Brief Communication

Amitriptyline Versus Amitriptyline Combined With Fluoxetine in the Preventative Treatment of Transformed Migraine: A Double-Blind Study

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Background and Objectives.—Antidepressants are often used to treat chronic daily headache disorders such as transformed migraine, in part because of the high prevalence of associated mood disorder. We conducted this study to evaluate the efficacy and tolerability of combined treatment with amitriptyline and fluoxetine compared with amitriptyline alone for chronic daily headache due to transformed migraine.

Patients and Methods.—Thirty-nine patients, 26 women and 13 men, aged 20 to 69 years (mean, 36.4; SD, 2.5) who fulfilled criteria for transformed migraine proposed by Silberstein et al were studied prospectively. Amitriptyline was dosed as follows: 8 mg/day for 6 days, 8 mg twice a day for 6 days, 20 mg/day for 6 days, and 20 mg twice a day for 45 days. In the group receiving combination therapy, fluoxetine was dosed and administered identically. The initial and end of the study (9 weeks) headache indices (frequency × intensity) were compared between groups.

Results.—Twenty-seven patients completed the study, 13 in the amitriptyline-alone group (group 1) and 14 in the combination-therapy group (group 2). The most frequent adverse event in both groups was dry mouth, and there was no significant difference in the occurrence of this or other adverse events between the two groups. Initial headache indices were similar for groups 1 and 2. The mean difference between the initial and final headache index for group 1 was 513.5 ($P<.0005$) and 893 ($P<.0017$) for group 2. The difference between the final headache index for the two groups was not significant ($P>.207$).

Conclusions.—We were unable to demonstrate any significant benefit from amitriptyline plus fluoxetine over amitriptyline alone in the treatment of chronic daily headache/transformed migraine. Because of the small number of subjects involved and the short duration of our study, a type II error cannot be excluded.

Key words: amitriptyline, fluoxetine, preventative treatment, transformed migraine

Abbreviations: CDH chronic daily headache, EM episodic migraine, TM transformed migraine, SMs symptomatic medications, SSRIs selective serotonin reuptake inhibitors, HIs headache indices

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Chronic daily headache (CDH) affects as much as 5% of the general adult population.[1] Most patients with CDH presenting to a tertiary center report episodic migraine (EM) in the past, with the gradual evolution of a pattern of daily or near-daily headache, an accompanying reduction in migraine features, and the development of clinical features characteristic of chronic tension-type headache.[2-4] This conversion of EM to daily headache is termed *transformation*, and some investigators have reported that over 80% of patients presenting with transformed migraine (TM) are overusing symptomatic medications (SMs).[5,6]

The headaches of TM are notoriously difficult to suppress, and there have been few scientific studies to evaluate their pharmacological management.[7] Because

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of its efficacy in the prophylaxis of EM and in view of the high prevalence of behavioral or psychiatric disturbances associated with CDH, amitriptyline often is used to treat TM.[8,9] Fluoxetine also has been investigated for its efficacy in treating EM and CDH.[10,11]

The tricyclic antidepressants commonly cause side effects such as drowsiness, dry mouth, constipation, weight gain, orthostatic hypotension, and tachycardia that may limit their utility.[7,8,12] Fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) are better tolerated and may be used with greater safety in the elderly and in patients with cardiac conditions, glaucoma, or constipation.[7] Fluoxetine has little affinity for dopamine D_2, 5-HT_{1A}, 5-HT_{2A}, α_1, beta, muscarinic, and histaminic receptors, therefore causing fewer side effects.[7,8] Side effects of fluoxetine include nausea, dry mouth, insomnia, headache, agitation, and reduced libido.[7,12]

Although the mechanisms by which antidepressants exert their action in migraine prevention remain speculative,[13] the combination of two antidepressant agents from different classes may increase efficacy,[14] decrease the required dosage of the tricyclic administered (therefore decreasing side effects), and thereby improve clinical outcome in patients with EM and CDH (Dr. Alan Rapoport, oral communication, June 2000). We conducted this study to evaluate the efficacy and tolerability of combined treatment with amitriptyline and fluoxetine compared with amitriptyline alone in the prophylactic treatment of CDH due to TM.

PATIENTS AND METHODS

Thirty-nine patients, 26 women and 13 men, aged 20 to 69 years (mean, 36.4; SD, 2.5) who fulfilled the criteria for diagnosis of TM with SM overuse proposed by Silberstein et al were prospectively studied.[15] All patients had their overused medications abruptly suspended, completed a 6-day course of oral prednisone (60 mg/day for 2 days, 40 mg/day for 2 days, and 20 mg/day for 2 days), and were randomly assigned to begin one of two prophylactic treatment regimens. There were no differences between the two groups with regard to the amount and type of SMs overused. None of the patients were taking medication for migraine prophylaxis or receiving chronic treatment for other clinical or psychiatric conditions at the time of randomization. Women of childbearing potential who were not using an effective contraceptive method were excluded, as were patients who could not maintain a detailed headache diary. Written informed consent was obtained from all patients.

During the first 35 days of study participation, patients were allowed only indomethacin (suppository) 100 mg once weekly as SM. After 5 weeks, patients were allowed to use SMs of various kinds but restricted use to no more than twice per week.

Group 1 included 19 patients (7 men and 12 women) who received amitriptyline only (8 mg/day as a single bedtime capsule for 6 days, 8 mg twice a day for 6 days, 20 mg/day as a single bedtime capsule for 6 days, and 20 mg twice daily for 45 days). Group 2 included 20 patients (6 men and 14 women) who received fluoxetine and amitriptyline together in single capsules identical in appearance to those taken by group 1; a double-blind design was maintained. The dosing regimen for group 2 was: fluoxetine 8 mg and amitriptyline 8 mg daily for 6 days in a single bedtime dose, fluoxetine 8 mg and amitriptyline 8 mg twice daily for 6 days, fluoxetine 20 mg and amitriptyline 20 mg daily for 6 days as a single bedtime dose, and fluoxetine 20 mg and amitriptyline 20 mg twice daily for 45 days.

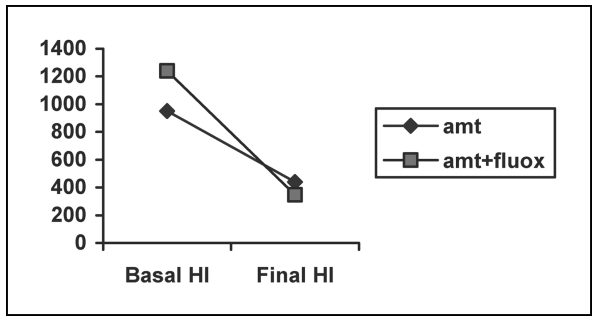
Initial headache indices (HIs) were calculated for the two groups by multiplying headache frequency (total number of headache days over the 30-day baseline period) by intensity (addition of all headache intensities: 0 = no headache, 1 = mild, 2 = moderate, 3 = severe, and 4 = severe/requiring bed rest) for each patient and calculating the mean for all patients in the group. Headache indices again were calculated at the end of the treatment period. Intragroup and intergroup HIs were compared.

Statistical Analysis.—Statistical comparisons were performed using the Mann-Whitney rank sum and the Wilcoxon signed rank tests, using graphpad Prisma software, version 2 (San Diego, Calif). The Mann-Whitney test was used to compare intragroup HIs (ie, pretreatment versus posttreatment). The Wilcoxon test was used for intergroup comparisons (unpaired test). The contingency table was analyzed by the Fisher exact test. Differences were considered significant with a two-tailed *P* value of less than .05.

Side Effects*

Side Effects	Group 1 Amitriptyline	Group 2 Amitriptyline and Fluoxetine	Total Percentage
Dry mouth	6 (46.1)	6 (42.8)	44.5
Weight gain	4 (30.8)	4 (28.6)	29.6
Heartburn	4 (30.8)	4 (28.6)	29.6
Somnolence	2 (15.4)	2 (14.2)	14.8
Constipation	2 (15.4)	2 (14.2)	14.8
No side effects	2 (15.4)	3 (21.4)	18.5

*Values are number (percentage) of patients.



Comparison of mean initial and final headache indices (HI) for the amitriptyline (amt) and amitriptyline plus fluoxetine (amt + fluox) groups.

RESULTS

Twenty-seven patients completed the study, 13 in group 1 and 14 in group 2. Six group 1 patients dropped out; 4 due to incomplete diary keeping and 2 due to worsening of headache. In group 2, 3 patients dropped out due to incomplete diary keeping, 2 due to side effects of the study medication, and 1 due to headache worsening and consequent resumption of SM overuse. The most frequent adverse event in both groups was dry mouth (44.5% overall: 46% in group 1 and 43% in group 2); there were no significant differences between the two study groups with regard to this side effect or the other commonly reported side effects (Table).

Group 1 (amitriptyline alone) had a mean baseline headache frequency of 27.4 headache days per month, with a mean intensity of 51. Group 2 (amitriptyline plus fluoxetine) had a mean baseline frequency of 24.2 headache days per month, with a mean intensity of 42.1. The initial HIs for the two groups were 940 for group 1 and 1146 for group 2; this difference was not statistically significant ($P>.61$). The differences between the initial and final HIs for group 1 were 513.5 ($P<.0005$) and for group 2, 893 ($P<.0017$) (see Figure); the difference between the two groups of patients was not significant ($P>.27$).

COMMENTS

Amitriptyline is a favored drug for the treatment of CDH,[7,16] and imipramine (the *N*-dimethyl derivative of amitriptyline), nortriptyline, and doxepin also are widely used for this purpose.[7,17,18] These drugs often impose adverse effects that may prohibit their use or prevent dose escalation to a therapeutic level.[19] Because clinical improvement in depression or headache may require several weeks of therapy, the uncomfortable side effects that often appear early in treatment may result in poor compliance.

Amitriptyline has been studied in several uncontrolled and double-blind studies since the sixties.[16] In a small, placebo-controlled study involving CDH/chronic tension-type headache, treatment with amitriptyline 75 mg/day led to improvement in most cases.[20] In a study involving 34 nondepressed patients with chronic tension-type headache treated with citalopram (an SSRI), placebo, or amitriptyline, amitriptyline was the only treatment successful in reducing frequency and duration of attacks, as well as daily analgesic use.[21] Other trials have indicated amitriptyline's superiority over placebo in the prevention of migraine with doses ranging from 10 to 150 mg/day, but none of these trials were performed according to current International Headache Society (IHS) criteria and IHS guidelines.[22]

Fluoxetine, an SSRI used primarily in the management of depression, obsessive-compulsive disorders, and bulimia has been proposed as a treatment for CDH.[7] Saper et al administered fluoxetine 40 mg/day to 64 patients with CDH and migraine, and 47% of the patients with CDH reported an increase in headache-free days and at least a 50% improvement in overall headache status relative to baseline.[11] Fluoxetine 20 mg/day was compared to amitriptyline 50 mg/day in 38 patients with CDH; both treatments led to improved scores on a pain total index and the Hamilton Rating Scale for Depression (HRSD).[10]

Proposed mechanisms for amitriptyline's effect in treating migraine and CDH/TM include increasing the synaptic norepinephrine or serotonin (through reuptake inhibition), down-regulation of 5-HT_2 receptors, reduction in beta receptor density, and enhancement of endogenous opiate receptor actions.[12] Fluoxetine induces a gradual down-regulation in central 5-HT_2 receptors and β-adrenoceptors and is a more potent 5-HT reuptake inhibitor than amitriptyline.[8,12] That both drugs have similar effects on the central nervous system presents the possibility that combined therapy would result in a profound effect on the serotonergic and noradrenergic systems and improved efficacy. Specifically, as β-adrenergic receptor density and function consistently are diminished by tricyclic antidepressants but not by SSRIs, the combination of both drugs may lead to more rapid desensitization of those receptors; whether this pharmacologic effect conveys clinical implications for treatment of migraine and TM remains unclear.[14]

We could not demonstrate superiority for the combination amitriptyline and fluoxetine over amitriptyline alone in treating TM. This result may reflect the relatively small number of patients involved or the short duration of the trial rather than intrinsic inadequacy of the combined therapy. Theoretically, fluoxetine may not exert its therapeutic effect on chronic headache until more than several months have passed.[23] Similar studies involving a larger number of subjects and a longer duration of therapy will be required to confirm or refute our results.

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Editor's Note.—*This commendable effort by Krymchantowski and colleagues underscores three sad truths related to CDH and its management. First, despite the prevalence of the condition, we continue to lack any treatment for CDH that meets the standard for scientifically demonstrable efficacy we should demand of our headache therapies. Second, no single center is likely to have resources sufficient to undertake a trial of the magnitude required to provide a clear and accurate assessment of therapies for CDH. Third, there is currently no consensus as to the methodology that should be employed if such a trial were initiated; not only have we failed to agree upon a primary outcome variable (reduction in "attack" frequency? headache days? quality-of-life scale?) . . . we can't even join in embracing a diagnostic classification system that will enable investigators consistently to evaluate the same CDH subpopulations.*

This is regrettable. Our continued ignorance in this area is embarrassing, a throwback to the days of "treatment by anecdote." Surely our patients deserve better. Corporate industry, currently the source of so much of our research support, has been largely reluctant to confront the CDH population. Accordingly, this may represent an excellent opportunity for headache investigators to take the lead in determining the direction of future research, to seek alternative sources of funding for that research, and by their efforts to eventually bring relief to the enormous "underclass" of individuals with chronic headache.

J.F.R.

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