Management of Chronic Tension-Type Headache With Tricyclic Antidepressant Medication, Stress Management Therapy, and Their Combination

A Randomized Controlled Trial

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Context Chronic tension-type headaches are characterized by near-daily headaches and often are difficult to manage in primary practice. Behavioral and pharmacological therapies each appear modestly effective, but data are lacking on their separate and combined effects.

Objective To evaluate the clinical efficacy of behavioral and pharmacological therapies, singly and combined, for chronic tension-type headaches.

Design and Setting Randomized placebo-controlled trial conducted from August 1995 to January 1998 at 2 outpatient sites in Ohio.

Participants Two hundred three adults (mean age, 37 years; 76% women) with diagnosis of chronic tension-type headaches (mean, 26 headache d/mo).

Interventions Participants were randomly assigned to receive tricyclic antidepressant (amitriptyline hydrochloride, up to 100 mg/d, or nortriptyline hydrochloride, up to 75 mg/d) medication (n=53), placebo (n=48), stress management (eg, relaxation, cognitive coping) therapy (3 sessions and 2 telephone contacts) plus placebo (n=49), or stress management therapy plus antidepressant medication (n=53).

Main Outcome Measures Monthly headache index scores calculated as the mean of pain ratings (0-10 scale) recorded by participants in a daily diary 4 times per day; number of days per month with at least moderate pain (pain rating ≥5), analgesic medication use, and Headache Disability Inventory scores, compared by intervention group.

Results Tricyclic antidepressant medication and stress management therapy each produced larger reductions in headache activity, analgesic medication use, and headache-related disability than placebo, but antidepressant medication yielded more rapid improvements in headache activity. Combined therapy was more likely to produce clinically significant (≥50%) reductions in headache index scores (64% of participants) than antidepressant medication (38% of participants; $P=.006$), stress management therapy (35%; $P=.003$), or placebo (29%; $P=.001$). On other measures the combined therapy and its 2 component therapies produced similar outcomes.

Conclusions Our results indicate that antidepressant medication and stress management therapy are each modestly effective in treating chronic tension-type headaches. Combined therapy may improve outcome relative to monotherapy.

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TENSION-TYPE HEADACHES often occur every day or nearly every day in individuals who seek treatment,[1-3] but headaches must occur 15 or more days per month for at least 6 months to meet International Headache Society diagnostic criteria for chronic rather than episodic tension-type headache.[4] The 1-year prevalence rate for chronic tension-type headache in the general population is about 3% in women and 1.5% in men,[5,6] with just less than half of those with chronic tension-type headache reporting headache-related impairment in work performance. Chronic tension-type headaches are a risk factor for the overuse of analgesic medications and thus the development of analgesic abuse headaches.[2,4,6,7] Continuous headaches and frequent comorbid psychiatric or analgesic use problems often render chronic tension-type headaches difficult to manage in primary practice.[1,2,8,9]

Tricyclic antidepressants are the primary drug therapy for chronic tension-type headache, with amitriptyline hydrochloride the first-line treatment.[2,9-12] However, recent trials have reported little (≤30%) or no improvement in chronic tension-type headaches[13-15] with amitriptyline. Additional information is therefore needed to confirm the benefits of this widely used medication for chronic tension-type headache.

See also Patient Page.

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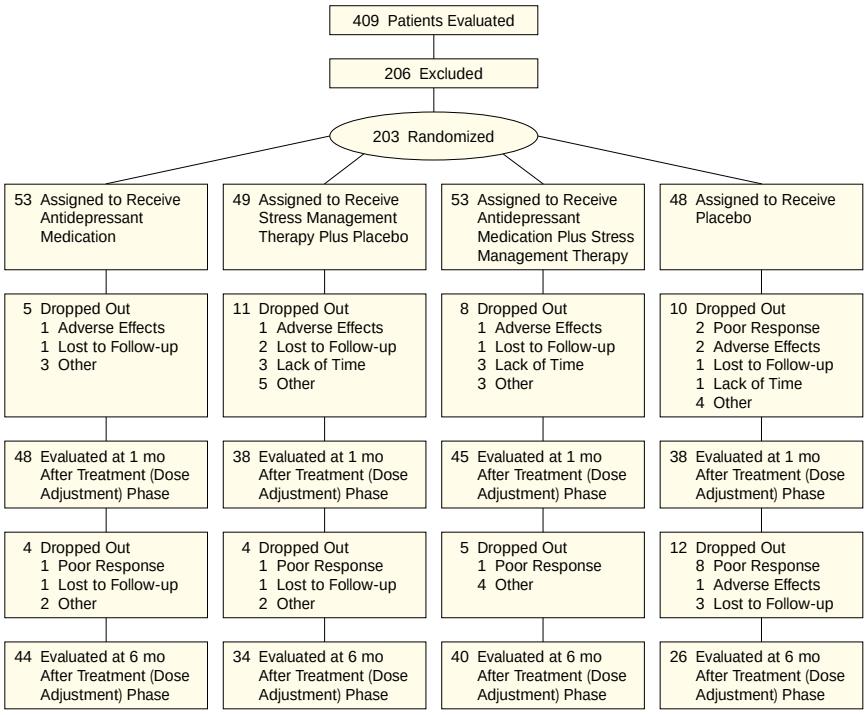
Behavioral therapies, primarily relaxation, biofeedback, and cognitive behavior (stress management) therapies appear to be effective in managing tension-type headache.[16-24] However, trials of behavioral therapies also have methodological shortcomings: results typically have not been reported specifically for participants with chronic tension-type headache and few trials have included placebo controls.[25] Additional information is thus needed to confirm the effectiveness of behavioral therapy for chronic tension-type headache. The possibility that behavioral therapy can enhance outcomes obtained with antidepressant medication (AM) also needs to be evaluated.[13,24]

This study was intended to evaluate the separate and combined effects of tricyclic antidepressant (amitriptyline and nortriptyline hydrochloride) medication (AM) and brief stress management therapy (SMT) for chronic tension-type headache.

Figure 1. Participant Flow in the Study



METHODS

Participants

Participants were recruited from primary practice referrals and by local advertisements at 2 outpatient sites. Inclusion criteria were age between 18 and 65 years and receipt of an International Headache Society diagnosis of chronic tension-type headache[4] at 2 separate evaluations. Exclusion criteria were: International Headache Society diagnosis of analgesic-abuse headaches[4]; current use of AM or other prophylactic medication for headache, or regular (≥15 d/mo) use of anxiolytic medication; current psychotherapy; current or planned pregnancy or breastfeeding; medical contraindication to amitriptyline; migraine headache more than 1 day a month; pain disorder (eg, arthritis) other than headache as primary pain problem; psychiatric (eg, suicide risk) or medical disorder requiring immediate treatment; and failure to complete baseline diary recordings of headache activity and medication use. All participants provided written informed consent according to procedures approved by the Ohio University Human Subjects Committee.

Study Design and Treatments

After completing the baseline assessment that included 1 month of headache and medication diary recordings, participants were randomly assigned in blocks of 4 participants to 4 treatments (FIGURE 1): AM, placebo, SMT plus placebo, and SMT plus AM. The AM and placebo therapies were administered in a standard double-blind fashion. Treatment conditions were blinded only for the medication component and not for the administration of SMT. This trial was conducted between August 1995 and January 1998.

Each treatment protocol required 3 clinic visits and 2 telephone contacts during the 2-month treatment (dose adjustment) phase, during which SMT was administered and the medication dose was adjusted. Clinic visits were scheduled at weeks 1, 4, and 8 of this treatment (dose adjustment) phase; telephone contacts were scheduled at the beginning of weeks 3 and 7. In the subsequent 6-month evaluation phase, clinic visits were scheduled 1, 3, and 6 months following completion of the treatment (dose adjustment) phase. The 1- and 6-month evaluations included review of 1 month of daily headache and medication diaries, neurological evaluation, and psychosocial testing. The 3-month evaluation included only medication checks and brief evaluation.

Tricyclic Antidepressant Medication and Placebo. In this double-blind protocol, we attempted to maximize the efficacy and tolerability of AM by using a low starting dose and recommended target doses for the treatment of chronic tension-type headache,[11,26-29] by treating participants who were unable to tolerate amitriptyline with nortriptyline and by use of an adherence intervention designed to increase AM adherence.[30] Treatment was initiated with 1 lead-in capsule of medication to be taken at bedtime (12.5 mg of amitriptyline hydrochloride or matched placebo) and increased to 3 regular (25 mg or matched placebo) capsules by week 6, as tolerated. At week 8, dose level was stabi-

lized at the highest tolerated level. If a participant did not tolerate the first medication, at least 2 regular capsules (50 mg) of amitriptyline hydrochloride or matched placebo, and, in the treating neurologist's (F.J.O., G.E.C.) judgment was unimproved, the patient was switched (with blindness maintained) to the second medication, nortriptyline, or matched nortriptyline placebo for participants who had been receiving placebo. Participants initially received a single 25-mg nortriptyline hydrochloride capsule or matched placebo. The dose was increased at the next visit to 2 capsules (50 mg) as tolerated. At week 8, the dose was stabilized at the highest tolerated level. In the evaluation phase, an increase to 4 capsules of amitriptyline hydrochloride (100 mg) or matched placebo or to 3 capsules of nortriptyline hydrochloride (75 mg) or matched placebo was allowed.

Stress Management Therapy. A psychologist or counselor administered SMT in three 1-hour sessions at the same 3 clinic visits used for medication dose adjustments. This primarily home-based treatment teaches both relaxation and cognitive coping skills for preventing and managing stress and headaches.[24,31] In the first treatment session, instruction manuals and audiotapes[32] that guide the acquisition and application of stress management skills at home were reviewed, and deep muscle relaxation training of 16 muscle groups[33,34] was introduced. At the second treatment session, active cognitive coping[35-37] or problem solving techniques[37-39] for preventing and managing headache-related stresses were introduced. At the third treatment session, the application of relaxation and cognitive coping skills to pain management was covered and the participant's experience with the headache management skills in the previous 2 months was reviewed. For participants receiving SMT, the week 3 and 7 telephone contacts were used for both the medication adherence intervention and the correction of problems encountered in the application of behavioral headache management skills.

Measures

Participants recorded headaches and the use of analgesic and study medication in a daily diary.[24,40-42] Headache activity was recorded 4 times a day using an 11-point rating scale with 5 anchors that ranged from 0, which indicated no pain, to 10, which indicated extremely painful or "I can't do anything when I have a headache." Diary recordings were obtained during the 1-month baseline phase, during the 2-month treatment (dose adjustment) phase, and, in months 1 and 6 of the 6-month evaluation phase.

The primary outcome measure was the headache index. The headache index was the mean of all diary ratings for a 1-month period, and it provides a measure of overall headache activity.[24,40] Secondary outcome measures were the number of days per month with a headache of at least moderate severity (pain rating ≥ 5),[3] analgesic medication consumption (number of pills weighted by analgesic potency),[40,43] and headache-related disability as assessed by the Headache Disability Inventory.[44,45] The primary end point for all measures was the 6-month evaluation (Figure 1). Psychophysiological, psychodiagnostic, and psychosocial measures also were collected to address different questions. Data from these latter measures will be reported elsewhere.

Hypotheses and Statistical Analysis

The study was designed to: (1) confirm that AM alone and that SMT alone are more effective than placebo; (2) determine whether either AM or SMT is more effective than the other; and (3) determine whether the combination therapy is more effective than either AM or SMT.

Planned comparisons were conducted to examine each hypothesis . All analyses were conducted on the intent-to-treat sample of all 203 randomized participants with the last data point carried forward for dropouts. For the continuous measures, after adjusting for baseline scores, F tests were used to evaluate each of 5 planned comparisons, 1 for each hypothesis. For the categorical headache measure, the proportion of participants showing clinically significant improvement (defined as a 50% or greater reduction in headache index scores[46]), Fisher exact tests were used. A modified Bonferroni procedure[47] was used to control the familywise type I error rate for the 5 comparisons at .05. One-tailed tests were used to compare AM and SMT with placebo; 2-tailed tests were used to compare active treatments.

We used χ^2 and Fisher exact tests to determine whether the proportion of dropouts varied among the 4 treatment groups. Analyses of covariance and log-linear analyses were conducted to determine whether the effectiveness of the treatments varied by study site or for participants who received and did not receive a comorbid migraine diagnosis. It did not. All analyses were conducted using SPSS Inc, Chicago, Ill.

The planned 200 subjects provided a power of 0.77 to detect a 0.75 difference in headache index scores and power of 0.69 to detect a difference of 4 in at least moderately severe headache-days per month, differences that were judged to be meaningful.

RESULTS

Participant Characteristics

Demographic and clinical characteristics for the 203 participants are given in TABLE 1. Sixty-three percent of participants recorded daily or near-daily headaches ($\geq$25 headache d/mo). Of the 203 participants, 160 (79%) reported having previously consulted a physician specifically for headache problems. However, 79 (49%) of these individuals were *lapsed consulters*,[48] defined as not having consulted a physician in at least 6 months despite persistent headache problems.

Attrition

Participant flow through the trial is displayed in Figure 1. There were 206 excluded participants: 54 chose not to be evaluated for the study or did not complete the pretreatment evaluation; 53 did not receive a primary diagnosis of

chronic tension-type headache or received a diagnosis of analgesic-abuse headaches[4] at the baseline evaluation; 26 experienced migraines more than 1 day a month; 19 were using AM, other prophylactic headache medication, or anxiolytics regularly (≥15 d/mo); 31 presented with a medical or psychiatric disorder that required referral; 10 were currently receiving psychotherapy; 6 were pregnant or planned a pregnancy; 6 had a pain disorder other than headache as their primary pain problem; and 1 had a medical contraindication to amitriptyline.

At the 1-month evaluation, the number of dropouts did not differ among the 4 treatment groups (Figure 1). However, by the 6-month evaluation, differential dropout was observed across treatment groups ($P=.01$), with significantly lower attrition from the AM ($P=.002$) and AM plus SMT ($P=.04$) groups than from the placebo group. Attrition because of a poor treatment response was especially high with placebo, with participants in the placebo group 5.6 times more likely to discontinue the study than participants in the active treatment groups ($P=.006$). After their exit from the study, participants who terminated treatment because of a poor treatment response or inability to tolerate medication generally requested additional treatment for their headaches. All such participants from the placebo group (n=13) requested additional treatment. This was provided without charge for 9 months.

Dosing and Protocol Adherence

At the 1-month evaluation, 84 (90%) of the 93 participants in the 2 active medication groups were taking amitriptyline hydrochloride (3 at 25 mg, 8 at 50 mg, 73 at 75 mg) and 9 were taking nortriptyline hydrochloride (3 at 25 mg, 6 at 50 mg). At the 6-month evaluation 70 (83%) of the 84 participants were taking amitriptyline hydrochloride (3 at 25 mg, 14 at 50 mg, 44 at 75 mg, 9 at 100 mg) and 14 were taking nortriptyline hydrochloride (4 at 25 mg, 9 at 50 mg, 1 at 75 mg).

Daily diary recordings indicated that at least 90% of participants were adherent for 80% or more days in the 4 months, where diaries were collected following the initiation of medication therapy. Neurologists (F.J.O., G.E.C.) rated at least 95% of participants as at least 90% adherent at the 4 neurological visits following the initiation of medication treatment. Adherence with the SMT protocol also was high. At the completion of SMT participants reported in a computer assessment that, on average, they had completed 15 of 17 (range, 3-17) workbook chapters and audiotapes and had attempted to use 9 of the 11 (range, 4-11) headache management strategies that had been presented.

Outcome

FIGURE 2 shows that all 3 active treatments, but not the placebo, yielded improvements in headache activity by the 6-month evaluation, but improvement occurred more rapidly with AM than with SMT. At the 6-month evaluation, the AM and SMT groups each showed significantly larger reductions in headache index scores than the placebo group. However, improvement was more rapid in the AM group than in the SMT group because the AM group showed larger reductions in

Table 1. Demographic and Clinical Characteristics*

	Antidepressant Therapy (n = 53)	Stress Management Therapy (n = 49)	Antidepressant Plus Stress Management Therapy (n = 53)	Placebo (n = 48)	Total (N = 203)	*P* Value†
Demographics						
Age at entry, mean (SD), y	35.6 (1.5)	37.4 (1.7)	37.1 (1.7)	37.8 (1.9)	37.0 (0.85)	.82
Women	66.0	79.6	81.1	79.2	76.4	.84
White	98.1	91.3	93.9	97.9	95.1	.91
Income level, US$						
1-15 000	3.8	13.6	14.9	7.5	9.8	
15 001-30 000	30.2	15.9	23.4	17.5	22.3	
30 001-45 000	18.9	25.0	23.4	37.5	25.5	.25
45 001-60 000	13.2	15.9	21.3	10.0	15.2	
>60 000	34.0	29.5	17.0	27.5	27.2	
Headache characteristics, mean (SD)						
Headache index	2.8 (0.18)	2.8 (0.20)	2.8 (0.17)	2.7 (0.21)	2.8 (0.09)	.91
Headache, d/mo	26.2 (0.74)	26.5 (0.70)	26.1 (0.65)	25.1 (0.72)	26.0 (0.35)	.57
At least moderate severity, d/mo‡	14.1 (1.1)	13.5 (1.2)	13.5 (1.2)	13.5 (1.2)	13.7 (0.58)	.97
Comorbid migraine diagnosis	20.8	24.5	28.3	25.0	24.6	.84
Disease duration, mean (SD), y						
Problem headaches	11.9 (1.2)	12.3 (1.7)	14.6 (1.8)	11.1 (1.6)	12.6 (0.79)	.44
At current frequency	7.2 (1.0)	7.6 (1.2)	7.5 (1.3)	5.7 (0.98)	7.0 (0.57)	.62

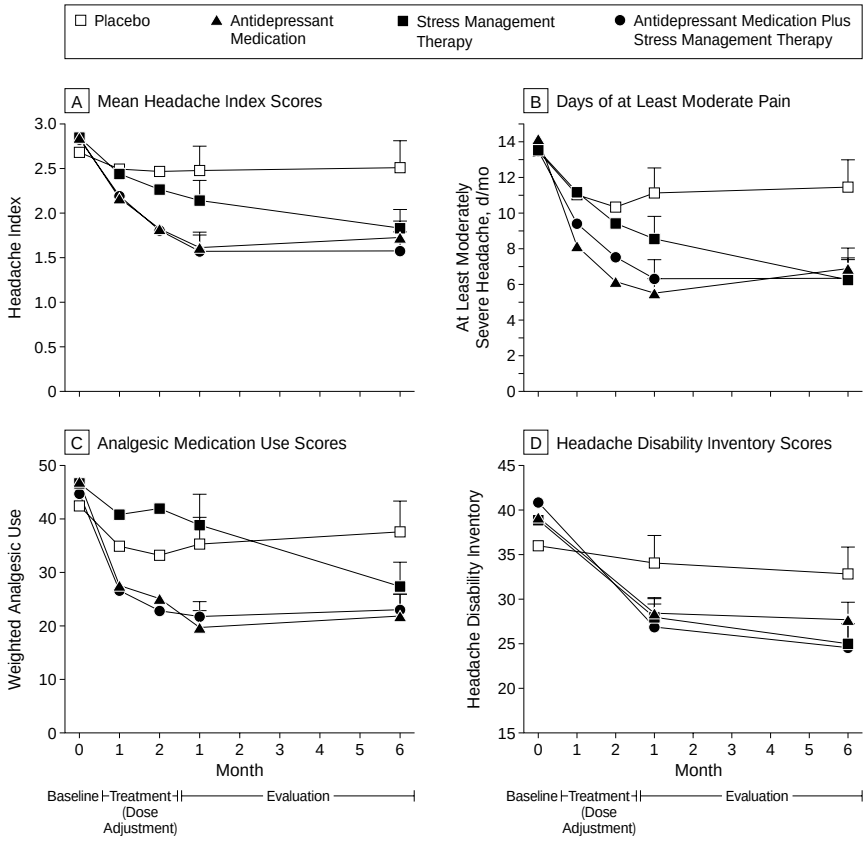
*Data are presented as percentages unless otherwise indicated.
†Results from χ^2 analyses on discrete variables and analyses of variance for continuous variables.
‡Pain rating ≥5 on an 11-point rating scale (0-10).

headache index scores than the SMT group at the 1-month evaluation (TABLE 2). The combined AM plus SMT treatment group and the SMT and AM treatment groups all showed similar improvements in headache index scores at the 6-month evaluation, but headache index scores improved more rapidly in the AM plus SMT treatment group than in the SMT only group. A greater proportion of participants in the AM plus SMT group (34 [64%] of 53) also showed clinically significant (≥50%)[46] reductions in headache index scores compared with only 20 (38%) of 53 in the AM group (P=.006), 17 (35%) of 49 in the SMT group (P=.003), and 14 (29%) of 48 in the placebo group (P=.001).

Improvements in secondary outcome measures paralleled improvements in headache index scores with only 2 exceptions. For the "days of at least moderate pain" variable, improvement was not significantly more rapid in the AM plus SMT than in the SMT only group; for Headache Disability Inventory scores, improvements were equally rapid in all 3 active treatment groups (Figure 2B, 2C, and 2D and Table 2).

The differential dropout rate of participants who complained of a poor treatment response from the placebo group renders a completor analysis biased because unimproved participants were differentially removed from the placebo group in this analysis. Effect sizes for active treatments were smaller when calculated from end point data than from completor data, suggesting end point data yielded a more conservative estimate of treatment effect size than completor data. Nevertheless, completor analysis revealed the same results at the 6-month evaluation as did the end point analysis, with 2 exceptions on secondary outcomes: in the completor analysis the SMT group and the placebo group did not differ significantly on the weighted analgesic-use variable; also, the AM group and the placebo group did not differ significantly on headache disability scores. When 2 imputation procedures (imputation of either the treatment group mean or the mean of previous data points for the participant) were used to replace missing headache index data at the 6-month evaluation, instead of carrying actual end point data forward, the results from both analyses were the same as the end point analysis.

Figure 2. Mean Headache Activity, Medication Use, and Disability Scores



A, Headache index is calculated as mean of daily pain ratings (range, 0-10) over a 1-month period. B, A day of at least moderate pain is indicated by a rating of ≥5 (scale, 0-10). C, A medication score of 40, for example, could reflect intake of 40 pills per month of simple or combined nonprescription analgesic (weight, 1), 20 pills per month of prescription-strength nonsteroidal anti-inflammatory agents (weight, 2), or 13.3 pills per month of a compound (eg, butalbital containing) analgesic (weight, 3). In A-D, error bars indicate SEs.

Adverse Effects

Among 187 participants who completed at least the first dose adjustment session, 78 (80%) of 97 participants who received AM and 27 (30%) of 90 participants who received placebo reported adverse effects (P=.001). Of 9 reported adverse effects caused by AM (dry mouth, drowsiness, weight gain, dizziness, sweating, constipation, abdominal pains, nervousness, increased appetite), only dry mouth and drowsiness were reported by more than 10% of participants in either treatment group; 51 participants (53%) in the AM group reported dry mouth vs 12 (13%) in the placebo group (P=.001) and 43 participants (44%) in the AM group reported drowsiness vs 10 (11%) in the placebo group (P=.001).

COMMENT

To our knowledge, this is the first placebo-controlled trial to examine the separate and combined effects of behavioral and drug therapies for a chronic headache disorder. Results indicate that AM and SMT, alone and in combination, are effective in reducing

chronic tension-type headaches, analgesic medication consumption, and headache-related disability. All 3 active treatments produced improvements in each of these variables, while chronic tension-type headaches proved unresponsive to even 8 months of clinical attention and treatment with placebo. However, reductions in headache activity and in analgesic medication consumption (but not headache-related disability) occurred more rapidly with AM than with SMT. In addition, observed reductions in headache activity were clinically meaningful but were only moderate in magnitude. For example, each of the active treatments reduced the average number of days of at least moderately severe headache pain by half, from about 14 days to fewer than 7 days a month.

These results provide needed empirical support for the use of tricyclic AM in the management of chronic tension-type headaches.[13] Although amitriptyline dose levels did not differ appreciably in this study compared with previous studies that reported negative or marginal findings,[13,14] our medication protocol did include a brief adherence intervention[30] and did permit substitution of a second tricyclic antidepressant. Although our results provide clear support for the efficacy of tricyclic AM in the management of chronic tension-type headaches, specific findings may not generalize to treatment protocols that do not include these features. In spite of the positive results observed with tricyclic AM, only about one third of participants in the AM-only treatment group recorded substantial (≥50%) reductions in headache activity.

Brief SMT also effectively reduced chronic tension-type headache activity, producing improvements in headache activity, use of analgesic medication, and headache-related disability comparable to improvements observed with AM alone. However, improvements in headache activity and in analgesic medication use with SMT were not fully evident until the 6-month evaluation, probably because acquired stress-management skills must be applied for several months before they have an affect on daily or almost daily headaches. Our results provide the first evidence that chronic tension-type headaches are responsive to behavioral therapy but suggest that there may be a time lag before the full-treatment response is evident. Brief SMT thus appears to offer a viable alternative to AM. Nonetheless, monotherapy with brief SMT also produced substantial (≥50%) reductions in headache activity in only about one third of participants.

Table 2. Planned Comparisons Testing Differences in Effectiveness of Treatments at 1-Month and 6-Month Evaluations*

	1-Month Evaluation			6-Month Evaluation		
	F Value†	*P* Value‡	Mean Difference§ (95% CI)	F Value	*P* Value	Mean Difference (95% CI)
Headache index						
AM vs placebo	20.95	.001‖	1.00 (0.57 to 1.43)	14.30	.001‖	0.92 (0.44 to 1.41)
SMT vs placebo	4.20	.02‖	0.46 (0.02 to 0.89)	10.08	<.01‖	0.79 (0.30 to 1.28)
AM plus SMT vs AM	0.01	.91	0.02 (−0.39 to 0.44)	0.29	.59	0.13 (−0.34 to 0.60)
AM plus SMT vs SMT	6.86	<.01‖	0.57 (0.14 to 1.00)	1.17	.28	0.26 (−0.22 to 0.74)
SMT vs AM	6.28	.01‖	−0.54 (−0.97 to −0.12)	0.30	.58	−0.13 (−0.61 to 0.35)
At least moderately severe headache, d/mo						
AM vs placebo	20.88	.001‖	6.0 (3.4 to 8.6)	12.26	.001‖	5.0 (2.2 to 8.0)
SMT vs placebo	3.57	.03	2.5 (−0.1 to 5.2)	12.51	.001‖	5.1 (2.3 to 8.0)
AM plus SMT vs AM	0.93	.34	−1.2 (−3.8 to 1.3)	0.01	.94	0.1 (−2.6 to 2.8)
AM plus SMT vs SMT	2.95	.09	2.3 (−0.3 to 4.8)	0.00	.98	0.0 (−2.8 to 2.8)
SMT vs AM	7.08	<.01‖	−3.5 (−6.1 to −0.9)	0.01	.92	0.1 (−2.7 to 2.9)
Weighted analgesic use						
AM vs placebo	11.85	.001‖	17.7 (7.6 to 27.8)	12.41	.001‖	18.0 (7.9 to 28.1)
SMT vs placebo	0.11	.37	−1.7 (−12.0 to 8.6)	5.14	.01‖	11.8 (1.5 to 22.1)
AM plus SMT vs AM	0.39	.54	−3.1 (−13.0 to 6.8)	0.23	.63	−2.4 (−12.2 to 7.5)
AM plus SMT vs SMT	10.16	<.01‖	16.3 (6.2 to 26.4)	0.57	.45	3.8 (−6.2 to 13.9)
SMT vs AM	14.42	.001‖	−19.4 (−29.5 to −9.3)	1.49	.22	−6.2 (−16.2 to 3.8)
Headache Disability Inventory score						
AM vs placebo	6.38	<.01‖	7.3 (1.6 to 12.9)	5.69	<.01‖	6.9 (1.2 to 12.6)
SMT vs placebo	6.29	<.01‖	7.3 (1.6 to 13.0)	9.91	.001‖	9.3 (3.5 to 15.1)
AM plus SMT vs AM	0.72	.40	2.4 (−3.1 to 7.9)	2.07	.15	4.1 (−1.5 to 9.6)
AM plus SMT vs SMT	0.67	.41	2.3 (−3.3 to 7.9)	0.34	.56	1.7 (−4.0 to 7.3)
SMT vs AM	0.01	.99	0.1 (−5.6 to 5.7)	0.69	.41	2.4 (−3.3 to 8.0)

*CI indicates confidence interval; AM, antidepressant medication; and SMT, stress management therapy.
†F value for comparison. Degrees of freedom for each test is 198, except for Headache Disability Inventory, for which degrees of freedom are 197 due to 1 missing data point.
‡*P* value for contrast. Two contrasts containing placebo are 1-tailed; all others are 2-tailed. Values <.001 are reported as .001.
§Difference in adjusted (for baseline score) means.
‖Statistically significant contrast with Hochberg's[47] modified Bonferroni procedure.

The combination of AM plus STM produced clinically significant reductions in headache activity in a greater proportion of participants than either AM or STM alone. Almost two thirds of participants treated with the combined treatment, but a little more than one third of participants in the AM or STM groups, showed clinically significant (≥50%) reductions in headache index scores. Although this finding suggests that combined therapy can improve outcomes relative to monotherapy, it must be qualified by the fact that no significant advantage for combined therapy was observed on other outcome variables.

Methodological limitations of this trial need to be kept in mind when interpreting these results. Although this is the largest trial that has compared the effectiveness of drug and nondrug therapies for chronic tension-type headache, this trial did not have power to detect small treatment effects.[49] Relatively high attrition also was observed, especially for participants treated with placebo, who were likely to exit the trial because of a poor treatment response. No previous trial has attempted to maintain a placebo control group for as long as 8 months; thus, it is probably not surprising that participants seeking relief from daily headaches requested alternate treatment before they went 8 months with no relief. Attrition did not differ significantly across the 3 active treatment groups but ranged from 17% to 31% at the final assessment.

Primary analyses were conducted using all randomized participants, carrying end point data forward. Alternate analyses using data from only the participants who completed the 6-month evaluation and using 2 alternate methods of imputing missing data for dropouts yielded similar results. The convergence of results from different analyses increases confidence in the findings, but it cannot eliminate the possibility that dropouts biased the estimates of treatment effects. It has been argued that administration of psychological treatment with placebo impairs the effectiveness of psychological therapy by reducing participants' involvement in psychological treatment.[50] Although empirical support for this contention is limited,[51] if this is true, our findings would underestimate the effectiveness of SMT. Finally, participants with a comorbid pain disorder as a primary presenting problem, with frequent comorbid migraines, or with a diagnosis of analgesic-abuse headaches were excluded to allow evaluation of the effects of treatment specifically on chronic tension-type headaches. Results thus cannot be readily generalized to participants with these comorbid medical problems. Future studies conducted in primary practice settings might thus examine outcome as a function of comorbid disorders.

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Acquisition of data: Holroyd, O'Donnell, Stensland, Lipchik, and Cordingley.
Analysis and interpretation of data: Holroyd, Stensland, Cordingley, and Carlson.
Drafting of the manuscript: Holroyd, Stensland, and Carlson.
Critical revision of the manuscript for important intellectual content: Holroyd, O'Donnell, Stensland, Lipchik, Cordingley, and Carlson.
Statistical expertise: Holroyd, Stensland, and Carlson.
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