Drug and nondrug treatment in tension-type headache

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Abstract: Tension-type headache (TTH) is a common primary headache with tremendous socioeconomic impact. Establishment of an accurate diagnosis is important before initiation of any treatment. **Nondrug management is crucial.** Information, reassurance and identification of trigger factors may be rewarding. Psychological treatments with scientific evidence for efficacy include relaxation training, EMG biofeedback and cognitive-behavioural therapy. Physical therapy and acupuncture are widely used, but the scientific evidence for efficacy is sparse. Simple analgesics are the mainstays for treatment of episodic TTH. Combination analgesics, triptans, muscle relaxants and opioids should not be used, and it is crucial to avoid frequent and excessive use of simple analgesics to prevent the development of medication-overuse headache. The tricyclic antidepressant amitriptyline is drug of first choice for the prophylactic treatment of chronic TTH. The efficacy is modest and treatment is often hampered by side effects. Thus, treatment of frequent TTH is often difficult and **multidisciplinary treatment strategies** can be useful. **The development of specific nonpharmacological and pharmacological managements for TTH with higher efficacy and fewer side effects is urgently needed.** Future studies should also examine the relative efficacy of the various treatment modalities; for example, psychological, physical and pharmacological treatments, and clarify how treatment programs should be optimized to best suit the individual patient.

Keywords: tension-type headache, treatment, amitriptyline

Introduction

Tension-type headache (TTH) is the most prevalent and costly headache [Stovner et al. 2007]. It is a complex disorder where a range of heterogeneous mechanisms are likely to play a role [Bendtsen and Jensen, 2006]. The treatment of the acute episode in patients with infrequent TTH is often straightforward, but in patients with frequent headaches, biological mechanisms, in particular increased sensitivity of the central nervous system [Bendtsen, 2000] as well as psychological mechanisms, often complicate the treatment. It is important to consider which mechanisms that may be important for the individual patient and to tailor the treatment accordingly.

A correct diagnosis should be assured by means of a headache diary [Russell et al. 1992] recorded over at least 4 weeks. The diagnostic problem most often encountered is to discriminate between TTH and mild migraines (Table 1). If the headache is strictly unilateral the debated entity cervicogenic headache should be considered [Haldeman and Dagenais, 2001]. The diary may also reveal triggers and medication overuse, and it will establish the baseline against which to measure the efficacy of treatments. Identification of a high intake of analgesics is essential as other treatments are largely ineffective in the presence of medication overuse [Katsarava and Jensen, 2007]. Significant comorbidity; for example, anxiety or depression, should be identified and treated concomitantly. It should be explained to the patient that frequent TTH can only seldom can cured, but that a meaningful improvement can be obtained with a combination of nondrug and drug treatments. These treatments are described separately in the following but should go hand in hand.
Nonpharmacological management

Information, reassurance and identification of trigger factors

Nondrug management should be considered for all patients with TTH and is widely used. However, the scientific evidence for efficacy of most treatment modalities is sparse [Vernon et al. 1999]. The very fact that the physician takes the problem seriously may have a therapeutic effect, particularly if the patient is concerned about serious disease; for example, a brain tumour, and can be reassured by thorough examination. A detailed analysis of trigger factors should be performed, since avoidance of trigger factors may have a long-lasting effect. The most frequently reported triggers for TTH are stress (mental or physical), irregular or inappropriate meals, high intake of coffee and other caffeine-containing drinks, dehydration, sleep disorders, too much or too little sleep, reduced or inappropriate physical exercise, psychological problems, as well as variations during the female menstrual cycle and hormonal substitution [Ulrich et al. 1996; Rasmussen et al. 1992]. Most triggers are self-reported and so far none of the triggers have been systematically tested.

Information about the nature of the disease is important. It can be explained that muscle pain can lead to a disturbance of the brain’s pain-modulating mechanisms [Buchgreitz et al. 2007; Bendtsen, 2000], so that normally innocuous stimuli are perceived as painful, with secondary perpetuation of muscle pain and risk of anxiety and depression. Moreover, the patient should be explained that the prognosis in the longer run is favourable, since approximately half of all individuals with frequent or chronic TTH had remission of their headaches in a 12-year epidemiological follow-up study [Lyngberg et al. 2005].

Psychological treatments

A large number of psychological treatment strategies have been used to treat TTH. Three strategies have reached reasonable scientific support for effectiveness [Holroyd et al. 2005] and will be described.

Relaxation training The goal of relaxation training is to help the patient to recognize and control tension as it arises in the course of daily activities. During the training, the patient sequentially tenses and then releases specific groups of muscles throughout the body. Later stages involve relaxation by recall, association of relaxation with a cue word, and maintaining relaxation in muscles not needed for current activities [Holroyd et al. 2005].

EMG biofeedback The aim of EMG biofeedback is to help the patient to recognize and control muscle tension by providing continuous feedback about muscle activity. Sessions typically include an adaptation phase, baseline phase, training phase where feedback is provided, and a self-control phase where the patient practices controlling muscle tension without the aid of feedback [Holroyd et al. 2005].

Cognitive-behavioural therapy The aim of cognitive-behavioural therapy is to teach the patient to identify thoughts and beliefs that generate stress and aggravate headaches [Holroyd, 2002]. These thoughts are then challenged, and alternative adaptive coping self-instructions are considered. A variety of exercises may be used to challenge thoughts and beliefs, including experimenting with the adoption of another person’s view of the situation, actively generating other possible views of a situation, and devising a behavioural experiment to test the validity of a particular belief [Holroyd et al. 2005].

Meta-analyses have concluded that the treatments described above reduce headache by...
37–50% with no significant difference among treatments [Penzien et al. 2004]. However, the exact degree of effect is difficult to estimate because of methodological difficulties of designing appropriate placebo procedures. The most useful information on efficacy is derived from a study by Holroyd et al. [2001] demonstrating similar improvements in patients with chronic TTH by cognitive-behavioural therapy, treatment with tricyclic antidepressants and a combination of the two treatments. All three treatment strategies reduced headache index by approximately 30% more than placebo after 6 months. Patients who received the combination of the two treatments were more likely to show substantial reductions in TTH than patients who received either treatment alone.

Although the psychological treatments seem to have similar efficacy in controlled trials, this is unlikely to be the case for the individual patient. Psychological treatments are relatively time-consuming, but unfortunately there are no documented guidelines for which psychological treatment(s) to choose for the individual patient. Therefore until scientific evidence is provided common sense must be used. Thus, it is, for example, likely that cognitive-behavioural therapy will be most beneficial for the patient where psychological problems or affective distress play a major role, while biofeedback or relaxation training may be preferable for the tense patient.

Physical therapy

Physical therapy is the most used nonpharmacological treatment of TTH and includes the improvement of posture, relaxation, exercise programs, hot and cold packs, ultrasound and electrical stimulation, but the majority of these modalities have not been properly evaluated [Jensen and Roth, 2005]. Active treatment strategies are generally recommended [Jensen and Roth, 2005]. A controlled study [Torelli et al. 2004] combined various techniques such as massage, relaxation and home-based exercises and found a modest effect. It was recently reported that adding craniofacial training to classical physiotherapy was better than physiotherapy alone [van Ettekoven and Lucas, 2006]. A recent study found no significant long-lasting differences in efficacy among relaxation training, physical training and acupuncture [Soderberg et al. 2006], and spinal manipulation has no effect for the treatment of episodic TTH [Astin and Ernst, 2002; Bove and Nilsson, 1998]. Oromandibular treatment with occlusal splints is often recommended but has not yet been tested in trials of reasonable quality and cannot be recommended in general [Graff-Radford and Canavan, 2005].

It can be concluded that there is a huge contrast between the widespread use of physical therapies and the lack of robust scientific evidence for efficacy of these therapies, and that further studies of improved quality are necessary to either support or refute the effectiveness of physical modalities in TTH [Biondi, 2005; Lensinck et al. 2004].

Acupuncture and nerve block

There are conflicting results regarding the efficacy of acupuncture for the treatment of TTH. A recent large trial found acupuncture better than no treatment but not superior to minimal acupuncture [Melchart et al. 2005], while another recent trial [Endres et al. 2007] found no significant effect of traditional Chinese acupuncture over sham puncture on the primary efficacy parameter, while secondary efficacy parameters indicated a modest effect of traditional acupuncture. Laser acupuncture has recently been reported effective [Ebnesahidi et al. 2005], while acupuncture-like electrical stimulation was not effective [Wang et al. 2007]. A recent study reported no effect of greater occipital nerve block in patients with chronic TTH [Leinisch-Dahlke et al. 2005].

Pharmacological management

Acute drug therapy refers to the treatment of individual attacks of headache in patients with episodic and chronic TTH. Most headaches in patients with episodic TTH are mild to moderate and the patients often can self-manage by using simple analgesics. The efficacy of simple analgesics tends to decrease with increasing frequency of headaches. In patients with chronic TTH, headaches are often associated with stress, anxiety and depression, and simple analgesics are usually ineffective and should be used with caution because of the risk of medication-overuse headache at a regular intake of simple analgesics above 14 days a month or triptans or combination analgesics above 9 days a month [Headache Classification Subcommittee of the International Headache Society, 2004]. Other interventions such as nondrug treatments and prophylactic pharmacotherapy should be considered. The following discussion on acute drug therapy mainly
addresses treatment of patients with episodic TTH, while the discussion on prophylactic drug therapy addresses treatment of chronic TTH.

**Acute pharmacotherapy**

*Simple analgesics* Most randomized placebo-controlled trials have demonstrated that aspirin in doses of 500 mg and 1000 mg [Steiner et al. 2003] and acetaminophen (paracetamol) 1000 mg [Steiner et al. 2003; Prior et al. 2002] are effective in the acute therapy of TTH. One study found no difference in efficacy between solid and effervescent aspirin [Langemark and Olesen 1987]. There is no consistent difference in efficacy between aspirin and acetaminophen. The nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen in doses of 200–400 mg, naproxen sodium 375–550 mg, ketoprofen 25–50 mg and diclofenac potassium 50–100 mg have all been demonstrated to be more effective than placebo in acute TTH [Mathew and Ashina, 2005; Ashina and Ashina, 2003]. Most, but not all, comparative studies report that the above-mentioned NSAIDs are more effective than acetaminophen and aspirin [Mathew and Ashina, 2005; Ashina and Ashina, 2003]. Although simple analgesics are effective in episodic TTH, the degree of efficacy has to be put in perspective. For example, the proportion of patients that were pain-free 2 hours after treatment with acetaminophen 1000 mg, naproxen 375 mg and placebo were 37%, 32% and 26%, respectively [Prior et al. 2002]. Thus, efficacy is modest and there is clearly room for better acute treatment of episodic TTH.

*Combination analgesics* The efficacy of simple analgesics is increased by combination with caffeine 64–200 mg [Ashina and Ashina, 2003; Diamond et al. 2000]. There are no comparative studies examining the efficacy of combination with codeine. Combination analgesics cannot generally be recommended because of the increased risk of medication-overuse headache.

*Triptans and muscle relaxants* Triptans have been reported effective for the treatment of interval headaches [Cady et al. 1997], which were most likely mild migraines [Lipton et al. 2002], in patients with migraine, but triptans do not have a clinically relevant effect in patients with episodic TTH [Brennum et al. 1996]. Muscle relaxants have not been demonstrated effective in episodic TTH.

**Prophylactic pharmacotherapy**

Prophylactic pharmacotherapy should be considered in patients with headaches on more than 15 days per month; that is, in patients with chronic TTH. For many years the tricyclic antidepressant amitriptyline has been used. More lately other antidepressants, NSAIDs, muscle relaxants, anticonvulsants and botulinum toxin have been tested in chronic TTH.

*Amitriptyline* The tricyclic antidepressant amitriptyline is the only drug that has proven to be effective in several controlled trials in TTH. Thus, five out of six placebo-controlled studies found a significant effect of amitriptyline [Bendtsen and Mathew, 2005]. The two most recent studies reported that amitriptyline 75 mg/day reduced headache index (duration x intensity) with 30% compared with placebo.

**Conclusions** Simple analgesics are the mainstays in the acute therapy of TTH (Table 2). Acetaminophen 1000 mg may be recommended as drug of first choice because of better gastric side-effect profile [Langman et al. 1994]. If acetaminophen is not effective, ibuprofen 400 mg may be recommended because of a favourable gastrointestinal side-effect profile compared with other NSAIDs [Langman et al. 1994]. Physicians should be aware of the risk of developing medication-overuse headache as a result of frequent and excessive use of analgesics in acute therapy [Katsarava et al. 2007]. Triptans, muscle relaxants and opioids do not have a role in the treatment of TTH.

### Table 2. Recommended dosages for acute and prophylactic management of tension-type headache.

<table>
<thead>
<tr>
<th>Acute management</th>
<th>Prophylactic management</th>
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<tr>
<td>Acetaminophen 1000 mg</td>
<td>Amitriptyline 10–75 mg/day</td>
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<tr>
<td>Ibuprofen 200–400 mg</td>
<td>Mirtazapine 30 mg/day</td>
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<tr>
<td>Naproxen sodium 375–550 mg</td>
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<tr>
<td>Ketoprofen 25–50 mg</td>
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<td>Diclofenac potassium 50–100 mg</td>
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Physicians should be aware of the risk of developing medication-overuse headache as a result of frequent and excessive use of analgesics in acute therapy. Dosages in prophylactic management with amitriptyline are increased until efficacy or side effects are reported.
The effect was long-lasting (at least 6 months) [Holroyd et al. 2001] and not related to the presence of depression [Bendtsen et al. 1996]. It is important that patients are informed that this is an antidepressant agent but has an independent action on pain. Amitriptyline should be started at low dosages (10 mg/day) and titrated by 10 mg weekly until the patient has either good therapeutic effect or side effects are encountered. The maintenance dose is usually 30–70 mg daily administered 1–2 hours before bedtime to help to circumvent any sedative adverse effects. A significant effect of amitriptyline may be observed already in the first week on the therapeutic dose [Bendtsen et al. 1996]. It is therefore advisable to change to other prophylactic therapy, if the patient does not respond after 3–4 weeks on maintenance dose. The side effects of amitriptyline include dry mouth, drowsiness, dizziness, obstipation and weight gain. Dry mouth was observed in 75% and drowsiness in 53% of CTTH patients [Bendtsen et al. 1996]. Discontinuation should be attempted every 6–12 months.

Other antidepressants The tricyclic antidepressant clomipramine and the tetracyclic antidepressants maprotiline and mianserin have been reported to be more effective than placebo, while the selective serotonin reuptake inhibitors (SSRIs) have not been found to be effective [Bendtsen and Mathew, 2005]. Interestingly, antidepressants with action on both serotonin and noradrenaline seem to be as effective as amitriptyline with the advantage that they are tolerated in doses needed for the treatment of a concomitant depression. Thus, the noradrenergic and specific serotonergic antidepressant mirtazapine 30 mg/day reduced headache index by 34% more than placebo in difficult-to-treat patients including patients who had not responded to amitriptyline [Bendtsen and Jensen, 2004]. The serotonin and noradrenaline reuptake inhibitor venlafaxine 150 mg/day [Zissis et al. 2007] reduced headache days from 15 to 12 per month. However, the latter study is difficult to compare with the other studies mentioned, because it was a small parallel group study performed in a mixed group of patients with either frequent episodic or chronic TTH. A recent study demonstrated that low-dose mirtazapine 4.5 mg/day alone or in combination with ibuprofen 400 mg/day was not effective in chronic TTH. Interestingly, ibuprofen alone increased headache indicating a possible early onset of medication-overuse headache [Bendtsen et al. 2007].

Miscellaneous agents A recent open study reported an effect of the anticonvulsant topiramate 100–mg/day [Lampl et al. 2006]. Tizanidine, botulinum toxin, propranolol or valproic acid can at the present not be recommended for the prophylactic treatment of TTH [Bendtsen and Mathew, 2005].

Conclusions In general, the initial approach to prophylactic pharmacotherapy of chronic TTH is through the use of amitriptyline (Table 2). Concomitant use of daily analgesics should be avoided. If the patient does not respond to amitriptyline, mirtazapine could be attempted. Venlafaxine or SSRIs could be considered in patients with concomitant depression if tricyclics or mirtazapine are not tolerated. The physician should keep in mind that the efficacy of preventive drug therapy in TTH is often modest, and that the efficacy should outweigh the side effects. More efficient prophylactic drugs with fewer side effects are urgently needed for the preventive treatment of TTH.

As neither nonpharmacological nor pharmacological management is highly efficient it is usually recommended to combine multiple strategies, although proper evidence is lacking. It is therefore reassuring that the first study that has evaluated the efficacy of a multidisciplinary headache clinic reports positive results [Zeeberg et al. 2005]. Treatment results for all patients discharged within 1 year were evaluated. Patients with episodic TTH demonstrated a 50% reduction in frequency, 75% reduction in intensity, and 33% in absence rate, whereas chronic TTH patients responded with 32%, 30% and 40% reductions, respectively [Zeeberg et al. 2005].

Conflict of interest statement None declared.


