Chapter 84

Prophylactic Pharmacotherapy of Tension-Type Headache

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Prophylactic pharmacotherapy should be considered in patients with chronic tension-type headache (CTTH). Quality of life is substantially reduced in these patients and they are often difficult to treat. Simple analgesics are generally ineffective and medication-overuse may worsen the headache. Identification of a high intake of analgesics is essential as other treatments are ineffective in the presence of medication-overuse. Second, avoidance of risk factors such as unphysiological working positions or psychosocial stress is important.

Pharmacotherapy, behavioral modalities and physical medicine are effective for prophylaxis. Stress management, including relaxation therapy, physical exercise, and proper time-management strategies should go hand in hand with prophylactic pharmacotherapy. Significant comorbidities, e.g., anxiety or depression, should be treated concomitantly. In this respect, for example, a single medicine, such as tricyclic antidepressants to treat CTTH and comorbid depression, might be chosen. Medications that have been used for prophylaxis of CTTH include antidepressants, botulinum toxin, muscle relaxants, nonsteroidal antiinflammatory agents (NSAIDs), and miscellaneous agents.

ANTIDEPRESSANTS

Pharmacology of Antidepressants

The tricyclic antidepressant amitriptyline is the only drug that has proven to be effective in several controlled trials in tension-type headache (1). The general information on antidepressants will therefore mainly focus on amitriptyline. The tricyclic antidepressants all inhibit the presynaptic reuptake of serotonin (5-HT) and norepinephrine (NE) in the central nervous system, thus potentiating the activity of these neurotransmitters. Amitriptyline and doxepin mainly inhibit the reuptake of serotonin, whereas desipramine has its greatest effect on the inhibition of noradrenaline reuptake. However, the tricyclic antidepressants have numerous other actions. Amitriptyline is a potent blocker of muscarinic cholinergic receptors, H_1-histamine receptors, α_1-adrenergic receptors and several 5-HT receptors, e.g., 5-HT_{2A} receptors, while the affinity for α_2-adrenergic receptors is low (2,3). Moreover, amitriptyline potentiates the effect of endogenous opioids (4) and may act as a N-methyl-D-aspartate (NMDA) receptor antagonist (5). The selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, fluvoxamine, paroxetine and citalopram, have, as the name implies, a rather selective action on the serotonergic system, while novel antidepressants like mirtazapine and venlafaxine potentiate serotonin and noradrenaline neurotransmission.

Amitriptyline is lipid-soluble and rapidly absorbed after oral administration with peak concentrations achieved after 3–4 hours. The bioavailability is relatively low (45%) because of a large first-pass effect. Amitriptyline is mainly metabolized in the liver and its half-life ranges from 13–36 hours (6). Steady-state plasma concentrations are achieved within 7–10 days. Metabolism is slower in elderly patients, which may result in increased plasma concentrations. The pharmacokinetics of amitriptyline is characterized by large interpatient variability and there is no clear relationship between plasma concentrations and analgesic effect (6).

Mechanism of Action

The multiple actions exerted by amitriptyline makes it difficult to determine the exact mechanism(s) by which amitriptyline exerts its prophylactic effect in tension-type headache. The analgesic effect of amitriptyline seem unrelated to its antidepressant effect (7) and it cannot be ascribed solely to the inhibition of 5-HT reuptake (8,9). An effect on central pain pathways via inhibition of 5-HT

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and NE reuptake, potentiation of endogenous opioids and attenuation of central sensitization via NMDA receptor antagonism are probably of importance (10,11), but the peripheral analgesic actions (12) of amitriptyline could also play a role. A recent study found that amitriptyline elicits its analgesic effect in CTTH by reducing the transmission of painful stimuli from myofascial tissues rather than by reducing overall pain sensitivity, and it was suggested that this effect could be caused by a segmental reduction of central sensitization in combination with a peripheral antinociceptive action (13). The efficacy of the noradrenergic and specific serotonergic antidepressant mirtazapine in tension-type headache (14) indicate that the analgesic effect of antidepressants is mediated through serotonergic, noradrenergic and opioid mechanisms (15).

Review of Clinical Trials of Antidepressants

The placebo effect must be taken into account in any study of treatment for headache. Therefore, only placebo-controlled trials and trials comparing a well-documented treatment with a new treatment allow definitive statements about efficacy in tension-type headache. Because of the limited number of placebo-controlled trials, however, controlled trials comparing two potentially active treatments are included. It should be kept in mind, however, that when both treatments are seemingly effective and no difference between studies can be detected the results may be falsely positive.

Placebo-Controlled Trials of Amitriptyline

In 1964, Lance and Curran (16) conducted a crossover trial of amitriptyline 10–25 mg three times daily in 27 patients with CTTH (Table 84-1). Twelve patients had no improvement during treatment with either amitriptyline or placebo, 12 patients reported a response only to amitriptyline and 3 patients responded to both treatments. These results were significantly in favor of amitriptyline. The response to treatment was not correlated with the presence or absence of depressive symptoms.

Diamond and Baltes (17) tested two different dosage ranges of amitriptyline, a lower one between 10 and 60 mg/d and a higher one between 25 and 150 mg/d (Table 84-1). All patients were also suffering from anxiety or depression. The results suggested that the lower dose range reduced headache more than placebo, while there was no significant effect of the higher dose range.

Göbel et al. (18) evaluated amitriptyline 75 mg/d (Table 84-1). Patients with depression were excluded. Compared with placebo, headache duration was reduced significantly in the last week of the 6-week study. Neither headache frequency nor headache intensity were presented. Nevertheless, as headache duration decreased consistently throughout all 6 weeks of active treatment but not throughout placebo treatment, the study is in favor of an effect of amitriptyline.

Pfaffenrath et al. (19) investigated amitriptyline 50 to 75 mg/d and amitriptylinoxide 60 to 90 mg/d (Table 84-1). No significant difference in headache reduction was found between active treatments and placebo. However, also the frequencies of side-effects were similar on amitriptyline and placebo. Usually, amitriptyline has marked side-effects and the inability to detect known side-effects suggests insensitivity of the trial for reasons which remain obscure.

Bendtsen et al. (8) evaluated amitriptyline 75 mg daily and the SSRI citalopram 20 mg daily (Table 84-1). The patients had been resistant to numerous previous treatments and were not suffering from depression. Amitriptyline reduced the area under the headache curve (calculated as headache duration times headache intensity) by 30%

TABLE 84-1 Summary of Randomized, Double-Blind, Placebo-Controlled Studies of Antidepressants in Chronic Tension-Type Headache

Study	*Drugs Tested/Design*	*N*	*Results*
Lance, Curran (16)	Amitriptyline/crossover	27	Significantly more responders on AM (15/27) than on PL (3/27), P not given
Diamond, Baltes (17)	Amitriptyline/parallel	85	Effect of AM 10–60 mg/d, $P < 0.01$, but not of AM 25–150 mg/d
Göbel et al. (18)	Amitriptyline/parallel	53	Effect of AM in the last week of the 6-week study, $P = 0.007$
Pfaffenrath et al. (19)	Amitriptyline and AO/parallel	197	No significant effect of AM or AO
Bendtsen et al. (8)	Amitriptyline and CI/crossover	34	Effect of AM (headache reduced by 30%), $P = 0.002$, no significant effect of CI
Holroyd et al. (20)	ADM and SMT/parallel	144	Effect of ADM (headache reduced by 30%), $P = 0.001$, and SMT, $P < 0.01$
Fogelholm, Murros (22)	Maprotiline/crossover	30	Effect of maprotiline, $P < 0.01$
Langemark et al. (23)	Clomipramine and mianserin/parallel	82	Effect of CL and MI (headache reduced by 22% and 20%), $P < 0.02$
Singh, Misra (24)	Sertraline/parallel	50	No effect on headache, analgesics reduced
Bendtsen, Jensen (14)	Mirtazapine/crossover	22	Effect of mirtazapine (headache reduced by 34%), $P = 0.01$

Data on headache reduction are active drug compared with placebo. AM: amitriptyline; PL: placebo; AO: amitriptylinoxide; CI: citalopram; ADM: antidepressant medication (amitriptyline 83% or nortriptyline 17%); SMT: stress management therapy; CL: clomipramine; MI: mianserin; *N*: number of patients included in evaluation of primary efficacy parameter.

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compared with placebo, which was highly significant, while citalopram had only a slight (12%) and insignificant effect. Amitriptyline also significantly reduced the secondary efficacy parameters of headache duration, headache frequency and intake of analgesics. The majority of patients reported dry mouth and drowsiness during treatment with amitriptyline, but the number of dropouts was lowest during amitriptyline treatment.

Holroyd and colleagues (20) treated patients with antidepressants (83% took amitriptyline median dose 75 mg daily and 17% took nortriptyline median dose 50 mg daily) and compared this with stress management therapy and with a combination of stress management and antidepressant treatment (Table 84-1). After 6 months, all three treatments reduced headache index with approximately 30% more than placebo, which was highly significant. Patients with depression were not excluded and data on the relation between changes in mood and headache were not presented. This makes it unclear whether the beneficial effects were due to specific antiheadache effects or to antidepressant actions. However, in a subsequent correspondence regarding this question the authors wrote that reductions in depression scores did not differ between patients who received active drug and placebo (21). The study is important in demonstrating a long-lasting effect of amitriptyline in CTTH.

Placebo-Controlled Trials of Other Antidepressants

The tetracyclic antidepressant maprotiline 75 mg daily was reported effective by Fogelholm and Murros (22), while Langemark et al. (23) reported both the tricyclic antidepressant clomipramine 75–150 mg daily and the tetracyclic antidepressant mianserin 30–60 mg daily effective (Table 84-1). Bendtsen et al. (8) found no effect of the SSRI citalopram. Singh and Misra (24) reported reduced intake of analgesics but no effect on headache of the SSRI sertraline (Table 84-1). Bendtsen and Jensen (14) reported that the noradrenergic and specific serotonergic antidepressant mirtazapine reduced area under the headache curve by 34% more than placebo in difficult to treat patients including patients who had not responded to amitriptyline (Fig. 84-1). This response is similar to that previously obtained with amitriptyline by the same group (8). Mirtazapine was well-tolerated.

Controlled Trials Comparing Two Potentially Active Treatments without Inclusion of Placebo

The selective 5-HT_2 and 5-HT_{1C} antagonist ritanserin was reported to be as effective as amitriptyline in patients with CTTH and depression (25). This was not confirmed in a subsequent placebo-controlled trial in non-depressed patients (26). The latter study was only presented as a letter. Holroyd et al. (27) compared amitriptyline 25 to 75 mg/d with cognitive-behavioral therapy. They found a significant effect of both treatments with a tendency to more positive outcomes of cognitive-behavioral therapy. Langemark et al. (28) compared the SSRI paroxetine 20 to 30 mg/d with sulpiride, a dopamine antagonist used as a neuroleptic. Patients improved with both treatments with a tendency to better efficacy of sulpiride. Manna and colleagues (29) reported significant effect of both fluvoxamine 50 to 100 mg/d and mianserin 30 to 60 mg/d.

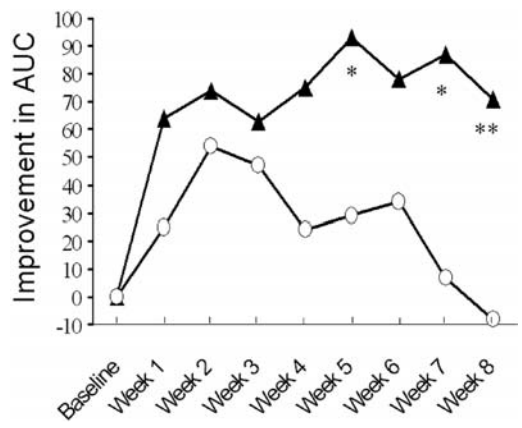

FIGURE 84-1. Prophylactic treatment with mirtazapine, a noradrenergic and specific serotonergic antidepressant, in patients with chronic tension-type headache. Mirtazapine reduced area under the headache curve (AUC)(duration × intensity) by 34% more than placebo in the four last weeks of treatment, $P = 0.01$. Mirtazapine also significantly reduced headache duration, frequency and intensity. Figure shows improvement in AUC values during all 8 weeks of treatment. *: $P < 0.05$. **: $P = 0.008$. Triangles = mirtazapine; circles = placebo. Reproduced from (14) with permission.

Controlled Trials in Patients Suffering from Both Tension-Type Headache and Migraine

Morland et al. (30) found doxepin 100 mg daily to have significantly better results than placebo. Mathew (31) reported amitriptyline 50 to 75 mg/d superior to propranolol 120 to 160 mg/d. Saper and colleagues (32) found fluoxetine 20 to 40 mg/d more effective than placebo in the last month of a 3-month study. Krymchantowski et al. (33) found no difference between amitriptyline and a combination of amitriptyline and fluoxetine.

Summary on Efficacy of Antidepressants

Five out of six placebo-controlled studies found a significant effect of amitriptyline. The two most recent studies reported that headache index was reduced with 30% compared with placebo. The tricyclic and tetracyclic

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antidepressants clomipramine, maprotiline and mianserin have been reported effective in one study each. Two studies found no effect of the SSRIs citalopram and sertraline. It was recently reported that the noradrenergic and specific serotonergic antidepressant mirtazapine has an effect comparable to that of amitriptyline with a more favorable side-effect profile.

BOTULINUM TOXIN

Pharmacology of Botulinum Toxin

Botulinum toxins (BTX) are products of the anaerobic bacterium *clostridium botulinum*. Type A, B, C1, D, E, F and G are the seven immunologically distinct serotypes of these extremely potent neurotoxins. Only types A and B are currently available for routine clinical use. Two botulinum toxin type A (BTX-A) preparations are commercially available, Botox (Allergan, Irvine, California) and Dysport (Ipsen Ltd, Berkshire, UK). Type B is currently commercially available as Myobloc in the United States and Neurobloc in Europe.

BTX-A cleaves a protein involved in the release of acetylcholine from axonal terminal, synaptosome associated SNAP-25, which results in flaccid muscle paralysis (34). Improvements in the symptoms usually occurs within one to 14 days, peaks within three to six weeks, and begins to wear off by 10 to 12 weeks postinjections. Functional recovery of neurotransmitter junctions takes about three to six months (35,36). Besides motor effects following BTX, inhibition of release of substance P and other nociceptive neuropeptides from either cholinergic neurons or from C or A delta fibers has been suggested (37).

Review of Clinical Trials of Botulinum Toxin in Chronic Tension-Type Headache

Seven placebo-controlled trials of BTX-A have been reported in CTTH (38–44) (Table 84-2). Two out of seven studies (41,42) were positive, with the primary endpoints of reduction of headache intensity or increase in headache-free days. One study (40) reported only improvement in the affective variables, West Haven, Yale, multidimensional pain inventory (WHYMPI), without a significant improvement in the other endpoints.

The other four studies (38,39,43,44) reported no significant benefit from BTX-A in CTTH. A number of methodologic problems have to be pointed out. Rollnik et al. (43) had only five patients with CTTH, far too small a number for any meaningful conclusion. Göbel et al. (38) used only a total of 40 units of BTX-A, a dosage far too low and there were only ten patients with CTTH. Padberg et al. (39) injected only the muscles with increased tenderness, without having an opportunity to use widespread injection sites.

The studies (41,42) which reported the best results had used 100 to 200 units of BTX-A. Clinical experience indicates that a dosage around 200 units appears to give best results. The injection site (location and number) varied from study to study accounting for the differences in response. Ondo et al. (41) who showed positive results used the "follow the pain" injection strategy, meaning, injecting the area of the head and neck where pain is felt more consistently.

More studies are clearly needed before the use of BTX for tension-type headache can be recommended.

MUSCLE RELAXANTS

Tizanidine

Tizanidine hydrochloride is a centrally acting muscle relaxant that has been reported to inhibit polysynaptic, rather than monosynaptic, reflexes in animal studies (45,46). It also has an analgesic property. Like clonidine, it is a centrally acting alpha-2-adrenergic agonist that reduces the release of noradrenaline in the CNS (46). It is suggested that some patients with tension-type headache might have an increase in central adrenergic metabolic activity (47).

Clinical Trials

The efficacy of tizanidine in CTTH was compared with placebo in a randomized, double-blind crossover study in 37 women aged 20 to 59 years who had a history of headache for 7 months to 30 years (median, 5 years) (48). The treatment periods were 6 weeks, with an intervening 2-week washout period. Treatment began with 6 mg daily divided into three doses, and the daily dose could be increased to 18 mg, depending on the treatment response. The effect of the treatment was measured by visual analogue scale, verbal rating scale, number of headache-free days, number of analgesics needed, and the dose of trial medication needed. In all these measurements, tizanidine was statistically significantly more effective than placebo. The pretrial Beck Depression Inventory score did not predict the response to treatment, nor did the level of electromyographic activity of the trapezium muscle. Side effects of drowsiness and dry mouth were significantly more common during tizanidine treatment, but they were usually mild. The results of this trial suggest that tizanidine is effective in the treatment of CTTH in women.

The absence of correlation between electromyographic levels and clinical response may indicate that tizanidine may act through its central α_2-agonist action, reducing the release of noradrenaline in the CNS. Shimomura and colleagues (47) reported higher levels of plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) in tizanidine responders. Levels of MHPG decreased significantly after treatment with tizanidine.

TABLE 84-2 Controlled Trials of Botulinum Toxin Type A, in Chronic Tension-Type Headache (CTTH) Prophylaxis

Authors	*Study Design*	*Headache Category*	*Sample (N)*	*Dosage*	*Sites of Injection*	*Endpoints*	*Results*	*Comments*
Smuts et al. 1999 (42)	Double-blind, placebo-controlled, parallel	CTTH with disorder of pericranial muscles	37	100 units BTX-A vs Placebo	Posterior and temporal muscles	Headache severity score and days without headache	Improved on BTX-A, 3 month post-injection ($P = 0.001$)	
Schmitt et al. 2001 (40)	Double-blind, placebo-controlled, randomized, parallel	CTTH	59	20 units BTX-A	Frontal and temporal muscles	Affective variables, pain intensity, analgesic intake, and activity level	Significant benefit for affective variables (WHY MPI) at one month. But no change in others	Lack of posterior injections—short observation period
Ondo et al. 2004 (41)	Double-blind, placebo-controlled, parallel, 12 week study followed by 12 week open label	CTTH Chronic migraine	46	200 units BTX-A or placebo	Variable "Follow the Pain" strategy; masseter injection in 7 patients	Headache-free days (primary), global impression, use of abortive medications, muscle palpation scores	With BTX-A headache-free days improved from week 8–12 ($P<0.05$). Subject global impression ($P<0.05$). Subject changes in headache impressions ($P<0.005$) and investigator global impression ($P<0.001$). Muscle palpation scores did not change.	Open label extension was a good strategy to assess the effectiveness of BTX-A on repeated use
Rollnik et al. 2000 (43)	Double-blind, placebo-controlled	CTTH	5	200 units BTX-A (4) or placebo (1)		Headache frequency, analgesic consumption, muscle tenderness, quality of life	Negative for BTX-A	Extremely small numbers of patients to make any conclusions
Göbel et al. 1999 (38)	Double-blind, placebo-controlled	CTTH	10	40 units BTX-A	10 units frontalis, 10 units temporalis, 20 units splenius capitis	Number of headache days	No significant response to BTX-A	Small number of patients, small dose of BTX-A and limited sites of injection are limitations of the study
Padberg et al. 2004 (39)	Double-blind, placebo-controlled, randomized	CTTH	46	100 units BTX-A	In muscles with increased tenderness	Headache intensity (VAS), mean number of headache days, headache hours per day, days of symptomatic treatment, and analgesic intake	Negative study	Injection confined to muscles of increased tenderness and lack of more widespread injection sites may be a limitation
Schulte-Mattler et al. 2004 (44)	Double-blind, placebo-controlled, randomized, multicentre	CTTH	107	500 units BTX-A (Dysport)	In 11 pericranial muscles on each side	Area under headache curve (intensity times duration), number of headache days	No significant response to BTX-A	

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In a recent study, modified-release formulations of tizanidine in dosages up to 12 mg did not differ from placebo (49). The results from these trials demonstrate the need for more trials on the effects and safety of muscle relaxants before they can be recommended for routine use.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Even though NSAIDs are used frequently for symptomatic relief for headache, no studies have been reported that showed significant benefit of long-term use for CTTH. Because long-term use may result in gastric and renal dysfunction, these agents should be instituted with caution.

MISCELLANEOUS AGENTS

A number of other agents have been used in the treatment of chronic headaches, usually the mixed variety of migraine and CTTH. In an open trial, a significant success was reported with the use of propranolol or a combination of propranolol plus amitriptyline (31). Valproic acid in doses of 1,000 mg to 2,500 mg was reported to be effective in the treatment of mixed migraine and CTTH in an open trial of 30 subjects (50). In this study, a 67% improvement in the headache index and 30% improvement in headache-free days per month were found after 3 months on valproic acid therapy. Because these were open studies, further confirmation with double-blind studies are necessary.

THERAPEUTIC USE

In general, the initial approach to prophylactic pharmacotherapy of CTTH is through the use of tricyclic antidepressants. It is important that patients are informed that these medications are antidepressant agents but have an independent action on pain. Amitriptyline should be started at low dosages (10 to 25 mg/d) and titrated by 10 to 25 mg weekly until the patient has either good therapeutic effect or side effects are encountered. Low starting doses are particularly important for elderly patients, who may be sensitive to the adverse effects of the tricyclic antidepressants. The maintenance dose is usually 50 to 75 mg/d administered 2 to 3 hours before bedtime to help to circumvent any sedative adverse effects. Occasionally, patients will benefit from higher doses (up to 200 mg/d). In such cases, monitoring of blood levels should be done to ensure that the patient does not develop toxicity to the medication. A significant effect of amitriptyline may be observed already in the first week on the therapeutic dose (8). It is therefore advisable to change to other prophylactic therapy if the patient does not respond after 3 to 4 weeks on maintenance dose. The side effects of amitriptyline include dry mouth, drowsiness, dizziness, constipation, weight gain, slowing of urination, orthostatic hypotension, and blurred vision. Dry mouth was observed in 75% and drowsiness in 53% of CTTH patients (8). The most serious side effects include cardiac arrhythmia, glaucoma, and urinary retention. Adverse effects are usually mild, however, and amitriptyline is generally well tolerated (8). Some tolerance may develop to the sedative and, to a lesser extent, to the anticholinergic side effects. Amitriptyline should be administered with caution in patients with prostatic hypertrophy, glaucoma, constipation, impaired liver function, or cardiovascular disease and should be avoided in patients who have heart block or arrhythmias and should not be administered immediately after myocardial infarction, in patients with urinary retention or severe liver disease, or during pregnancy and breastfeeding. If the patient does not respond to amitriptyline, mirtazapine should be attempted. This may also be drug of first choice, if side effects is a major concern. The SSRIs could be considered in patients with concomitant depression if tricyclics or mirtazapine are not tolerated.

Botulinum toxin Type A may be considered in patients with CTTH with very significant disability who are refractory to amitriptyline and mirtazapine, or those who have excessive intolerance to antidepressants. Behavioral therapies and physiotherapy should also have been tried. It should be made clear to the patient that there is no clear evidence that botulinum toxin works.

The centrally acting muscle relaxant tizanidine may have some promise in the prophylactic treatment of CTTH. Further large placebo-controlled, double-blind studies are necessary. In the meantime, the clinician may try this medicine in patients who do not respond to antidepressants. Most of the centrally acting muscle relaxant agents cause drowsiness, which limits their clinical use, even though there may be an occasional patient who does well on such medications. Peripherally acting agents, like dantrolene sodium, offer no significant benefit in CTTH.

How long should prophylactic agents be continued? It is a common practice to attempt to discontinue agents after 6 months. Withdrawal must be gradual. Many patients continue to maintain improvement for a long time, but many revert to experiencing CTTH. It is not uncommon for a significant number of patients with CTTH to be on prophylaxis for an indefinite time. Concomitant use of daily analgesics should be avoided.

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