Tramadol and Acetaminophen Combination Tablets in the Treatment of Fibromyalgia Pain: A Double-Blind, Randomized, Placebo-Controlled Study

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PURPOSE: To evaluate the efficacy and safety of a combination analgesic tablet (37.5 mg tramadol/325 mg acetaminophen) for the treatment of fibromyalgia pain.

METHODS: This 91-day, multicenter, double-blind, randomized, placebo-controlled study compared tramadol/acetaminophen combination tablets with placebo. The primary outcome variable was cumulative time to discontinuation (Kaplan-Meier analysis). Secondary measures at the end of the study included pain, pain relief, total tender points, myalgia, health status, and Fibromyalgia Impact Questionnaire scores.

RESULTS: Of the 315 subjects who were enrolled in the study, 313 (294 women [94%], mean [± SD] age, 50 ± 10 years) completed at least one postrandomization efficacy assessment (tramadol/acetaminophen: n = 156; placebo: n = 157). Discontinuation of treatment for any reason was less common in those treated with tramadol/acetaminophen compared with placebo (48% vs. 62%, P = 0.004). Tramadol/acetaminophen-treated subjects also had significantly less pain at the end of the study (53 ± 32 vs. 65 ± 29 on a visual analog scale of 0 to 100, P <0.001), and better pain relief (1.7 ± 1.4 vs. 0.8 ± 1.3 on a scale of −1 to 4, P <0.001) and Fibromyalgia Impact Questionnaire scores (P = 0.008). Indexes of physical functioning, role-physical, body pain, health transition, and physical component summary all improved significantly in the tramadol/acetaminophen-treated subjects. Discontinuation due to adverse events occurred in 19% (n = 29) of tramadol/acetaminophen-treated subjects and 12% (n = 18) of placebo-treated subjects (P = 0.09). The mean dose of tramadol/acetaminophen was 4.0 ± 1.8 tablets per day.


Fibromyalgia is a common syndrome characterized by widespread pain and tenderness (1). The standardization of diagnostic criteria for fibromyalgia (2) has stimulated research on this disorder, and better understanding of the scientific basis of pain over the last decade has led to the reformulation of fibromyalgia as a chronic pain state with disordered sensory processing and a heterogeneous clinical presentation (3–6). The generally accepted approach to treating fibromyalgia is a multimodal regimen that includes patient education, cognitive behavioral therapy, gentle exercise, and medications to help with sleep and pain (7).

No medication is currently approved for the treatment of fibromyalgia in the United States. Nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, and calcitonin are not more effective than placebo (8,9). Some success has been reported with other pharmacologic agents, such as tricyclic antidepressants and fluoxetine (10–15), as well as nonpharmacologic therapies (16,17). Amitriptyline is used commonly, although only 25% to 30% of patients improve and the beneficial effects are not sustained (16). One study reported that opioids were prescribed to about 15% of fibromyalgia patients in a tertiary care setting (18). The adverse effects of opioids are often a deterrent to patient acceptance, however, and regulatory issues may deter physician prescribing (19).

There is an increasing realization that a polypharmacologic approach to pain management in fibromyalgia, by targeting different levels in the pain pathways, needs to be explored (20). In clinical trials, a 37.5-mg tramadol/325-mg acetaminophen combination tablet has been effective for pain relief among patients who underwent dental surgery (21), and as add-on therapy in the treatment of pain due to osteoarthritis not controlled by NSAIDs (22).

Tramadol is a centrally acting analgesic that is useful in the treatment of many pain disorders, including neuropathic pain and fibromyalgia (23–30). Tramadol has a unique mechanism of action that combines mu-opioid activity with inhibition of serotonin/norepinephrine re-
uptake (31). Acetaminophen is often combined with other medications to enhance therapeutic efficacy. For example, subactive amounts of acetaminophen and morphine exert analgesic effects when given in combination (32). Acetaminophen acts centrally via mechanisms that appear to involve a synergistic interaction between spinal and supraspinal sites (33,34). The approximately 1:8 mg-to-mg tramadol:acetaminophen ratio was based on demonstrated synergy in animal models (35).

Fibromyalgia is a central pain state involving disturbances of neurochemical pathways that are thought to be affected by both tramadol and acetaminophen. The purpose of this study was to examine the analgesic efficacy and safety of 37.5-mg tramadol/325-mg acetaminophen tablets in the treatment of fibromyalgia pain.

METHODS

Study Design and Sample
This outpatient multicenter, randomized, double-blind, placebo-controlled study was conducted in adult subjects aged 18 to 75 years with at least moderate pain from fibromyalgia, defined as ≥40 mm on a 100-mm pain visual analog scale. All subjects fulfilled the 1990 American College of Rheumatology classification guidelines for the diagnosis of fibromyalgia (2). Subjects were also required to be in general good health, and women were required to be practicing contraception or incapable of pregnancy.

Exclusion criteria included previous failure of tramadol therapy (4 patients excluded), use of tramadol in the prior 30 days, and any other pain that was more severe than the fibromyalgia pain. Patients were allowed to take a low-dose selective serotonin reuptake inhibitor (SSRI) or St. John’s wort (but not both) for depression, and zolpidem and flurazepam for sleep, provided they had been on a stable dose of these drugs for at least 1 month. We excluded patients who had used other antidepressants, cyclobenzaprine, antiepileptic drugs for pain, acupuncture, or transcutaneous electrical nerve stimulation within 3 weeks before enrollment; recent use (within 5 half-lives) of other sedative hypnotics, short-acting analgesics (including acetaminophen), topical medications/anesthetics, or muscle relaxants; tender point anesthetic injections within 2 months; systemic steroids within 3 months; or any investigational drug/device in the prior 30 days.

The study was designed in accordance with the Declaration of Helsinki, and an independent Institutional Review Board approved the study protocol. Investigators at 27 sites participated (Appendix).

Intervention
Before entry into the double-blind phase of the study, all subjects completed a screening and washout phase of up to 3 weeks’ duration. Subjects were then randomly assigned to receive tramadol/acetaminophen (37.5-mg/325-mg tablet, ULTRACET™, Ortho-McNeil Pharmaceutical, Raritan, New Jersey) or matching placebo (Figure 1). Study medication was titrated over a 10-day period from one tablet per day to four tablets per day. Thereafter, subjects took one to two tablets four times daily, to a maximum of eight tablets per day (total of 300 mg tramadol/2600 mg acetaminophen). Doses were selected on the basis of previous studies of tramadol and acetaminophen for chronic pain, including fibromyalgia pain.

Figure 1. Design of the study. Subjects underwent a 3-week washout phase, followed by enrollment and randomization, with dose escalation (see Methods). bid = two times daily; hs = at night; tid = three times daily; qd = four times daily.
had completed therapy and the database had been finalized.

**Outcome Measures**

Visits were scheduled for days 1, 14, 28, 56, and 91 (Figure 1). The primary efficacy variable was defined in the protocol as cumulative time to discontinuation due to lack of efficacy. However, because discontinuation due to lack of efficacy may be underestimated owing to competing risks, discontinuation for any reason was also analyzed and this more conservative analysis is highlighted here to reflect clinical practice.

Secondary variables measured at each visit included pain on a visual analog scale (100-mm line, from no pain to extreme pain [100]) and a pain relief rating scale (complete = 4, a lot = 3, moderate = 2, slight = 1, none = 0, worse = −1). At the first and last visits, investigators determined the number of tender points (of 18) and myalgic score (no pain = 0, patient complains of pain only = 1, patient reacts to pain emotionally = 2, patient withdraws or flinches = 3); an average myalgic score was calculated. Subjects also completed the 10-item Fibromyalgia Impact Questionnaire (36), the Short Form 36 (SF-36) health survey (37), and a 12-item sleep questionnaire at the first and last visit (38). The Sleep Questionnaire is a 12-question survey used to evaluate sleep habits during the previous 4 weeks, administered on day 1 and at the final visit. Scores are transformed to a 0 to 100 scale and used to derive two overall sleep indexes: Sleep Index 6 (from six of the questions) and Sleep Index 9 (from nine of the questions). Lower values represent better sleep.

A complete medical history, physical examination, and urinalysis were performed at the screening visit (day −21) and the final visit. Vital signs (sitting pulse, blood pressure, and weight) were measured at baseline and at each visit. Chemistry and hematology laboratory tests were performed at screening and at visits on days 28, 56, and 91.

Adverse events were recorded at each visit, whether spontaneously reported or in response to general, nondirected questioning. Adverse events were summarized by World Health Organization Adverse Reaction Terminology body system and preferred term. If a subject discontinued treatment, all efficacy and safety variables that were planned for the final visit were recorded at the time of discontinuation.

**Statistical Analyses**

Efficacy analyses were performed on the intent-to-treat sample, comprised of all enrolled subjects who took at

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* Took at least dose of double-blind study medication but did not complete at least one post-randomization efficacy evaluation.

Figure 2. Flow chart of subject disposition.
least one dose of study medication and for whom a post-randomization efficacy measurement was available. Time to discontinuation was examined by survival analysis techniques, and statistical significance was assessed with the generalized Wilcoxon test. Cox proportional hazards analyses were performed for two outcomes: discontinuation due to any reason and discontinuation due to lack of efficacy; these analyses adjusted for baseline pain and clinical center. Data from small centers (<10 subjects) were pooled for this purpose. Secondary efficacy variables were summarized and assessed with analysis of covariance adjusting for baseline pain in vital signs and clinical laboratory values were also assessed. Proportions of subjects with adverse events were compared using the Fisher exact test. Statistical significance was set at \( P < 0.05 \) (two-sided). The sample size was determined to have 90% power to detect a 20% difference in discontinuation rates due to lack of efficacy (55% vs. 75%). The calculated sample size of 112 subjects per group was increased approximately 30% to compensate for patients who dropped out because of adverse events, for a total of 150 subjects in each group. All analyses were performed with SAS Version 6.12 software (Cary, North Carolina).

**RESULTS**

A total of 315 subjects were assigned randomly to tramadol/acetaminophen (\( n = 158 \)) or placebo (\( n = 157 \)), of whom 313 were evaluable for efficacy and 312 were evaluable for safety (Figure 2). Subjects ranged in age from 19 to 75 years; most were women and white (Table 1). The mean (± SD) pain score at baseline (on a 0- to 100-mm visual analog scale) was 72 ± 15 mm (Table 2). There were no significant baseline differences between the two groups (Tables 1 to 3).

**Primary Efficacy Outcome**

The cumulative rate of discontinuation of therapy for any reason was significantly lower in the tramadol/acetaminophen group (48% by day 91) than in the placebo group (62% by day 91; \( P = 0.004 \); Figure 3A). The cumulative rate of discontinuation due to lack of efficacy was also significantly lower in the tramadol/acetaminophen group (29% by day 91) than in the placebo group (51% by day 91; \( P < 0.001 \); Figure 3B).

**Secondary Outcome Measures**

Compared with placebo, the mean final pain score was about 12 mm (18%) lower in the tramadol/acetaminophen group (Table 2; \( P < 0.001 \)). Similarly, mean final pain relief was significantly better in the tramadol/acetaminophen group than in the placebo group (Table 2;

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**Table 1.** Demographic Characteristics of the Sample of Subjects with Fibromyalgia*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tramadol/ Acetaminophen (( n = 156 ))</th>
<th>Placebo (( n = 157 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 11</td>
<td>51 ± 10</td>
</tr>
<tr>
<td>Female sex</td>
<td>145 (93)</td>
<td>149 (95)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>151 (97)</td>
<td>147 (94)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (3)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Only patients included in the intention-to-treat analyses for efficacy are included in this and subsequent tables.

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**Table 2.** Pain and Symptoms at Baseline and the Final Visit  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Final Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tramadol/ Acetaminophen (( n = 156 ))</td>
<td>Placebo (( n = 157 ))</td>
</tr>
<tr>
<td>Pain score (mm)</td>
<td>72 ± 14</td>
<td>72 ± 15</td>
</tr>
<tr>
<td>Pain relief score</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Number of tender points</td>
<td>16 ± 2.2</td>
<td>16 ± 2.3</td>
</tr>
<tr>
<td>Average myalgic score</td>
<td>1.7 ± 0.6</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>Sleep questionnaire</td>
<td>62 ± 16</td>
<td>61 ± 17</td>
</tr>
<tr>
<td>Sleep Index 6</td>
<td>62 ± 16</td>
<td>61 ± 16</td>
</tr>
<tr>
<td>Sleep Index 9</td>
<td>62 ± 16</td>
<td>61 ± 16</td>
</tr>
</tbody>
</table>

* Comparison between final values based on analysis of covariance adjusting for clinical center and baseline values.

1. 0 mm (no pain) to 100 mm (extreme pain) on a visual analog scale.
2. Complete relief = 4, a lot = 3, moderate = 2, slight = 1, none = 0, worse = −1.
3. Calculated from myalgic scores at each tender point, where no pain = 0, patient complains of pain only = 1, patient reacts to pain emotionally = 2, and patient withdraws or flinches = 3.
4. Lower scores represent better sleep, on a 0 to 100 scale.
P < 0.001). Subjects in the tramadol/acetaminophen group also had a significantly greater decrease in the number of tender points during the trial, and lower average myalgic scores at the end of the trial (Table 2).

Forty-two percent (65/156) of the tramadol/acetaminophen group had at least a 30% reduction in pain score, compared with 24% (37/157) of the placebo group (18% difference; 95% confidence interval [CI]: 8% to 28%; P < 0.01). Similarly, 35% (n = 54) of the tramadol/acetaminophen-treated subjects had at least a 50% reduction in pain, compared with 18% (n = 29) of the placebo-treated subjects (16% difference; 95% CI: 7% to 26%; P < 0.01).

Significant differences favoring the tramadol/acetaminophen group were also found for the total Fibromyalgia Impact Questionnaire score, as well as for six of the 11 individual subscales, at the end of the study (Table 3). There were also significant differences in several measures of health status at the end of the study (Table 3).

Table 3. Measures of Symptoms (Using the Fibromyalgia Impact Questionnaire) and Overall Health Status (Using Short Form 36) at Baseline and Final Visit

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Final Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tramadol/</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td></td>
<td>(n = 156)</td>
<td>(n = 157)</td>
</tr>
<tr>
<td>Fibromyalgia Impact Questionnaire†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>54 ± 11</td>
<td>55 ± 11</td>
</tr>
<tr>
<td>Physical impairment</td>
<td>4.4 ± 2.4</td>
<td>4.8 ± 2.2</td>
</tr>
<tr>
<td>Feel good</td>
<td>2.1 ± 2.3</td>
<td>2.1 ± 2.0</td>
</tr>
<tr>
<td>Work missed</td>
<td>0.9 ± 2.1</td>
<td>0.8 ± 1.9</td>
</tr>
<tr>
<td>Do job</td>
<td>6.1 ± 2.2</td>
<td>6.4 ± 2.4</td>
</tr>
<tr>
<td>Pain</td>
<td>7.2 ± 1.7</td>
<td>7.2 ± 1.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.0 ± 1.7</td>
<td>8.1 ± 1.6</td>
</tr>
<tr>
<td>Rest</td>
<td>8.1 ± 1.6</td>
<td>8.2 ± 1.6</td>
</tr>
<tr>
<td>Stiffness</td>
<td>7.7 ± 1.8</td>
<td>7.9 ± 1.6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.5 ± 2.9</td>
<td>5.8 ± 2.9</td>
</tr>
<tr>
<td>Depression</td>
<td>5.0 ± 2.9</td>
<td>5.0 ± 2.9</td>
</tr>
<tr>
<td>SF-36 health survey‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>40 ± 23</td>
<td>37 ± 21</td>
</tr>
<tr>
<td>Body-physical</td>
<td>11 ± 23</td>
<td>12 ± 25</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>29 ± 13</td>
<td>27 ± 13</td>
</tr>
<tr>
<td>General health</td>
<td>48 ± 20</td>
<td>45 ± 22</td>
</tr>
<tr>
<td>Vitality</td>
<td>20 ± 17</td>
<td>20 ± 16</td>
</tr>
<tr>
<td>Social functioning</td>
<td>52 ± 24</td>
<td>47 ± 27</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>38 ± 41</td>
<td>46 ± 42</td>
</tr>
<tr>
<td>Mental health</td>
<td>59 ± 20</td>
<td>60 ± 19</td>
</tr>
<tr>
<td>Reported health transition</td>
<td>63 ± 24</td>
<td>64 ± 24</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>29 ± 7.2</td>
<td>28 ± 7.5</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>41 ± 11</td>
<td>42 ± 11</td>
</tr>
</tbody>
</table>

* Comparison between final values, based on an analysis of covariance adjusting for clinical center and baseline values.
† Total score measured on a 0 to 100 scale; others on a 0 to 10 scale. Lower values represent lesser effects of fibromyalgia, except for “feel good.”
‡ Higher values (on a 0 to 100 scale) indicate a better quality of life, except for “reported health transition.”
SF-36 = Short Form 36.
(76%) in the tramadol/acetaminophen group reported at least one adverse event, compared with 87 subjects (56%) in the placebo group ($P < 0.001$; Table 4).

Treatment-related adverse events (deemed by the investigators to be related to the study medication) occurred in 32 (21%) of tramadol/acetaminophen subjects and 14 (9%) of placebo subjects ($P = 0.005$). The most commonly occurring (>3%) treatment-related adverse events in the tramadol/acetaminophen group were nausea (n = 14 [9%]), dizziness (n = 5 [3%]), somnolence (n = 5 [3%]), and constipation (n = 5 [3%]). The most commonly occurring treatment-related adverse events in the placebo group were nausea (n = 7 [4%]) and somnolence (n = 5 [3%]). No serious adverse event was considered by the investigators to be related to the study medication.

No clinically relevant trends were identified in changes in vital signs or hematology, chemistry, or urinalysis values. All markedly abnormal laboratory values during the trial were transient, or were thought by the investigator to be not clinically important or to be attributable to causes other than study medication.

Figure 3. Kaplan-Meier estimate of time to discontinuation for any reason (A) or for lack of efficacy (B). The $P$ values were computed using Cox proportional hazards regression analysis adjusting for clinical center and baseline pain. APAP = acetaminophen.
The results of this study demonstrate that a 37.5-mg tramadol/acetaminophen combination tablet is a safe, moderately effective, and well-tolerated medication for the treatment of fibromyalgia pain and related symptoms. Although subjects in the tramadol/acetaminophen group had a statistically significant improvement in the primary outcome measure and many of the secondary outcome measures as compared with placebo-treated subjects, improvements from baseline values in the placebo group were also seen (Tables 2 and 3). This is not unexpected, as pain is responsive to the placebo effect. However, pain scores improved by 25% in the tramadol/acetaminophen group compared with 5% in the placebo group, and more subjects in the tramadol/acetaminophen group had a statistically significant improvement in the Fibromyalgia Impact Questionnaire score compared with placebo-treated subjects. Thus, it seems likely that the overall benefit of tramadol/acetaminophen treatment is clinically meaningful.

TREATMENT FAILURE IS COMMON IN FIBROMYALGIA. A meta-analysis of 33 medication studies reported that antidepressants, muscle relaxants, and assorted other medications had significant effects on physical status and fibromyalgia symptoms (16). However, these effects were greater in open-label studies than in placebo-controlled studies. The reasons for the relative lack of success of many pharmacologic treatments for fibromyalgia are not entirely clear. In an attempt to design scientifically rigorous studies in this area, most previous studies have required discontinuing sleep medications and antidepressants. However, poor sleep and depression are associated with increased symptoms of fibromyalgia. Thus, extensive washout protocols may be self-defeating, and many rheumatologists believe that medications that are only marginally effective for fibromyalgia in controlled studies often seem more effective when used as part of a multidimensional treatment program. For this reason, antidepressants for the management of depression (but not pain) and two commonly used hypnotics (zolpidem and flurazepam) were permitted in this study. Furthermore, subjects were asked not to alter their nonpharmacologic therapies during the study.

Tramadol alone has been shown to be safe and efficacious for the management of fibromyalgia (31). The risk of abuse and dependence with tramadol has been found to be very low—approximately one reported case per 100,000 patient exposures. Reported cases of abuse and dependence have occurred predominantly (97%) among persons with a previous history of substance abuse and dependence (39).

Acetaminophen has a low therapeutic/toxic ratio, and patients should be informed about the inclusion of acetaminophen in the combination tablet. Adverse events are rare with therapeutic doses of acetaminophen (≤4 g/d), but given the large number of products, both prescription and over-the-counter, which contain acetaminophen, there is a potential for accidental toxicity when several acetaminophen products are combined.

Fibromyalgia is a chronic disorder that often requires lifelong treatment using a multimodal approach to management (7,40). The current study shows that tramadol/acetaminophen is of moderate benefit over a 13-week period. Further study is needed to determine whether the long-term use of tramadol/acetaminophen will provide enduring benefit in the management of fibromyalgia pain and symptoms.

**REFERENCES**


APPENDIX
The lead investigators and sites for the study are as follows: Barry Bockow, MD, Arthritis Northwest, Seattle, Washington; David G. Borenstein, MD, Arthritis and Rheumatism Associates, Washington, D.C; Jacques Caldwell, MD, Gainesville Clinical Research Center, Gainesville, Florida; Ronald D. Emkey, MD, Emkey Arthritis & Osteoporosis Clinic, Inc., Wyomissing, Pennsylvania; Mark Ettinger, MD, Clinical Research Center of South Florida, Stuart, Florida; Geoffrey Gladstein, MD, Stanford Therapeutics Consortium, Stamford, Connecticut; Maria Greenwald, MD, AIM, Rancho Mirage, California; Alan Kaell, MD, Rheumatology Associates of Long Island, Port Jefferson, New York; Ahmad Kashif, MD, Nalle Clinic, Charlotte, North Carolina; Warren A. Katz, MD, Presbyterian Medical Center/Arthritis Associates of Philadelphia, Philadelphia, Pennsylvania; Alan Kivitz, MD, Altoona Center for Clinical Research, Duncansville, Pennsylvania; Larry Moreland, MD, The University of Alabama at Birmingham Spain Rehabilitation Center, Birmingham, Alabama; R. Zorba Paster, MD, Dean Medical Center--Oregon, Oregon, Wisconsin; Dianne L. Petrone, MD, Arthritis Centers of Texas/Research Associates of North Texas, Dallas, Texas; Ronald Rapoport, MD, Phase III Clinical Research, Fall River, Massachu-
Tramadol/Acetaminophen for Fibromyalgia/Bennett et al

May 2003  THE AMERICAN JOURNAL OF MEDICINE®  Volume 114  545