not favour increased activity, muscular inflammation, or disturbed metabolism of the pericranial muscles as important pathogenic factors in CTTH.

Tenderness and pain thresholds

The role of myofascial factors in TTH has been investigated by assessment of pericranial tenderness on manual palpation or pain detection and tolerance thresholds with a pressure algometer. The results obtained with these methods are not similar, for methodological reasons. Pressure pain thresholds are usually recorded from one or two locations on the cranium, mainly the anterior temporal region, which is a precise spot that has low tenderness on manual palpation in patients with TTH.[22] Tenderness scores on manual palpation are usually the sum of scores from several pericranial locations. There is, nonetheless, a substantial inverse relation between local tenderness and pressure pain thresholds.[23–27]

Tenderness on manual palpation is assessed over seven or eight locations on both sides of the cranium. Pain is scored between 0 and 3, and the scores are summed to obtain a total tenderness score, which has been proved to be reliable.[28] Pericranial tenderness is increased during headache-free intervals[22,29] and increases further as the headache persists[30] in most patients with TTH. Nevertheless, a recent study reported normal pericranial neck and shoulder tenderness in a large group of 12-year-old children from Finland with TTH.[31] In a cross-sectional population study, the increase in the prevalence of TTH between 1989 and 2001 was associated with an increase in sensitivity to pericranial pain, particularly in women.[32]

Bendtsen and co-workers[33] described an abnormal, linear stimulus–response curve for pressure versus pain recorded in the temporalis muscle in patients with CTTH that was associated with the degree of tenderness. A similar abnormality was seen in patients with fibromyalgia.[34] This qualitatively altered response could be caused by activity in low-threshold mechanosensitive afferent nerves, which do not normally mediate pain[33–35] but have a similar linear stimulus–response function. Central sensitisation after strong peripheral nociceptive input can unmask previously ineffective synapses and lead to new effective contacts between low-threshold mechanosensitive afferent nerves and superficial, dorsal horn, nociceptive neurons that normally receive input from high-threshold mechanoreceptors.[36–37] Therefore, the qualitatively altered nociception from tender muscles in patients with chronic myofascial pain was deemed most likely to be due to central sensitisation of second-order nociceptors.

Myofascial trigger points are defined as hyperirritable spots that are associated with a taut band in a skeletal muscle.[38] They are painful when compressed and stretched and usually give rise to a typical pattern of referred pain. Active myofascial trigger points are a cause of clinical symptoms, such as referred pain and restricted motion of the affected tissues, whereas latent myofascial trigger points might not be an immediate source of pain but can lead to dysfunctions in other muscles, such as fatigue and restricted range of motion. More active or latent myofascial trigger points were found in patients with TTH than in healthy people in a non-blinded study.[39] This was confirmed in a series of blinded controlled studies, in which myofascial trigger points were assessed in patients with ETTH or CTTH and were associated with the usual headache pattern, neck mobility, forward head posture, and severity of the disorder.[40–45] Neck mobility and forward head posture were ameliorated after a 3-week course of physical therapy but, surprisingly, they were not associated with any headache parameter or with treatment outcome. These results confirm that myogenic referred pain caused by active myofascial trigger points in the head, neck, and shoulder muscles might contribute to patterns of head pain in patients with TTH, and that persistent peripheral sensitisation in

active myofascial trigger points could lead to sensitisation of second-order nociceptive neurons in the spinal trigeminal nucleus.[46]

Pressure pain thresholds, as determined with an algometer, are decreased on average in patients with CTTH[47] but the difference in pressure pain thresholds compared with healthy volunteers is less pronounced than the pressure pain thresholds for manual palpation. In patients with ETTH, pressure pain thresholds at cephalic sites are not different from those in healthy controls.[22,26,27,48,49] Pressure pain thresholds in CTTH were also abnormal at extracephalic sites, for example at the Achilles tendon,[47] in paravertebral muscles,[7] or in the fingers,[23] which is more evidence that diffuse disruption of the central pain-modulating systems is one of the pathophysiological hallmarks of CTTH. Pressure pain thresholds are lower in the cranium than in the extremities,[49] which might explain why a general reduction of pain thresholds (increased sensitivity) can result in head pain without pain in the rest of the body.[50]

In fibromyalgia, pressure pain thresholds are unchanged or decrease during isometric muscle contraction, which contrasts with the clear increase in pressure pain thresholds in healthy controls, and this finding favours central sensitisation.[51] We have shown that the same abnormal contraction-induced variation in pressure pain thresholds is seen in patients with CTTH at the level of the temporalis muscle and in patients with CTTH and fibromyalgia at the temporalis and forearm extensor muscles, which suggests sensitisation of the second-order trigeminal nociceptors in the former, and sensitisation of the trigeminal and spinal second-order nociceptors or sensitisation of third-order thalamic nociceptors in the latter.[52–53]

After injections of algogenic substances into the trapezius muscles, patients with ETTH report substantially more local pain than healthy controls do, but none of the patients with ETTH developed headache.[54] The results of concomitant psychophysical measures indicate that peripheral sensitisation of the myofascial sensory afferent nerves is responsible for the muscular hypersensitivity in these patients.[55] The results of these studies suggest that temporal or spatial summation of peripheral stimuli, or both, might have a role in people predisposed to the mechanisms of ETTH.

Sensitivity to electrical stimuli was investigated in a recent study,[56] which compared suprathreshold single and repetitive (2 Hz) stimulations of muscle and skin in cephalic (temporal and trapezius muscles) and extracephalic (anterior tibial muscle) regions. The results favoured a generalised increase in pain sensitivity (generalised hyperalgesia) in patients with CTTH, which suggests that pain processing in the CNS is abnormal. The results also indicated that suprathreshold stimuli are more sensitive than pain thresholds for the evaluation of generalised pain perception.

Nociceptive reflexes and pathways

Brainstem reflexes are a non-invasive means to investigate the central processing of sensory information from the cephalic region, whereas the flexion reflex in the biceps femoris muscle after electrical stimulation of the sural nerve is a spinally mediated nociceptive reflex. Both reflexes have been extensively investigated in patients with TTH.

Exteroceptive silent periods in the temporalis muscle

Painful stimuli in the trigeminal region induces two successive suppressions of voluntary activity, as seen on electromyography, in the jaw-closing muscles (temporalis and masseter), called ES1 and ES2, and mediated respectively by oligosynaptic and polysynaptic interneuronal brainstem circuits.[57] The second temporalis exteroceptive silent period (ES2) was absent or reduced in patients with CTTH in some groups,[58–63] which led to the hypothesis that inhibitory interneurons[58] might be inadequately activated because of a dysfunction in the descending control from the limbic system (periaqueductal grey, amygdala, hypothalamus, and orbitofrontal cortex) through the nucleus raphe magnus. In patients with ETTH, the duration of ES2 is normal.[60–62] Although recent studies have confirmed the reduction in the duration of ES2 in patients with CTTH,[64–65] the duration of ES2 was normal in patients with CTTH in several other studies,[66–70] and the laser-evoked early suppression in the temporalis muscle was also normal.[65] Such discrepancies could be method-related or patient-related.[71] The results of the pharmacological modulation of ES2 suggest that the inhibitory interneurons that mediate the duration of ES2 are inhibited by serotoninergic pathways and activated by nicotinic cholinergic mechanisms.[72] The theory is partly supported by the finding[69] that amitriptyline, which blocks serotonin reuptake, reduces the duration of ES2 in patients with CTTH.

Injection of hypertonic saline[73]or nerve growth factor[74] into the neck muscles of mice has been proposed as a means to study TTH in animals because such interventions induce long-term potentiation of the jaw-opening reflex. The exteroceptive silent period in jaw-closing muscles, which is the counterpart to the jaw-opening reflex, would also be expected to increase in this model; however, this is a hallmark of migraineurs and not of patients with TTH.[58]

Blink reflex

Studies of the blink reflex, which is mediated by bulbo–pontine excitatory interneurons, have been of little use to understand the pathogenesis of TTH. The positive association between R1 latency and disease duration in patients with TTH[75] might indicate that hypoactivity of brainstem neurons can develop over time. Normal R2 amplitude and area have been reported in patients with TTH.[70,75–77] The R2 recovery cycle after double supraorbital stimulation was decreased in patients with TTH, which

suggests reduced excitability of excitatory brainstem interneurons.[70]

A concentric electrode that delivers topical, high-density current has been developed to activate more selectively the Aδ nociceptive fibres and better identify the nociception-specific component of the R2 blink reflex;[78] however, up to now, it has mainly been used in patients with migraine.

Biceps femoris flexion reflex

Lower thresholds of the nociceptive flexion reflex and lower pressure pain thresholds were seen in patients with CTTH than in controls.[79–80] The slope of the stimulus intensity or visual analogue scale pain rating response curve was also steeper in patients with CTTH. These findings might be explained by the dysfunction of endogenous antinociceptive systems and reduced tone and recruitment of descending inhibitory control.

Laser-evoked nociceptive potentials

Cortical potentials (P2 component) evoked by supraorbital laser heat stimulation have increased amplitude in patients with CTTH, whereas heat pain thresholds are normal in these patients.[81] The increase is proportional to the increase in the total pericranial tenderness score and is attenuated after treatment with amitriptyline.[82]

Structural brain changes

Schmidt-Wilcke and co-workers found significant decreases in tissue mass, using MRI voxel-based morphometry, in several brain areas in the pain matrix in patients with CTTH.[83] The decrease was not seen in patients with medication-overuse headache. Although CTTH and medication-overuse headache share a common clinical feature—frequent, almost daily, head pain—the underlying pathophysiology can differ substantially. Reduced density of the cortical grey matter was first seen with MRI voxel-based morphometry in patients with chronic low back pain.[84] Similar changes were seen in the upper brainstem of patients with chronic lower back pain[85] and with phantom limb pain.[86] The precise significance of this tissue atrophy is not known but it might be due to excessive chronic activation of the structures involved.[84] The voxel-based morphometry brainstem findings in patients with CTTH contrast with the increased tissue densities found in the upper brainstem in patients with migraine, who have hyperintense, deep white matter lesions on MRI.[87]

Neurotransmitters

Nitric oxide

Glyceryl trinitrate, a nitric oxide donor, induces an immediate headache, which is thought to be due to vasodilatation, and a delayed typical migraine attack in patients with migraine.[88] In patients with CTTH, glyceryl trinitrate also produces an immediate headache and, after several hours, a typical tension-type headache.[89] The immediate headache is not accompanied by an increase in pericranial tenderness[90] but it might be associated with endogenous production of nitric oxide and sensitisation of perivascular sensory afferent nerves.[91] The co-occurence implies that, similar to migraine, CTTH might be associated with central supersensitivity to nitric oxide; this theory is supported by the reduction of headache and muscle hardness after giving an inhibitor of nitric oxide, such as L-NG-monomethyl arginine citrate (L-NMMA).[92–93]

Neuropeptides

Calcitonin-gene-related peptide (CGRP) is a neurotransmitter that is active in the trigeminovascular system; plasma concentrations of CGRP are raised during migraine and cluster headache attacks.[94] In patients with CTTH, plasma concentrations of CGRP are healthy, irrespective of the headache state, and do not increase after giving glyceryl trinitrate.[95] However, in patients with CTTH with a pulsating pain, plasma concentrations of CGRP are raised interictally.[96] Certain patients who fulfil the International Headache Society criteria for TTH might, therefore, have headaches that are pathophysiologically related to migraine, if their headache has a pulsating quality.

Plasma concentrations of substance P, neuropeptide Y, and vasoactive intestinal peptide in the cranial and the peripheral circulation do not differ between patients with CTTH and healthy people, and the concentrations are unrelated to the presence or absence of headache.[97] In patients with ETTH, higher concentrations of substance P were found in the platelets, and lower concentrations of β-endorphin were found in peripheral blood mononuclear cells;[98] the concentrations of substance P and β-endorphin were inversely related, and pressure pain thresholds were negatively associated with the concentrations of substance P. A study that compared patients with migraine and patients with TTH found that the latter were characterised by low platelet and high plasma met-enkephalin concentrations, whereas the opposite was true in migraineurs.[99] Increased concentrations of met-enkephalin were found in the CSF of patients with CTTH,[100] which further supports the hypothesis that there is an imbalance between pronociceptive and antinociceptive mechanisms in this disorder.

Serotonin (5-HT)

The results of studies of 5-HT metabolism in patients with TTH are, in part, contradictory but tend to show increased 5-HT turnover, which is opposite to the findings in migraine. Plasma and platelet 5-HT concentrations are raised in patients with ETTH, whereas peripheral 5-HT metabolism seems to be normal in patients with CTTH.[101–102] Other groups, however, have reported decreased concentrations of 5-HT in the platelets of patients with ETTH.[98,103–104] Uptake of 5-HT in the platelets was decreased in patients with ETTH but healthy in

patients with CTTH. Plasma 5-HT concentrations increased during a headache attack in a mixed group of patients (ETTH and CTTH)[105] and a negative correlation was found between plasma 5-HT concentrations and headache frequency.[102] Growth hormone and prolactin secretion was blunted in patients with CTTH in response to subcutaneous injections of sumatriptan,[106] which was thought to indicate reduced sensitivity of the hypothalamic 5-HT1_D serotonin receptors. The results of two independent studies suggest that sumatriptan, the 5-HT$1_{B/D}$ serotonin agonist that is highly effective for acute migraine attacks, might also be effective in patients with TTH.[107–109] Moreover, the results of a large study of migraineurs showed that mild headaches, which phenotypically resembled TTH, responded to oral sumatriptan.[109]

Psychological studies

Emotional disturbances have been implicated as risk factors for TTH; stress and mental tension are the most common factors that cause TTH,[110,111] and a positive association between headache and stress has been shown in patients with TTH.[112]

There is evidence that chronic recurrent headache, mainly CTTH, is associated with an increase in the frequency and severity of minor life events and so-called daily hassles.[113]

With Cloninger's tridimensional personality questionnaire, Di Piero and co-workers[114] found significantly higher scores for harm avoidance in patients with TTH, which is thought to indicate serotoninergic transmission. By contrast, if patients with migraine also scored high on harm avoidance, they had a significantly lower score in the novelty seeking (dopaminergic) criteria and a higher score in the persistence (glutamatergic) criteria.

Several investigators[115] have reported increased scores on depression scales in patients with CTTH but not overt depression, although it is difficult to determine whether the depressive mood is primary or secondary in these patients. However, the finding that patients who have headache and are depressed are more vulnerable to headache induced by a laboratory stressor has pathological relevance.[116]

Genetics

Genetic epidemiological studies of people with TTH in the general population or in twin pairs report an increased genetic risk of CTTH[117] but not ETTH.[118] The genetic risk of ETTH was confirmed in a study of 11199 twin pairs, in whom the genetic influence was found for frequent ETTH but not for infrequent ETTH; no firm conclusion could be drawn for CTTH because of the small number of affected individuals.[119]

Genotype results are sparse for patients with TTH. Both increased harm avoidance scores and the prevalence of homozygosity for the short allele of the 5-H transporter-gene-linked polymorphic promoter region (5-HTTLPR) were found in Korean patients with CTTH,[120] and both findings were more pronounced in patients with medication overuse.[121] These results are intriguing but need to be replicated. Indeed, in the general Korean population, the 5-HTTLPR short allele is not associated with harm avoidance,[122] and in a meta-analysis, the 5-HTTLPR short allele had a significant association with neuroticism but a non-significant association with harm avoidance.[123]

Harm avoidance is an anxiety-related personality trait that has been linked to a locus on chromosome 8p21,[124,125] which, to the best of our knowledge, has not yet been investigated in patients with TTH.

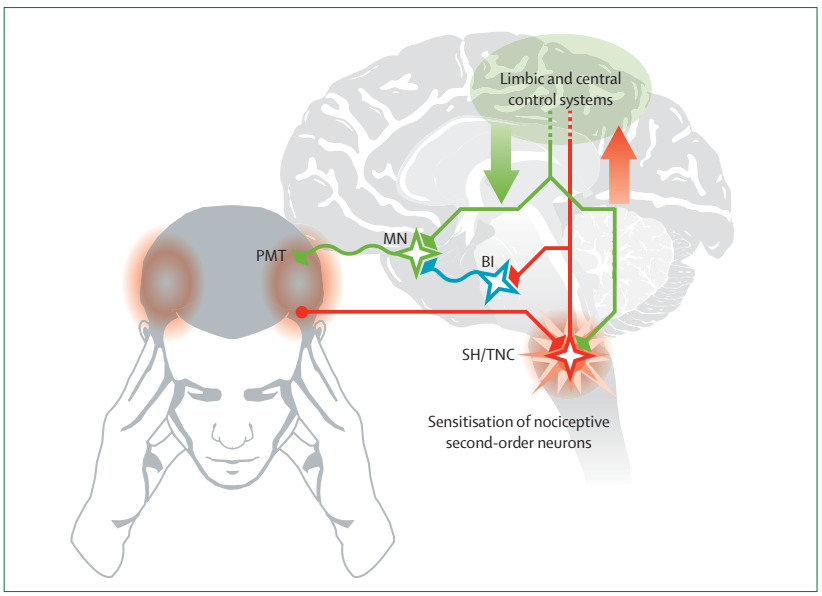

Figure 1: **A model for the pathophysiology of CTTH**
The nociceptive input from pericranial myofascial tissues (red lines) is increased for unknown reasons, which results in plastic changes (sensitisation of nociceptive second-order neurons) in the spinal dorsal horn (second and third cervical segments) and trigeminal nucleus. The nociceptive input to the supraspinal structures will, therefore, be considerably increased, which might result in increased excitability of supraspinal neurons and decreased inhibition or increased nociceptive transmission in the spinal dorsal horn and trigeminal nucleus (green lines). The central neuroplastic changes can also increase the drive to motor neurons, both at the supraspinal and at the segmental levels, which results in slightly increased muscle activity and in increased muscle hardness. PMT=pericranial myofascial tissue. BI=brainstem interneurons. MN=motor nuclei. SH/TNC=spinal horn and trigeminal nucleus caudalis. Figure adapted with permission from Lippincott, Williams and Wilkins and Blackwell Publishing.[126,127]

A model for TTH pathogenesis

The various pathophysiological abnormalities of TTH, and the differences between TTH types, led to the proposal of a model of TTH as a working hypothesis (figure 1).[126,127]

TTH might result from the interaction between changes in the descending control of second-order trigeminal brainstem nociceptors and interrelated peripheral changes, such as myofascial pain sensitivity and strain in the pericranial muscles. An acute episode of ETTH can occur in people who are otherwise perfectly healthy, and episodes can be brought on by physical stress, usually combined with psychological stress, or by non-

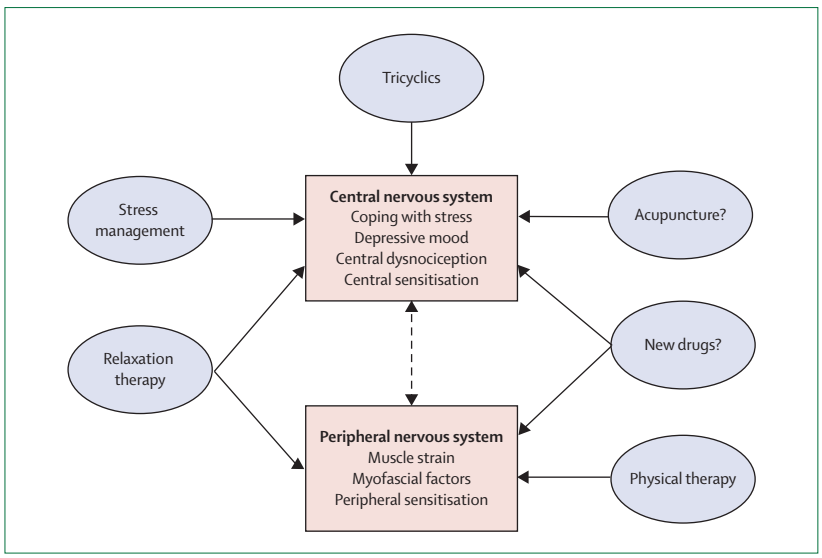

Figure 2: **Putative pathophysiological targets of preventive therapies for TTH**
Adapted with permission from Elsevier.[130]

physiological working positions. In such cases, increased nociception from strained muscles might be the primary cause of the headache, possibly favoured by a central temporary change in pain control due to stress. Emotional mechanisms increase muscle tension through the limbic system and, at the same time, reduce tone in the endogenous antinociceptive system. With more frequent episodes of headache, central changes become increasingly important. Long-term potentiation or sensitisation of nociceptive neurons and decreased activity in the antinociceptive system gradually lead to CTTH; these central changes probably predominate in frequent ETTH and CTTH. The relative importance of peripheral and central factors might, however, vary between patients and over time in the same patient. Genetic components are likely to promote the psychological and central changes that lead to CTTH, whereas environmental factors are the main cause in ETTH.

This model explains why TTH is pathophysiologically related to other functional pain disorders in which peripheral myofascial and central factors interact, such as fibromyalgia[128] and regional myofascial pain.

The pathogenic models that propose that TTH and migraine are the opposite ends of a phenotypic spectrum of the same disorder[129] are unlikely to apply to most patients with TTH. Although these models might apply to patients with migraine who also present with tension-type-like interval headaches, a large proportion of people with TTH never present with full-blown migraine attacks or respond to anti-migraine treatments.

Treatment

The complex interrelation among the various pathophysiological aspects of TTH might explain why this disorder is so difficult to treat, and various therapeutic approaches should be used in sequence or in combination. In the future, specific trials could be designed to determine whether the relative importance of peripheral and central mechanisms in individual patients is relevant to therapeutic choice (figure 2).[130] The management of TTH should aim, by all means, to prevent the condition from becoming chronic.

Therapies for TTH can be subdivided into the short-term, abortive (mainly pharmacological) treatment of each attack and long-term, prophylactic (pharmacological or non-pharmacological) treatments.

Acute pharmacotherapy

There have been many controlled studies of simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) for treating TTH, with the headache attack as a model for acute pain. Several of the studies fulfil the standards recommended for drug trials in TTH by the International Headache Society,[131] and the results of these studies suggest that NSAIDs are the first-line drugs of choice. A review of randomised controlled trials that compared various NSAIDs and simple analgesics[132] found that a hierarchical classification of compounds emerges when efficacy data are studied, although the observed differences between drugs can be small or variable.

Aspirin (500 mg or 1000 mg) is more effective than placebo for the relief of acute TTH; the efficacy of aspirin is comparable to that of paracetamol (500 mg or 1000 mg). In most trials, however, simple analgesics were inferior to NSAIDs.[130,131]

Ibuprofen (800 mg) is currently the first choice for acute TTH, followed by naproxen sodium (825 mg) because of their overall better gastrointestinal tolerability.[130] Several studies have shown that ibuprofen is associated with the lowest risk of gastrointestinal bleeding or perforation (odds ratio [OR]=2·9), naproxen has a higher risk (OR=9·1), and ketoprofen has the highest risk (OR=23·7).[133,134] Lumiracoxib, a COX-2 inhibitor, was efficacious in patients with TTH at 200 mg and 400 mg doses in a double-blind, double-dummy, placebo-controlled trial;[135] however, until the results of comparative trials are available, the advantages of COX-2 inhibitors over non-specific NSAIDs need to be determined. The therapeutic efficacy of NSAIDs in the treatment of TTH is undisputable; however, there is clearly room for better acute treatments of TTH and a need for prophylactic therapy for frequent TTH attacks.

The combination of analgesics and caffeine, sedatives, or tranquillisers might be more effective in some patients than simple analgesics or NSAIDs; however, in many cases, this finding comes from the suboptimum doses of NSAIDs. The adjunction of caffeine (130 mg or 200mg) significantly increases the efficacy of simple analgesics[136] and ibuprofen[137] in controlled trials.

Flupirtine, a non-narcotic analgesic with neuronal potassium channel opener and NMDA receptor antagonist properties, had similar efficacy to paracetamol

	Drugs tested	N	Results	Significance
Lance and co-workers [141]	Amitriptyline (75 mg/day) *vs* placebo	27	Improvement in 56% (amitriptyline) *vs* 11% (placebo)	p=0·01
Diamond and co-workers[142]	Placebo *vs* amitriptyline 10 mg (up to 6 tablets/day) or amitriptyline 25 mg (up to 6 tablets/day)	29 *vs* 28 or 28	Improvement in intensity of headache 33% (placebo) *vs* 54% (amitryptyline 10 mg) or 38% (amitryptyline 25 mg)	p=0·05
Morland and co-workers[143]	Doxepin *vs* placebo	23	Headache days decreased by 15% in group taking doxepin *vs* placebo	p=0·05
Fogelholm and co-workers[144]	Maprotiline (75 mg/day) *vs* placebo	30	Headache intensity diminished by 25% and headache-free days increased by 40% in group taking maprotiline	p=0·001
Langemark and co-workers[145]	Placebo *vs* clomipramine or mianserin	36 *vs* 28 or 28	Reduction in intensity at day 43: 49% (placebo) *vs* 57% (clomipramine) or 54% (mianserin)	Not significant
Pfaffenrath and co-workers[146]	Placebo *vs* amitriptyline (50–75 mg/day) or amitriptylinoxide (60–90 mg/day)	64 *vs* 67 or 66	50% reduction in duration x frequency and in intensity 21·9% (placebo) *vs* 22·4% (amitryptyline) 30·3% (amitryptyline oxide)	Not significant
Göbel and co-workers[147]	Placebo *vs* amitriptyline (75 mg/day)	29 *vs* 24	Change in mean daily duration –0·28 h (placebo) *vs* –3·2 h (amitryptyline)	p=0·001
Bendtsen and co-workers[148]	Triple cross-over trial Placebo *vs* citalopram (20 mg/day) or amitriptyline (75 mg/day)	34	Decrease in AUC (duration x intensity) per 4 weeks 10% (placebo) *vs* 23% (citalopran) or 37% (amytripyline)	Not significant, p=0·02
Fogelholm and co-workers[149]	Tizanidine (6–18 mg/day) *vs* placebo	37	Percentage headache-free days over 6 weeks 54·9% (tizanidine) *vs* 43·7% (placebo)	p=0·05
Bettucci and co-workers[150]	Tizanidine (4 mg/day) and amitriptyline (20 mg/day)	18	Effective combination therapy (first month of treatment) compared with amitriptyline alone in terms of frequency (–52·3% *vs* –40·7%), intensity (–59·51% *vs* –20·39%), and duration (–53·17% *vs* –36·16%)	p<0·05
Bendtsen and co-workers[151]	Mirtazapine (15–30 mg/day) *vs* placebo	24	Decrease in AUC (duration x intensity) by 34% more than placebo Decrease in headache frequency, intensity, and duration	p=0·01 p=0·05, p=0·03, p=0·03
Leinisch-Dahlke and co-workers[152]	Bilateral block of the greater occipital nerve (50 mg 1% prilocaine and 4 mg dexamethasone)	15	No effect in 14 patients and worsening of pain in 4 patients	Not significant
Lampl and co-workers[153]	Open-label study, topiramate (100 mg/day for 3 months)	51	Decrease in headache frequency (from 23·5 days/month to 12·58 days/month) Decrease in average intensity of headache (from 6·13 to 2·07) Decrease in the duration of headache (from 8 h/day to 3 h/day)	p<0·0001 p<0·0001 p<0·0001
Zissis and co-workers[154]	Extended-release venlafaxine (150 mg/day for 12 weeks) *vs* placebo	34 *vs* 26	Decrease in mean number of days with headache (–44·8% in treatment group *vs* –15·7% in placebo group) Number to treat for responders (>50% reduction in days with headache)=3·48	p=0·023

AUC=area under the curve.

Table 1: **Controlled studies of prophylactic pharmacotherapy for TTH**

in children with TTH.[138] To our knowledge, no randomised controlled trials are available for flupirtine in adults with TTH.

The topical application of Tiger Balm[139] or peppermint oil[140] on the forehead is superior to placebo for the treatment of TTH; however, the effect of these interventions was not significantly different from paracetamol. There is no scientific basis for the use of most muscle relaxants in the treatment of TTH.

Prophylactic pharmacotherapy

Tricyclic antidepressants are the most widely used first-line therapies for CTTH. Surprisingly, few controlled studies have been done and not all of them have found superior efficacy to placebo (table 1).[141–154] The drawbacks of these studies are the small patient numbers, inadequate efficacy parameters, or their short duration. Only a few of the trials can be deemed adequate according to the International Headache Society guidelines. One of the main problems with trials that report statistically significant differences between placebo and tricyclics is whether the observed effect is clinically relevant. A reduction in the average duration of daily headache was selected as the primary efficacy parameter in one study;[147] amitriptyline reduced daily headache duration from 11·1 hours per day to 7·9 hours per day (average 3·2 hours). Although this effect was significantly different from placebo, the clinical significance of such a reduction is questionable.

Nonetheless, in clinical practice the tricyclic antidepressants are the most useful prophylactic drugs for CTTH or frequent ETTH: amitriptyline is the most frequently used; clomipramine might be slightly superior but has more side-effects; nortriptyline has fewer side-effects; and other antidepressants, such as doxepin, maprotiline, or mianserin, can be used as a second choice.

The initial dose of tricyclics should be low (10–25 mg amitriptyline or clomipramine before bed), and many patients will be satisfied by such a low dose. The average dose of amitriptyline for patients with CTTH, however, is 50–75 mg per day.[155] The recommendations for use of

amitriptyline are not generally accepted but most authorities recommend the discontinuation of treatment after 6 months, regardless of the efficacy.[155] A decrease in the daily dose by 20–25% every 2–3 days might avoid rebound headache.

The mode of action of antidepressants in CTTH remains to be determined; their effects on CTTH might be partly independent from their antidepressant effects. Tricyclic antidepressants have various pharmacological activities: increases in serotonin by inhibition of its reuptake, endorphin release, or inhibition of NMDA receptors, which have a role in pain transmission, might all be relevant to the pathophysiology of TTH.

The selective serotonin reuptake inhibitors (SSRIs) have, as yet, not been convincingly proved as effective for prevention of TTH.[156] Paroxetine (20–30 mg per day) was less effective than sulpiride (200–400 mg per day) in one exploratory cross-over study;[157] however, in another study, paroxetine was not effective in patients with CTTH who had not responded to tricyclic antidepressants.[158] Citalopram was inferior to placebo in a trial[148] (table 1) in which amitriptyline was found to be superior. In clinical practice, SSRIs can sometimes be tried in subgroups of patients who do not tolerate tricyclics or are overweight.

More recently, mirtazapine (a noradrenergic and specific serotoninergic antidepressant) was effective in patients with CTTH at 15–30 mg per day.[151] Unfortunately, at this dose mirtazapine commonly causes fatigue and weight gain in patients with CTTH, and the lower dose of 4·5 mg per day was ineffective.[159]

Zissis and co-workers[154] reported a significant decrease in headache days in patients given extended-release venlafaxine (150 mg per day from the second month of treatment onwards) compared with placebo, and a higher proportion of responders with 50% or more improvement in the treatment group compared with those receiving placebo. There was, however, no effect on the headache intensity index, which suggests that venlafaxine mostly eliminated the days with mild headache, and the beneficial effect of venlafaxine was not related to depression. These results need to be confirmed in a larger study that compares the standard diagnostic criteria for TTH with the stricter criteria of the ICHD-II appendix to ensure exclusion of patients with mild migraine.

The antispasmodic drug tizanidine (6–18 mg per day) was just superior to placebo in a cross-over trial,[149] but this effect does not seem to be clinically useful in most patients (table 1). A recent open randomised study[150] found that the combination of tizanidine (4 mg per day) and amitriptyline (20 mg per day) during the first 3 weeks of treatment gave faster relief of headache in patients with CTTH than amitriptyline did alone.

In an open study, topiramate, the anticonvulsant with known effectiveness for migraine prophylaxis, was also effective in patients with CTTH at 100 mg per day,[153] although this result needs to be confirmed in a randomised controlled trial.

In recent years, botulinum toxin has been popular as a treatment for chronic headache, particularly in North America; the enthusiasm for this treatment contrasts with the lack of scientific evidence for its use in headache disorders.[160] Nowadays, botulinum toxin A has no role in the prophylactic treatment of ETTH, and the previously reported beneficial effects in open-label studies have not been confirmed in double-blind, placebo-controlled trials.[161–165] Whether botulinum toxin has some use in subgroups of patients with TTH needs to be determined.[165]

Non-pharmacological treatments

Psychological and behavioural techniques

There is solid scientific support for the usefulness of relaxation and electromyography (EMG) biofeedback therapies in the management of TTH. Relaxation training and EMG biofeedback training alone and in combination lead to a nearly 50% reduction in headache activity.[166] Improvement rates are similar for each treatment modality but substatially greater than those observed in untreated patients or patients with false or non-contingent biofeedback.[166] Nonetheless, these treatments do not seem to be interchangeable: some patients who fail to respond to relaxation training can benefit from subsequent EMG biofeedback training.

Cognitive behavioural interventions, such as stress management programmes, can effectively reduce TTH activity but they are most useful when combined with biofeedback or relaxation therapies in patients with higher levels of daily hassles.[167]

Limited contact treatment under the patient's own guidance at home with audiotapes and written materials and only three or four monthly clinical sessions might be a cost-effective alternative to therapist-administered treatment for many patients.[168] Despite this alternative, behavioural therapies are time consuming for patients and therapists. Although there are no infallible means to predict treatment outcome, several factors have been identified that might have predictive value. In one study,[169] a 50% reduction in EMG activity at the fourth session due to relaxation predicted a good outcome. Excessive use of analgesics or ergotamines limits the therapeutic benefits. Patients with continuous headache are less responsive to relaxation or biofeedback therapies, and patients with raised scores on psychological tests that assess depression or psychiatric disturbance have been reported to do poorly with behavioural treatment in some studies.[170]

The improvements produced by behavioural treatment might appear slowly compared with those produced pharmacologically; however, improvement is maintained for longer periods—up to several years—without monthly burst sessions or contact with the therapist.[171]

The combination of stress management therapy and amitriptyline (≤100 mg day) or nortriptyline (≤75 mg day) was more effective in patients with CTTH than either behavioural therapy or drug treatment alone. Headache

index scores were reduced by at least 50% in 64% of patients on the combination compared with 38% of patients on tricyclics, 35% of patients on stress management, and 29% of patients on placebo.[172]

Other non-pharmacological treatments

Various physical therapy techniques are used in the treatment of TTH, including positioning, ergonomic instruction, massage, transcutaneous electrical nerve stimulation, the application of heat or cold, and manipulations. None of these techniques has been proved as effective in the long term, although physical treatment, such as massage, can be useful for acute episodes of TTH. In the long term, physical therapy reduced the intensity of TTH by only 23% on average in one study, which was, nonetheless, superior to acupuncture, which was given as a comparator treatment.[173] A programme of physical treatment was shown to have some effect in chronic but not episodic TTH in a controlled study.[174] The programme, however, combined various techniques, such as massage, relaxation, and home-based exercises, and the effect was modest.

A systematic review of randomised clinical trials with physiotherapy and spinal manipulation in patients with TTH showed insufficient evidence to support or refute the effectiveness of such techniques.[175] The addition of a craniocervical training programme with a nucal latex band to classic physiotherapy[176] had better efficacy at long-term follow-up (6 months) compared with physiotherapy alone.

A study that compared acupuncture, relaxation techniques, and physical training for the treatment of CTTH[177] showed that relaxation techniques produced the most pronounced effects, immediately after the treatment period, compared with acupuncture and physical training. There were no long-lasting differences between the three interventions. The authors hypothesised that the combination of these techniques would perhaps generate the best result.

Most trials of acupuncture in patients with TTH are limited by small sample sizes and controversial results,[178–180] although two recent studies are methodologically more appropriate in terms of the model used and the statistical analysis. In a multicentre, randomised, double-blind trial of 270 patients with ETTH or CTTH,[181] needle acupuncture had a significant and clinically relevant effect compared with no treatment (patients on the waiting list). However, sham acupuncture (superficial needle insertion at points distant from traditional acupuncture points) had beneficial effects. In another single-blinded study with at least some acupuncture points in common with the previous study (GB20, LI4, and LU7),[182] laser acupuncture in 50 patients with CTTH was more effective than placebo.

Oromandibular treatment might be helpful for selected patients with TTH. Unfortunately, most studies that claim efficacy of treatments such as occlusal splints, therapeutic exercises for masticatory muscles, or occlusal adjustment are uncontrolled. Because of the large number of headache-free individuals who have signs and symptoms of oromandibular dysfunction,[183] caution should be taken not to advocate irreversible dental treatments for patients with TTH. A minority of selected patients might, however, benefit from oromandibular treatment.[82,184,185]

Search strategy and selection criteria

References for this Review were identified by searches in MEDLINE and the Cochrane database from 1960 to July, 2007, and from references from relevant articles. Many articles and book chapters were identified from the authors' own files. The search terms "tension-type headache", "epidemiology", "pathophysiology", and "treatment" were used. The final reference list was generated on the basis of originality and relevance to the topics covered in the Review. With one exception (German), only articles published in English were included.

Conclusions

Tension-type headache is clinically and pathophysiologically heterogeneous. Circumstantial evidence from therapeutic and clinical data implies that the diagnosis is erroneously made to patients with other headache conditions, in particular those suffering from mild migraine, but this needs to be studied in more detail. With regard to the pathogenesis, pericranial myofascial mechanisms are probably of importance in episodic TTH, whereas sensitisation of pain pathways in the CNS—due to prolonged nociceptive stimuli from pericranial myofascial tissues—and inadequate endogenous pain control seem to be responsible for the conversion from episodic to chronic TTH. Although acute therapy with NSAIDs is, in general, effective for the treatment of episodes of ETTH, there is little scientific evidence to guide the selection of treatment modalities in CTTH. The best treatment is often found by trial and error. The situation is unfortunate because the multifactorial aetiopathogenesis of TTH means that therapy should be tailored to each patient and that a combination of different therapeutic methods, such as the combination of pharmacological and non-pharmacological treatments, might produce better results than either treatment alone. To prove the superior efficacy of combination therapies, multidisciplinary collaborations and large-scale comparative trials are needed urgently. Finally, new targets for future treatment strategies have been found from recent pathophysiological findings, such as the source of peripheral nociception to prevent the development of central sensitisation and drugs that are able to reduce established central sensitisation.[127,186]

Contributors

AF drafted the paper and did the reference search. JS contributed to the Review at its various stages.

Conflicts of interest

We have no conflicts of interest.

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