Study Overview

Objective. To evaluate the efficacy and safety of tramadol/acetaminophen combination for the treatment of fibromyalgia.

Design. Multicenter, double-blind, randomized, placebo-controlled trial.

Setting and participants. Adults aged 18 to 75 years with at least moderate pain who fulfilled criteria for fibromyalgia recruited from outpatient clinics.

Main outcome measures. Primary outcome was the cumulative time to discontinuation (Kaplan-Meier analysis). Pain, pain relief, total tender points, myalgia, and health status were secondary outcomes.

Main results. Of the 443 patients screened, 315 met criteria for randomization. Average patient age was 50 years and almost all were white women. Patients treated with the tramadol/acetaminophen combination were less likely to discontinue their medication for any reason than patients assigned to the placebo group (48% versus 62%, \( P = 0.004 \)). Discontinuation due to lack of efficacy was also lower in the intervention (tramadol/acetaminophen) group compared to the control (placebo) group. Pain scores were better at the end of the study in the intervention patients than among control patients (53 ± 32 versus 65 ± 29 on a visual analog scale, \( P < 0.001 \)) as were the total scores on the Fibromyalgia Impact Questionnaire (44 ± 17 versus 50 ± 15, \( P = 0.008 \)). Tramadol/acetaminophen-treated patients were more likely to discontinue the drug due to side effects than were the placebo-treated patients (19% versus 12%, \( P = 0.09 \)).

Conclusion. Tramadol/acetaminophen combination was effective for reducing fibromyalgia pain.

Commentary

Fibromyalgia syndrome (FMS) is a chronic pain disorder with an important abnormal sensory perception component [1]. Patients with FMS may have concomitant illnesses such as depression [2]. Because of the varying clinical presentations of FMS, it has been a difficult clinical entity to study; however, the development of more rigorous diagnostic criteria has standardized clinical diagnoses and allowed clinical researchers to focus on a more homogeneous group of patients [3]. Although no therapies currently have Food and Drug Administration approval for use in patients with FMS, tricyclic antidepressants and fluoxetine as well as other nonpharmacologic therapies have been shown to be effective. Given the paucity of effective therapies, the study by Bennett and colleagues seems especially important.

Important features to consider when assessing the strengths and applicability of clinical trials include the adequacy of randomization (ie, Did everyone have an equal chance of being in either group?) and efficacy of blinding (ie, Was a placebo used for controls?). Adequacy of randomization can be assessed by examining the randomization methods (computer-generated codes are better than picking patients by day of the week) and by examining whether the 2 randomized groups appear similar. Bennett and colleagues used a randomized list of medication codes and given that baseline characteristics (eg, age, gender, race) and baseline pain scores were similar in both groups, randomization appears to have been effective. Assessing blinding can be difficult in some trials, as patients and providers are often able to guess at their randomization status, often due to particular features of the therapy (ie, peculiar side-effects). No assessment of efficacy of blinding is reported in this study.

Two other features of a trial should always be evaluated: (1) whether the patient population is representative of the kinds of patients seen in one’s practice and (2) whether the outcome is clinically meaningful. Bennett and colleagues offer us little information about how the patients were selected beyond the fact that they were recruited from outpatient settings in more than 1 clinical center. Other useful information might have been duration of fibromyalgia or whether patients were recruited from primary care clinics versus specialty clinics. The primary outcome chosen by the authors, time to discontinuation, is statistically appealing because survival time analysis has greater power to detect a difference than dichotomous outcomes, such as whether a patient felt significantly better at the end of the study. However, the

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clinical applicability of time to discontinuation is less clear. More appealing outcomes include percentage of patients who may be pain free, number of days that a patient reported feeling well, or number of patients who experience at least a 50% reduction in pain. The authors do report higher rates of 30% reduction in pain in the intervention group, but only a small percentage of patients achieved even this level of pain control.

Applications for Clinical Practice

Patients with fibromyalgia are difficult to treat because there are few therapeutic options available for improving their pain and quality of life. Bennett and colleagues have given physicians another therapeutic choice when treating patients with fibromyalgia by showing that tramadol/acetaminophen was more effective at relieving pain than placebo. However, nearly half the patients in this trial had abandoned this treatment by 90 days, and only a small number achieved significant relief. Therefore, though better than placebo, tramadol/acetaminophen offers only moderate hope to those with fibromyalgia.

—Review by Ashish K. Jha, MD

References

3. Crofford LJ, Clauw DJ. Fibromyalgia: where are we a decade after the American College of Rheumatology classification criteria were developed? Arthritis Rheum 2002;46:1136–8.