Letters to the Editor

Tizanidine Is Not a Cure for Chronic Daily Headache

The recent article by Saper and his coauthors reports the results of a double-blind,[1] placebo-controlled study of tizanidine, an alpha-adrenergic agonist, in patients with chronic daily headache (CDH). The conclusion stated that the drug is "an effective prophylactic adjunct" for this headache condition. This conclusion was based on a reduction of the overall headache index, a peculiar number reflecting the product of the days, intensity, and duration of headache in 4-week intervals.

Over 30% of the patients withdrew from the study. Those who took the drug recorded 5.7 headache days per week during the baseline and 4 headache days per week at the final visit, a result which clearly demonstrates that this drug does not stop CDH. The reported number of severe headache days per week was greater during the 9th through 12th weeks of treatment than recorded during the 5th through 8th weeks of treatment. These results are not impressive.

It is a proper function of *Headache* to print such studies. To help the casual reader, I would suggest that the titles of articles reporting such nonimpressive results be changed to read something like "Disappointing Results in a Double-Blind Study of Tizanidine for Chronic Daily Headache." Otherwise, the physician who skims the title of articles might be tempted to prescribe this relatively expensive agent ($180+ retail for 100 4-mg tablets) for patients with CDH who often already are receiving other ineffective and expensive agents (eg, the triptans).

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REFERENCE

1. Saper JR, Lake AE, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache.* 2002;42:470-482.

Response From Lake and Saper

Chronic daily headache (CDH) is a pervasive and often difficult to manage disorder. Since appropriate statistical analyses in our study demonstrated tizanidine to be more effective than placebo, we stand by our statement that tizanidine is an "effective prophylactic adjunct" for CDH. Despite Dr. Warner's titled assertion, the word *cure* was nowhere to be found in our article. To the contrary, we took great care to qualify our interpretation of the data and stated explicitly that the drug's usefulness as a monotherapy was not established.

Dr. Warner refers to our primary endpoint—the headache index ([frequency × average intensity × duration]/days in the observation period)—as a "peculiar number." Arguments for the validity of the headache index were advanced in our paper. We cited other studies relying on the index, including most of the studies on prophylactic therapy reviewed for the Evidence-Based Guidelines Report of the Quality Standards Committee of the American Academy of Neurology. The IHS Guidelines for Controlled Trials of Drugs in Migraine acknowledge that headache indexes may "better reflect the total suffering of patients."

The index was reduced during the third month of treatment to a level 54% below the single-blind placebo baseline, compared to a 19% reduction for those receiving placebo ($P = .0144$). Readers can judge for themselves the clinical significance of this difference. While we acknowledged that the reductions in *total* headache days were modest and only approached significance over placebo ($P < .0591$), the reduction in *severe* headache days per week was 55% versus 21% for placebo ($P < .0331$). The mean increase in severe headaches from weeks 5 through 8 to weeks 9 through 12 that provoked a comment from Dr. Warner was 0.1 severe headaches per week, or 9% of the baseline frequency of severe headaches, and not significant.

The proportion of patients withdrawn from the study after starting the active treatment phase did not