# Current and Potential Future Drug Therapies for Tension-type Headache

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**Current Headache Reports** 2003, **2:**466–474
Current Science Inc. ISSN 1539–3291


Tension-type headache is a common primary headache with tremendous socioeconomic impact. Establishment of an accurate diagnosis is important before initiation of any pharmacologic therapy. Simple analgesics and nonsteroidal anti-inflammatory drugs are the mainstays of treatment of episodic tension-type headache. The tricyclic antidepressant amitriptyline is the drug of choice in the preventive treatment of chronic tension-type headache. Progress in basic neuroscience has emphasized the importance of nitric oxide inhibition and *N*-methyl-D-aspartate and alpha-amino-3-hydroxy-5-methylisoxasole-4-propionic acid receptor antagonism in the treatment of chronic pain. It has been demonstrated that inhibition of nitric oxide is effective in chronic tension-type headache. These interesting data indicate that more specific and effective treatment possibilities will emerge in the future.

## Introduction

Tension-type headache is one of the most common primary headaches [1,2] and represents a considerable socioeconomic health problem. Despite the management of tension-type headache, the chronic form in particular continues to be a challenge for physicians. In the past 10 years, our knowledge on the pathophysiology of tension-type headache has been improved significantly. This article discusses the available pharmacotherapy based on controlled randomized trials and potential future preventive therapy based on recent experimental studies in patients with tension-type headache.

## Current Drug Therapies

### Acute therapy

Acute pharmacotherapy includes treatment of acute episodes of tension-type headache (*ie*, episodic tension-type headache according to the International Headache Society [IHS] criteria) [3]. Simple analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are used widely as an acute therapy. Unfortunately, there is no selective or specific therapy; therefore, this article focuses on available data on these drugs for the treatment of episodic tension-type headache.

*Simple analgesics*

Aspirin and acetaminophen are the analgesics used most commonly in the treatment of acute episodes of tension-type headache. In an early double-blind, placebo-controlled, crossover trial, aspirin at doses of 1000 mg, 500 mg, and 250 mg was shown to be more effective than placebo in the treatment of nonmigraineous headache [4]. Moreover, a significant dose-response relationship was established for aspirin; 1000 mg of aspirin was superior to 500 mg and 500 mg was superior to 250 mg. Several comparative, randomized, placebo-controlled trials have shown that aspirin [5–11] and acetaminophen [11–21] are effective in the acute therapy of tension-type headache. One of the first placebo-controlled trials demonstrated that 648 mg of solid aspirin and 648 mg of effervescent aspirin were more effective than placebo [6]; there was no difference between solid and effervescent aspirin. In another randomized, parallel, double-blind study, a subgroup consisting of 107 patients with tension headaches was treated with 1000 mg of acetaminophen, 650 mg of aspirin, and placebo [9]. Both drugs were more effective than placebo, but no difference was found between the drugs. Steiner *et al.* [11] reported that two different doses of aspirin (500 or 1000 mg) and 1000 mg of acetaminophen were more effective in treating 638 patients with episodic tension-type headache than placebo. The authors found that significant pain relief was noticed 1 hour after the administration of 1000 mg of aspirin; this was the case 2 hours after the administration of 500 mg of aspirin and 1000 mg of acetaminophen. Two studies reported no difference between acetaminophen and placebo [12,13]. In a small study by Dahlof and Jacobs [12], there was no difference between 500 and 1000 mg of acetaminophen and placebo. The authors suggested that the severity at baseline of the treated headache episodes and the low number of evaluated patients may explain the lack of efficacy. In another randomized, controlled study of 703 patients, the effects of 1000 mg of acetaminophen were not significantly different from placebo in 4-hour sum pain relief intensity differences scores [13]. The authors suggested that the spontaneous resolution of headaches could last less than the duration of the evaluation period.

**Table 1. Recommended dosages for acute and preventive therapy of tension-type headache***

| Acute therapy | Preventive therapy |
|---|---|
| 500 mg of aspirin<br>1000 mg of aspirin or 1000 mg of acetaminophen<br>200 mg of ibuprofen<br>25 mg of ketoprofen<br>400 mg of ibuprofen or 50 mg of ketoprofen | 10–75 mg of amitriptyline daily |

*Drugs used in acute therapy are classified hierarchically according to efficacy demonstrated in placebo-controlled trials. Dosages in preventive therapy are increased until efficacy or side effects are reported.

Martinez-Martin *et al.* [7] reported that a nonopioid analgesic and antipyretic dipyrone (not approved by the US Food and Drug Administration) was more effective than placebo in the treatment of 417 patients with moderate episodic tension-type headache. In addition, the authors observed a trend toward an earlier onset of a more pronounced pain relief of both dosages of dipyrone over 1000 mg of aspirin. In another placebo-controlled trial, 1000 mg of dipyrone administered intravenously also was shown to be effective 30 minutes after administration in the treatment of 30 patients with episodic tension-type headache compared with placebo [22].

Randomized, controlled trials demonstrated that acetaminophen and aspirin are effective in the treatment of acute episodes of tension-type headache and should be included in the treatment of mild or moderate episodes. Acetaminophen may be recommended as the first choice because of better gastric side-effect profiles. In addition, two studies have demonstrated the efficacy of dipyrone in the treatment of episodic tension-type headache. Recommended dosages of simple analgesics are shown in Table 1.

*Nonsteroidal anti-inflammatory drugs*

In one double-blind, randomized, placebo-controlled trial that included 70 patients with muscle-contraction headache (published before the IHS Classification), the effect of a single dose of ibuprofen was directly compared with placebo. The administration of 400 mg of ibuprofen was shown to be more effective than placebo 30 minutes after administration [23]. There are several comparative randomized, placebo-controlled trials regarding the efficacy of NSAIDs in episodic tension-type headache [5,8,10,12,13,15,16,20,21,24–27].

In one of the first comparative randomized trials, Ryan [10] reported that 400 mg of ibuprofen was as effective as 650 mg of aspirin in relieving pain in 50 patients with muscle-contraction headache compared with placebo. In another early double-blind, randomized, placebo-controlled trial that included 108 patients with muscle-contraction headache, 400 and 800 mg of ibuprofen and 650 mg of aspirin also were more effective than placebo at the 3-hour follow-up [5]. All of the active treatments were equally effective. In another comparative randomized, controlled trial, it was demonstrated that 153 patients who were administered 400 mg of ibuprofen had better pain relief than 151 patients who received 1000 mg of acetaminophen or 151 patients administered placebo [21]. Moreover, patients who were administered ibuprofen achieved pain relief faster than those who were administered acetaminophen. Nebe *et al.* [8] studied the effects of 200 mg of ibuprofen and 500 mg of aspirin in 65 patients with episodic tension-type headache in a double-blind, threefold, crossover, placebo-controlled study. The study showed that ibuprofen was significantly superior to aspirin and placebo in decreasing headache intensity on a visual analog scale by a minimum of 50% 1 hour after treatment. In a double-blind, parallel group, randomized trial that included 154 patients, a new solubilized formulation of 400 mg of ibuprofen was reported to be more effective than 1000 mg of acetaminophen and placebo in the treatment of episodic tension-type headache [15]. Pain relief was reported 39 minutes after administration of the solubilized formulation of ibuprofen, which was significantly faster than with acetaminophen (47 minutes) and placebo (113 minutes). Steiner and Lange [19] evaluated the efficacy of ketoprofen in the treatment of episodic tension-type headache in a multicenter, randomized, parallel group, placebo-controlled study; 25 mg of ketoprofen and 1000 mg of acetaminophen were equally effective in pain relief and superior to placebo. In a double-blind, randomized, parallel group study with 159 patients, two doses of ketoprofen (25 and 50 mg) were reported to be more effective than 200 mg of ibuprofen and placebo in the treatment of episodic tension-type headache [27]. Mehlisch *et al.* [13] conducted a double-blind, parallel-group, randomized study of 703 patients with episodic tension-type headache and demonstrated that low doses of ketoprofen (12.5 and 25 mg) also were more effective than placebo. In a comparative double-blind, randomized, controlled study by Dahlof and Jacobs [12] that included 30 patients, more headache relief was noted with 50 mg of ketoprofen than with 500 and 1000 mg of acetaminophen and placebo. In the same study, pain relief with 25 mg of ketoprofen was intermediate between that with 50 mg of ketoprofen and that with placebo and not statistically significant. This outcome likely was caused by the small number of patients.

The efficacy of naproxen has been evaluated in comparative, randomized, controlled trials only [16,20]. Thus, in a multicenter, double-blind, randomized, placebo-controlled trial, 375 mg of naproxen (321 patients) was reported to be

more effective than placebo (321 patients), but not better than 1000 mg of acetaminophen (321 patients) [16]. In a randomized, double-blind, three-way, parallel study that included 124 patients, 550 mg of naproxen sodium (rapidly absorbed formulation) was more effective than 650 mg of acetaminophen and placebo [20].

In a multicenter, double-blind, randomized trial, diclofenac potassium, known to be effective in the treatment of migraine headache at dosages of 50 or 100 mg [28], was shown to be more effective in the treatment of episodic tension-type headache than placebo at low dosages (12.5 and 25 mg) [26]. In addition, diclofenac potassium was found to be comparable with 400 mg of ibuprofen.

Intramuscular injection of 60 mg of ketorolac, which is an injectable NSAID approved for the management of acute pain, was found to be superior to placebo in relieving pain at 0.5 and 1 hour after administration in patients with tension-type headache compared with placebo [25].

Taken together, these data demonstrate that NSAIDs are effective and should be included in the treatment of moderate or severe episodes of tension-type headache. Recommended doses of NSAIDs are shown in Table 1.

*Combination analgesics*

In a double-blind, placebo-controlled trial, Schachtel *et al.* [17] showed that a combination of 1000 mg of aspirin with 64 mg of caffeine was more effective than 1000 mg of acetaminophen in the treatment of muscle-contraction headache. Headache relief was significantly greater with a combination of aspirin and caffeine compared with placebo at 40 minutes; significant headache relief with acetaminophen was noted at 60 minutes. In a randomized, double-blind, parallel, multicenter, single-dose, placebo- and active-controlled study with 301 patients, Diamond *et al.* [24] reported significantly better headache relief with a combination of 400 mg of ibuprofen and 200 mg of caffeine than with 400 mg of ibuprofen, 200 mg of caffeine, or placebo. Another comparative study reported that a combination of 500 mg of acetaminophen, 500 mg of aspirin, and 130 mg of caffeine and a combination of 1000 mg of acetaminophen and 130 mg of caffeine was more effective than 1000 mg of acetaminophen alone and placebo [14].

Codeine, an opioid analgesic, is another compound, which is combined in formulations containing aspirin or acetaminophen. One study reported that a combination of acetaminophen and codeine (doses not reported) was better than placebo in relieving pain in patients with tension headache who experienced an average of six attacks per month [29].

More randomized, controlled, and comparative studies are needed to evaluate the efficacy and safety of combination analgesics in the treatment of episodic tension-type headache.

*Muscle relaxants*

Muscle relaxants are not considered to be effective in treating acute episodes of tension-type headache because of insufficient studies and the risk of habituation [30,31•]. Therefore, these drugs generally are not recommended in the treatment of the acute episode of tension-type headache [30].

*Triptans*

The triptans, 5-HT agonists, are migraine-specific agents. In one study, Brennum *et al.* [32] reported that subcutaneous administration of 2 and 4 mg of sumatriptan induced a modest, but significantly greater headache relief than placebo in patients with chronic tension-type headache. It also has been reported that subcutaneous injections of 6 mg of sumatriptan in patients with tension-type headache and coexisting migraine headache had an effect equal to that experienced in migraine headache [33]. However, the oral formulation of sumatriptan 100 mg was not effective in the treatment of episodic tension-type headache [34]. The possible mechanism responsible for the modest effect of subcutaneous sumatriptan in the chronic form of tension-type headache could be a reduction of the increased excitability of neurons in the central nervous system. In support of this, animal studies have shown that 5-HT agonists can inhibit the excitability of neurons in the central nervous system [35]. Experimental studies of patients with chronic tension-type suggested increased excitability of the central nervous system [36]. The role of triptans in the treatment of tension-type headache is unclear.

*Conclusions on acute therapy*

Simple analgesics and NSAIDs are the mainstays in the acute therapy of tension-type headache (Table 1 and Fig. 1). Muscle relaxants and triptans are not recommended in the treatment of acute episodes of tension-type headache. In addition, physicians should be aware of the risk of developing medication-overuse headache as a result of frequent and excessive use of analgesics used in acute therapy.

## Preventive therapy

The preventive treatment generally is considered if the patient experiences a headache on more than 15 days each month (*ie,* chronic tension-type headache) [3]. For many years, physicians have been prescribing tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) for the treatment of chronic tension-type headache. In recent years, there has been increasing focus on botulinum toxin as a possible preventive therapy for chronic tension-type headache.

*Amitriptyline*

The tricyclic antidepressant amitriptyline is the most frequently prescribed drug for the treatment of chronic tension-type headache [37••]. In 1964, Lance and Curran [38] conducted the first controlled crossover trial and demonstrated the superiority of amitriptyline compared with placebo. Several years later, Diamond and Baltes [39] compared the efficacy of different dosages and found that the lower dose range, which was between 10 and 60 mg daily, was more effective than placebo. There was no significant effect of the higher dose range (between 25 and 150 mg daily). Gobel *et*

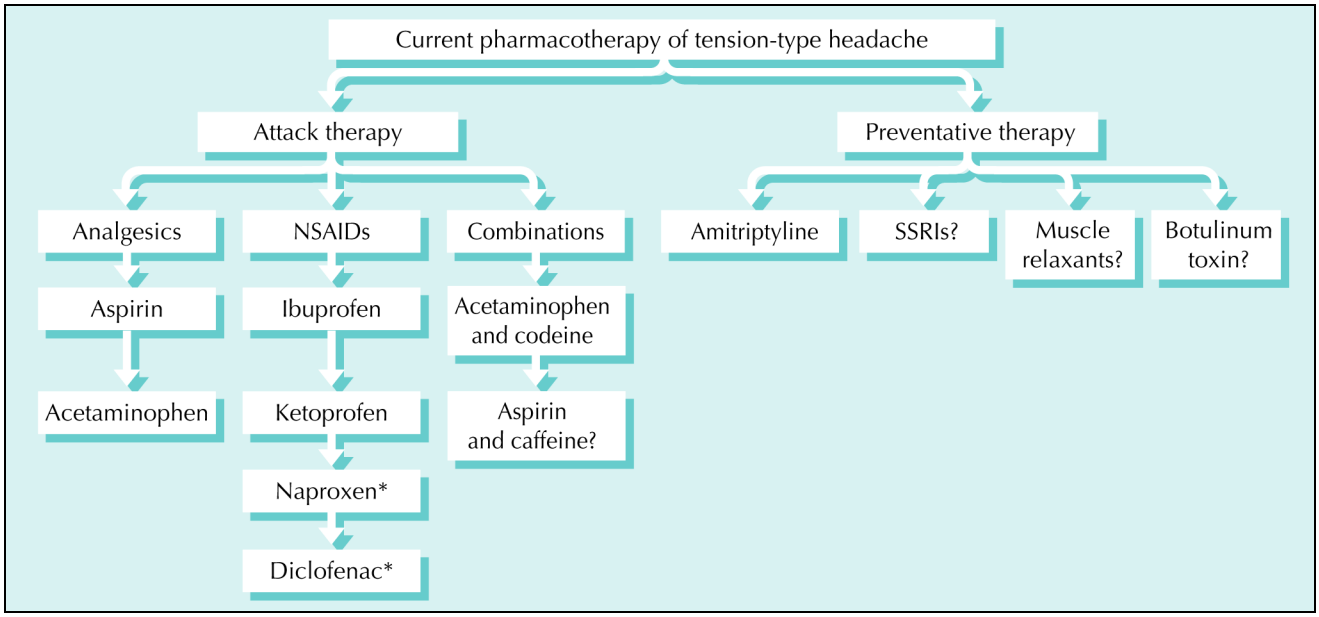


**Figure 1.** Overview of the recommended acute and preventive pharmacotherapies for tension-type headache. *Although naproxen and diclofenac are used in the acute therapy by many physicians, only few placebo-controlled trials are available on these drugs.

*al.* [40] demonstrated that 75 mg of amitriptyline administered daily significantly reduced headache duration compared with placebo in the last week of a 6-week study. A large multicenter, parallel group trial by Pfaffenrath *et al.* [41] reported no difference between 50 to 75 mg of amitriptyline administered daily, 60 to 90 mg of amitriptylioxide administered daily, and placebo in all of the recorded endpoints of the study. Amitriptyline has marked side effects, but there was no difference in side-effect report between the amitriptyline and placebo groups. Therefore, inability to detect side effects may suggest insensitivity of this study. Bendtsen *et al.* [42] conducted a three-way crossover trial of 75 mg/d of amitriptyline, the SSRI citalopram at 20 mg/d, and placebo for chronic tension-type headache. Amitriptyline reduced the area under the headache curve (calculated as headache duration multiplied by headache intensity) by 30% compared with placebo. In addition, amitriptyline reduced secondary efficacy parameters, such as headache duration and frequency, intake of analgesics, and myofascial tenderness [43]. In a comparative study by Holroyd *et al.* [44•], amitriptyline and the tricyclic antidepressant nortriptyline were compared with stress management therapy and a combination of stress management and antidepressants for the treatment of chronic tension-type headache. All of the treatments significantly reduced headache index by 30% more than placebo. Moreover, this study demonstrated a long-lasting effect of amitriptyline in chronic tension-type headache [44•]. The reduction of myofascial tenderness suggests that amitriptyline elicits its analgesic effect by reducing the transmission of painful stimuli from myofascial tissues and by reducing the increased excitability in the central nervous system in patients with chronic tension-type headache [43]. However, the exact mechanism of action of amitriptyline in tension-type headache is far from clarified. Possible mechanisms may include inhibition of serotonin (5-HT) and norepinephrine reuptake in the central nervous system, potentiation of endogenous opioids, *N*-methyl-D-aspartate (NMDA) receptor antagonism, and blockade of ion channels [45–47].

Collectively, controlled randomized trials have demonstrated that amitriptyline has a statistically significant and clinically relevant effect in the prophylactic treatment of chronic tension-type headache [42]. Amitriptyline should be considered as the first drug of choice in the preventive treatment of chronic tension-type headache (Table 1).

*Selective serotonin reuptake inhibitors*

Bendtsen *et al.* [42] compared the SSRI citalopram (20 mg/d) with amitriptyline (25–75 mg/d) and placebo in a three-way crossover study. Amitriptyline reduced the area under the curve, but citalopram had no significant effect on patients with chronic tension-type headache. In a double-blind, placebo-controlled, randomized trial, Singh and Misra [48] investigated the efficacy of sertraline in patients with chronic tension-type headache. Although the mean analgesic intake was significantly decreased in the sertraline group (25 patients) compared with the placebo group (25 patients), headache index, which combined severity, duration, and frequency of headache did not differ between groups.

In a double-blind trial, Manna *et al.* [49] randomized 20 patients to 50 to 100 mg/d of fluvoxamine and 20 patients to 30 to 60 mg/d of mianserin, which is a tetracyclic antidepressant, and found a significant effect of both drugs. In another comparative randomized, double-blind, crossover study, paroxetine (20–30 mg/d) was compared with sulpiride (200–400 mg/d), which is a $D_2$ antagonist, in 50 patients with chronic tension-type headache [50]. Both

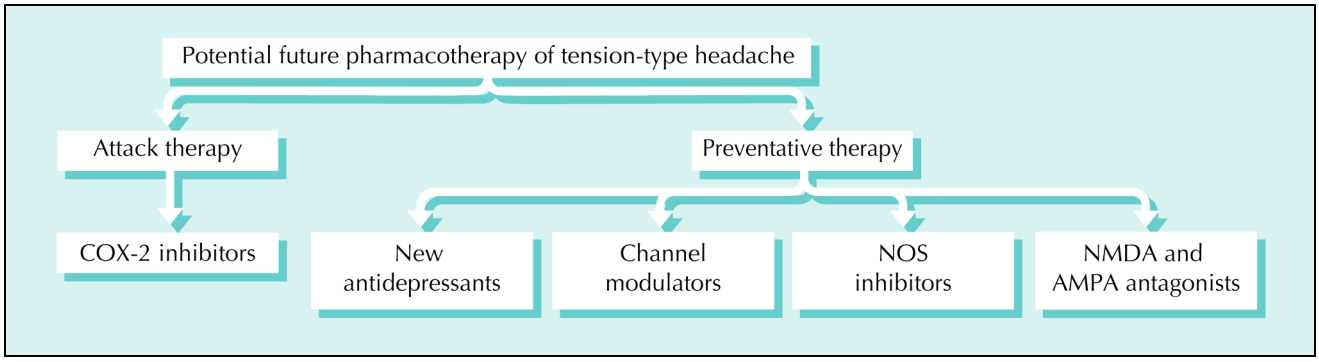


**Figure 2.** Overview of potential future acute and preventive pharmacotherapies for tension-type headache.

treatments resulted in modest improvement in headache scores and decreased analgesic intake. However, sulpiride showed significantly better relief than paroxetine. The serious methodologic reservation of these two comparative studies is the absence of placebo. Therefore, no conclusion on the efficacy of fluvoxamine and paroxetine can be drawn.

More placebo-controlled trials are needed to demonstrate the possible efficacy of SSRIs in the preventive treatment of chronic tension-type headache.

*Muscle relaxants*

The efficacy of muscle relaxants for tension-type headache has been investigated in two randomized, controlled studies. In a randomized, double-blind, placebo-controlled, crossover trial, Fogelholm and Murros [51] investigated the efficacy of tizanidine in 37 women with chronic tension-type headache. Six-week treatment began with 6 mg/d of tizanidine and, after 2 weeks, doses could be increased to 12 mg/d and to 18 mg/d after another 2 weeks if the patients responded poorly. Tizanidine was more effective than placebo at the end of the treatment period and the authors suggested that tizanidine was effective in the treatment of chronic tension-type headache in women [51]. In a recent study, modified-release formulations of tizanidine in dosages up to 12 mg did not differ from placebo [52]. The results from these two trials demonstrate the need for more trials on the effects and safety of muscle relaxants before they could be recommended for the preventive treatment of chronic tension-type headache.

*Botulinum toxin*

Botulinum toxin, which is a polypeptide produced by the anaerobic bacterium *Clostridium botulinum*, is used in the treatment of dystonia and myofascial pain syndrome. The rationale for the use of botulinum toxin in pain conditions is the antinociceptive action of this drug in the peripheral nervous system and the central nervous system [53]. Smuts *et al.* [54] reported a statistically significant improvement of headache in 37 patients with chronic tension-type headache 3 months after administration of botulinum toxin A compared with placebo. However, Göbel *et al.* [55] conducted a double-blind trial on 10 patients with chronic tension-type headache and could not demonstrate a difference between botulinum toxin and placebo treatments. In a small double-blind, placebo-controlled study, Rollnik *et al.* [56] studied the effect of botulinum toxin A in 16 patients with episodic and five patients with chronic tension-type headache and reported no beneficial effect compared with placebo. In a randomized, double-blind, placebo-controlled study of 60 patients with chronic tension-type headache, Schmitt *et al.* [57] found some improvement in affective variables, although there was no difference in pain intensity, the number of pain-free days, and consumption of analgesics between botulinum toxin treatment and placebo.

Data on the efficacy of botulinum toxin in the treatment of tension-type headache are based on the limited number of studies with several methodologic reservations. It appears that there is no common consensus on the number of injection sites and dosages in clinical trials. The results from trials demonstrate a need for more randomized, controlled trials with standard procedures before botulinum toxin can be recommended for the preventive treatment of chronic tension-type headache.

## Future Drug Therapies

### Acute therapy

*New nonsteroidal inflammatory drugs*

Selective cyclooxygenase-2 (COX-2) inhibitors were developed to maintain the therapeutic efficacy of NSAIDs and to provide improved gastrointestinal safety [58]. Controlled, randomized trials showed that COX-2 inhibitors have analgesic efficacy comparable with conventional NSAIDs [59]. There are no studies on the efficacy of COX-2 inhibitors in tension-type headache. Experimental studies in animals showed that COX-2 inhibitors may act in the central nervous system by reducing nociceptive transmission [60]. Therefore, it would be relevant to study the efficacy of COX-2 inhibitors in the treatment of tension-type headache (Fig. 2).

### Preventive therapy

*Antidepressants, 5-HT agonists, and channel modulators*

Antidepressants other than amitriptyline and SSRIs may become alternative preventive therapies for chronic tension-

type headache in the future. The tetracyclic antidepressant maprotiline has been shown to reduce total pain compared with placebo in patients with chronic tension-type headache [61]. However, the exact percentage reduction cannot be estimated because the data in the study are presented as figures. Langemark *et al.* [62] studied the effect of the tricyclic antidepressant clomipramine and the tetracyclic antidepressant mianserin. Both drugs showed significant reduction in headache compared with placebo. The summed visual analog scale headache score was reduced by 22% with clomipramine and by 20% with mianserin. Venlafaxine is a structurally novel third-generation heterocyclic antidepressant, which inhibits reuptake of 5-HT and norepinephrine and is structurally unrelated to tricyclic antidepressants [63,64]. In a retrospective study [65] that included patients with chronic tension-type headache and migraine headache resistant to several previous preventive medications, extended-release venlafaxine was effective in reducing the frequency of tension-type headache and migraine headache. This study had several limitations such as the retrospective collection of the data, lack of a placebo group, lack of washout period, and use of the prophylactic agents. In an open-label study [66], a newer third-generation heterocyclic antidepressant mirtazapine was reported to be effective and well tolerated in patients with tension-type headache and comorbid depression. Thus, data on clomipramine, mianserin, venlafaxine, and mirtazapine suggest that these drugs could be included in the future preventive therapy. However, randomized, controlled trials are warranted to confirm their efficacy.

The newer anxiolytic drug buspirone (30 mg/d), which is known as a partial agonist of 5-$HT_{1A}$ receptors, was compared with 50 mg/d of amitriptyline in the preventive treatment of chronic tension-type headache in an open and randomized clinical trial [67]. This study showed that buspirone exhibits similar analgesic efficacy to amitriptyline. This is an interesting observation, but requires further investigation in randomized, controlled trials.

The anticonvulsants topiramate and gabapentin also could be included in the future preventive treatment of tension-type headache. These drugs are known as channel modulators and they exhibit their action by reducing neuronal excitability through $Na^+$ and/or $Ca^{2+}$ channel blockade [68]. This mechanism of action has been proposed to underlie the analgesic activity of anticonvulsants [68]. In addition, topiramate was suggested to enhance GABAergic neurotransmission, which is involved in analgesia [69]. Topiramate and gabapentin have been reported to be effective in the prophylactic treatment of migraine headache [70,71]. Topiramate and gabapentin have not been tested in patients with chronic tension-type headache. Another anticonvulsant sodium valproate was tested and showed no efficacy in an open-label study of chronic tension-type headache [72]. Thus, topiramate and gabapentin are possible candidates for future prophylactic treatments and should be evaluated in randomized, controlled trials.

*Nitric oxide synthase inhibitors, N-methyl-D-aspartate, and alpha-amino-3-hydroxy-5-methylisoxasole-4-propionic acid receptor antagonists*

Substantial experimental evidence indicates that central sensitization (*ie,* increased excitability of neurons in the central nervous system) generated by prolonged nociceptive input from the pericranial myofascial tissues plays an important role in the pathophysiology of chronic pain [73] and chronic tension-type headache [36,74••]. Central sensitization is a complex process and involves various receptors and molecules [75]. NMDA receptor is considered to be responsible for the induction and maintenance phase of central sensitization [76]. Moreover, a change in the functional properties of the NMDA receptor appears to play a key role in the chronification of pain conditions [73]. Alpha-amino-3-hydroxy-5-methylisoxasole-4-propionic acid (AMPA) receptor is another receptor involved in central sensitization [75]. Subpopulations of dorsal horn neurons express AMPA receptors, which allow $Ca^{2+}$ influx sufficient to produce lasting facilitation of synaptic transmission in dorsal horn neurons [77,78]. The free radical nitric oxide (NO) is a messenger molecule involved in various biologic functions including neurotransmission. Animal studies have shown that central sensitization may be caused by or associated with the activation of neuronal nitric oxide synthase (NOS) and the generation of NO [79]. It also has been demonstrated that inhibition of NOS reduces central sensitization in animal models of persistent pain [80–82]. Thus, experimental evidence suggests that it would be relevant to test the efficacy of drugs acting directly or indirectly on NMDA or AMPA receptors in various chronic pain conditions including chronic tension-type headache. Unfortunately, the clinically available NMDA receptor antagonists have undesirable psychomimetic and psychomotor side effects. New classes of NMDA antagonists with better side-effect profiles are under development and may become novel principles in the future treatment of chronic tension-type headache. In patients with migraine headache, AMPA receptor antagonists were reported to be more effective than placebo and as effective as subcutaneous sumatriptan [83]. It would be interesting to study the efficacy of this drug in patients with chronic tension-type headache. To test the hypothesis that inhibition of NO and thus central sensitization would reduce tension-type headache, the authors' group investigated the analgesic effect of the NOS inhibitor L-$N^G$-methyl arginine hydrochloride (L-NMMA) in patients with chronic tension-type headache [84••]. In a double-blind, placebo-controlled, crossover study, 16 patients received 6 mg/kg of L-NMMA or placebo for 2 days. L-NMMA reduced headache intensity significantly more than placebo. In addition, pericranial muscle hardness and tenderness were significantly reduced after treatment with L-NMMA. Because a reduction of central sensitization is the most likely mechanism of action of L-NMMA, this observation supports the importance of central sensitization in chronic tension-type headache. It is probable that reduction of central sensitization

may become a novel principle in the future treatment of chronic headache and in other chronic pain disorders. However, there continues to be unanswered questions, which should be addressed in future studies. Thus, L-NMMA inhibits the three types of NOS (endothelial NOS, neuronal NOS, and inducible NOS) and study of selective inhibitors of NOS is needed to find out which type of NOS is involved in chronic tension-type headache and its exact site of action.

## Conclusions

The current pharmacotherapy of tension-type headache is nonspecific and includes simple analgesics and NSAIDs for the episodic form and the tricyclic antidepressant amitriptyline for the chronic form. We are only beginning to understand the complex mechanisms leading to chronic tension-type headache and the recent and interesting demonstration of the positive effects of NOS inhibition in chronic tension-type headache is promising and hopefully will lead to new treatment modalities in tension-type headache.

## Acknowledgments

We are grateful for the critical comments on this manuscript given by Dr. Lars Bendtsen and Dr. Peer Tfelt-Hansen. The work of the author reported in this article has been supported by the University of Copenhagen, the Danish Headache Society and the Danish Hospital Foundation for Medical research, the Region of Copenhagen, and the Faeroe Islands and Greenland.

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