Efficacy and Safety of Tramadol/Acetaminophen Tablets (Ultracet®) as Add-on Therapy for Osteoarthritis Pain in Subjects Receiving a COX-2 Nonsteroidal Antiinflammatory Drug: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of tramadol 37.5 mg/acetaminophen 325 mg combination tablets (tramadol/APAP) as add-on therapy for subjects with osteoarthritis (OA) pain inadequately controlled by COX-2 nonsteroidal antiinflammatory drugs (NSAID).

Methods. This 91-day, multicenter, randomized, double-blind, placebo-controlled trial enrolled subjects with symptomatic OA for ≥ 1 year who experienced at least moderate pain [visual analog scale (VAS) score ≥ 50/100 mm] despite treatment with stable doses of celecoxib (≥ 200 mg/day) or rofecoxib (≥ 25 mg/day). Tramadol/APAP or matching placebo was titrated to 4 tablets/day on Day 10 and thereafter as needed up to 8 tablets/day. The primary efficacy measure was final VAS score; secondary measures included final pain relief rating scores, subject/investigator overall medication assessments, rate and time to discontinuation due to lack of efficacy, and selected quality-of-life/physical functioning scores.

Results. Of 307 subjects randomized, 306 taking celecoxib (56.5%) or rofecoxib (43.5%) were included in the intent-to-treat population (n = 153 tramadol/APAP, 153 placebo). Mean final VAS scores for tramadol/APAP plus COX-2 NSAID were significantly lower than placebo plus COX-2 NSAID (41.5 vs 48.3; p = 0.025) and mean final pain relief rating scores were significantly higher (p = 0.002). Subjects taking tramadol/APAP showed significant improvements compared with placebo in subject/investigator medication assessments, as well as in the WOMAC Physical Function and the Medical Outcome Study Short Form-36 Role-Physical measures. The most common treatment-related adverse events for tramadol/APAP were somnolence (6.5%), nausea (4.6%), and constipation (3.3%). Mean tramadol/APAP dose was 4.1 tablets (154 mg tramadol/1332 mg APAP).

Conclusion. Tramadol 37.5 mg/APAP 325 mg combination tablets were effective and safe as add-on therapy with COX-2 NSAID for treatment of OA pain. (J Rheumatol 2004;31:150–6)

Key Indexing Terms:
OSTEOARTHRITIS PAIN TRAMADOL ACETAMINOPHEN
CYCLOOXYGENASE 2 CELECOXIB ROFECOXIB

Osteoarthritis (OA) is a condition that affects articular cartilage in one or more joints. It is the most common form of arthritis, afflicting over 20 million Americans[1]. Thirty percent of women and 17% of men age 60 and over have clinical OA[2], and over 70% of those age 65 and older show radiographic evidence of the disease[3]. As there is no known cure for OA, additional analgesic options are needed for those with OA pain.

Nonsteroidal antiinflammatory drugs (NSAID) — and more recently, cyclooxygenase-2–selective (COX-2) NSAID — are commonly prescribed as monotherapy for OA pain, although antiinflammatory medications alone may not provide adequate OA pain relief[4-6]. In one report of treatment of OA with celecoxib, 64% to 75% of subjects reported no improvement at 12 weeks in their global assessments[7], and similarly, 63% to 76% of subjects with OA flare showed no improvement at 12 weeks for Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain items after celecoxib therapy[8]. NSAID monotherapy has additional drawbacks in managing OA pain, including potentially serious gastrointestinal (GI) and renal toxicities

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Supported by Ortho-McNeil Pharmaceutical, Inc., Raritan, New Jersey, USA.

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Submitted January 29, 2003; revision accepted June 16, 2003.

with high dose, longterm use[9-11], especially in the elderly[12,13]. COX-2 NSAID are associated with a lower rate of upper GI toxicity and appear to have no effect on platelet aggregation[14,15], but they do not offer superior analgesic activity to nonselective NSAID[9]. Also, COX-2 NSAID may be associated with ceiling effects, as well as adverse renal or cardiovascular effects at higher doses[16].

Combining analgesics can potentially improve efficacy and safety and is recommended by the American College of Rheumatology (ACR)[17] and the American Medical Directors Association (AMDA)[18]. AMDA supports the addition of tramadol to acetaminophen (APAP) or NSAID, alone or in combination, for management of chronic pain, and the ACR recommends a combination of complementary analgesic agents or substitution of an alternative pharmacologic agent for patients who do not receive adequate relief from monotherapy with APAP, nonselective NSAID, or COX-2-specific inhibitors.

Tramadol 37.5 mg/APAP 325 mg tablet analgesic medication combines reduced amounts of 2 well established centrally-acting analgesics. APAP has multiple mechanisms of action, including inhibition of prostaglandin-E_2 release[19] and inhibition of nitric oxide synthesis[20], and tramadol acts as a μ-opioid receptor agonist that inhibits norepinephrine and serotonin reuptake[21]. In recent dental pain studies, combining tramadol and APAP provided faster onset of action compared to tramadol alone (17 min vs 51 min) and longer duration of action (5.03 h) compared with tramadol alone (2.03 h) or acetaminophen (3.05 h)[22]. Tramadol/APAP has demonstrated efficacy when used to relieve acute painful flares of joint pain due to OA in subjects taking stable doses of NSAID[23], and as monotherapy for the treatment of both chronic low back pain[24,25] and fibromyalgia[26].

We investigated if the addition of tramadol/APAP therapy could improve pain control for subjects whose OA-related joint pain was inadequately controlled by therapeutic amounts of COX-2-specific inhibitors (celecoxib or rofecoxib).

MATERIALS AND METHODS

Study design and population. This 91-day, multicenter, out-subject, randomized, double-blind, placebo-controlled trial was conducted in subjects who had symptomatic OA of the knee or hip for ≥ 1 year who were experiencing at least moderate OA pain [score on visual analog scale (VAS) ≥ 50/100 mm] despite treatment with a stable dose of celecoxib (≥ 200 mg/day) or rofecoxib (≥ 25 mg/day) for at least 2 weeks preceding the study. Subjects who could not tolerate rofecoxib 25 mg/day were permitted to enter the study if they were taking rofecoxib 12.5 mg/day for at least 5 days. After a 3-week screening and washout period of all non–COX-2 analgesics, subjects were randomized to receive tramadol/APAP or matching placebo for a total of 13 weeks. Study medication was titrated by one tablet every 3 days to a total of 4 tablets/day on Day 10, and thereafter as needed to a maximum of 8 tablets/day.

Subjects were selected if the symptomatic OA was evidenced by pain and by osteophytes confirmed by radiograph within the last 2 years. Women were required to be using an accepted method of contraception and to have a negative pregnancy test within one week of study entry, or to be postmenopausal and/or to be incapable of pregnancy due to surgery. Key exclusion criteria included use of antidepressants, cyclobenzaprine, or antiepileptic drugs for pain within 3 weeks of the double-blind phase, although subjects receiving a selective serotonin reuptake inhibitor (SSRI) for depression for at least one month prior to double-blind phase were permitted to continue. Also excluded were the use of sedative hypnotics, short-acting analgesics, topical medications and anesthetics, and/or muscle relaxants for < 5 half-lives of the given medication prior to the double-blind phase, the receipt of intraarticular injections of corticosteroids in the target joints within 2 months of study entry, receipt of hyaluronan injections in the target joint within 6 months of study entry, physical therapy prescribed by a health care professional within 3 weeks of the double-blind phase, or use of an investigational drug or device within 30 days of study entry. Individuals with history of rheumatoid arthritis, ankylosing spondylitis, active gout or active pseudogout, major trauma to the target joint within 6 months of study entry, apparent avascular necrosis in the target joint within 6 months of study entry, or anatomical deformities of the target joint that could interfere with evaluation were excluded. Other exclusion criteria were previous failure of tramadol therapy or discontinuation due to adverse events, receipt of tramadol within 30 days of study entry, diagnosis of a major psychiatric disorder or any disorder that could compromise the metabolism of the drug, or history of substance abuse or chronic heavy alcohol abuse.

Subjects were recruited from within investigators' medical practices and through advertising. Subjects (or their legal representatives) provided written consent to participate. The study was designed in compliance with the Declaration of Helsinki (including amendments of 1989), and Institutional Review Boards at the treatment centers approved the study protocol. Investigators at 28 sites participated. All subjects, investigators, and clinical personnel were blinded to treatment assignments until the trial was complete and the database had been finalized.

Outcome measures. The primary efficacy variable was VAS scores, which subjects rated from "no pain" (0 mm) to "extreme pain" (100 mm). Secondary outcomes included pain relief rating scores (scale 4 to –1: 4 = complete, 3 = a lot, 2 = moderate, 1 = slight, 0 = none, –1 = worse), overall medication assessment by both physicians and subjects at final visit, cumulative distribution of time to discontinuation due to lack of efficacy, proportion of subjects discontinuing due to lack of efficacy, WOMAC OA Index questionnaire scores, and Short-Form-36 (SF-36) Health Survey scores. The WOMAC OA Index questionnaire is a multidimensional measure of pain, stiffness, and physical functional disability composed of 24 questions and an overall score[27]. Items are scored by a numerical scale from 0 (no pain, symptoms, or physical disability) to 4 (extreme levels) on a Likert scale[28]. The Medical Outcome Study SF-36 Health Survey is a general health status measure used to evaluate the subject's physical, social, and mental well being. Efficacy analyses were performed on the intent-to-treat population, defined as all randomized subjects who took at least one dose of study medication and for whom a post-randomization efficacy measurement was available. Lack of efficacy was indicated by discontinuation due to insufficient pain relief, which was defined as subjects who felt that they were in need of rescue medication.

Safety assessments were performed on randomized subjects who took at least one dose of study medication and had at least one available post-baseline safety measurement. The number and percentage of subjects reporting adverse events and their severity were tabulated for both treatment groups, and subjects reporting serious adverse events or withdrawing due to an adverse event were recorded. An assessment of the relationship of adverse events to study medication was also conducted.

Statistical analyses. For the primary efficacy measure (VAS scores) and secondary measures of WOMAC and SF-36 scores, the statistical significance of any difference in the mean scores between the tramadol/APAP and placebo groups was assessed by an analysis of covariance (ANCOVA) with baseline score as covariate and treatment and center as qualitative factors. Similarly, pain relief rating scores and subject/investigator overall assess-

ments were analyzed by ANCOVA, with baseline pain intensity as covariate and treatment and center as qualitative factors. For analysis of primary and secondary endpoints with missing evaluations at a study visit that was otherwise completed, the last prior post-baseline evaluations were carried forward. This imputation algorithm did not include extrapolation of data to visits beyond the last recorded visit of any participant. The statistical significance of the difference between tramadol/APAP and placebo in the proportion of subjects who discontinued due to lack of efficacy was assessed using the logistic regression analysis with treatment and center as qualitative factors. The cumulative distribution of time to discontinuation due to lack of efficacy was estimated using the Kaplan-Meier method and compared using the log-rank test.

All statistical tests were conducted at the 2-sided, $\alpha = 0.05$ significance level. For analysis purposes, centers having 10 or fewer randomized subjects were pooled after the last subject was randomized in the study and prior to database-lock. A sample size of 143 subjects per group was required to have an 80% power to detect a mean difference of 10 mm on the VAS scale, assuming that the common standard deviation is 30 mm using a 2-group t test with a 0.05 2-sided level of significance. The sample size for this study was chosen to be at least 150 subjects per group.

RESULTS

Of 307 subjects randomized, 306 (n = 153 tramadol/APAP, n = 153 placebo) taking celecoxib (55.5%) or rofecoxib (43.5%) for the treatment of knee pain (77.5%) or hip pain (22.5%) were included in the intent-to-treat population. The disposition of subjects is shown in Figure 1. A summary of demographic and baseline characteristics of the intent-to-treat population is presented in Table 1. Of the 306 intent-to-treat subjects, 209 (68.3%) were women and 97 (31.7%) were men, and the mean age was 61 years (range 40–75). There were no statistically significant differences ($p > 0.05$) between treatment groups with respect to baseline demographics and other variables.

Mean baseline VAS scores in the intent-to-treat population were similar for the tramadol/APAP and placebo groups (69.0 mm and 69.5 mm, respectively) (Table 2). The tramadol/APAP group had a significantly lower mean final VAS score (41.5 mm) than the placebo group (48.3 mm; $p = 0.025$). The mean change from baseline was greater in the tramadol/APAP group (–27.5 mm) than in the placebo group (–21.2 mm). In addition, a categorical responder analysis that found 59.5% of the tramadol/APAP group, compared with 47.7% of the placebo group, had ≥ 30% reduction in mean pain visual analog score ($p = 0.029$), a favorable responder rate that is consistent with a clinically meaningful response.

Final pain relief rating scores were significantly higher

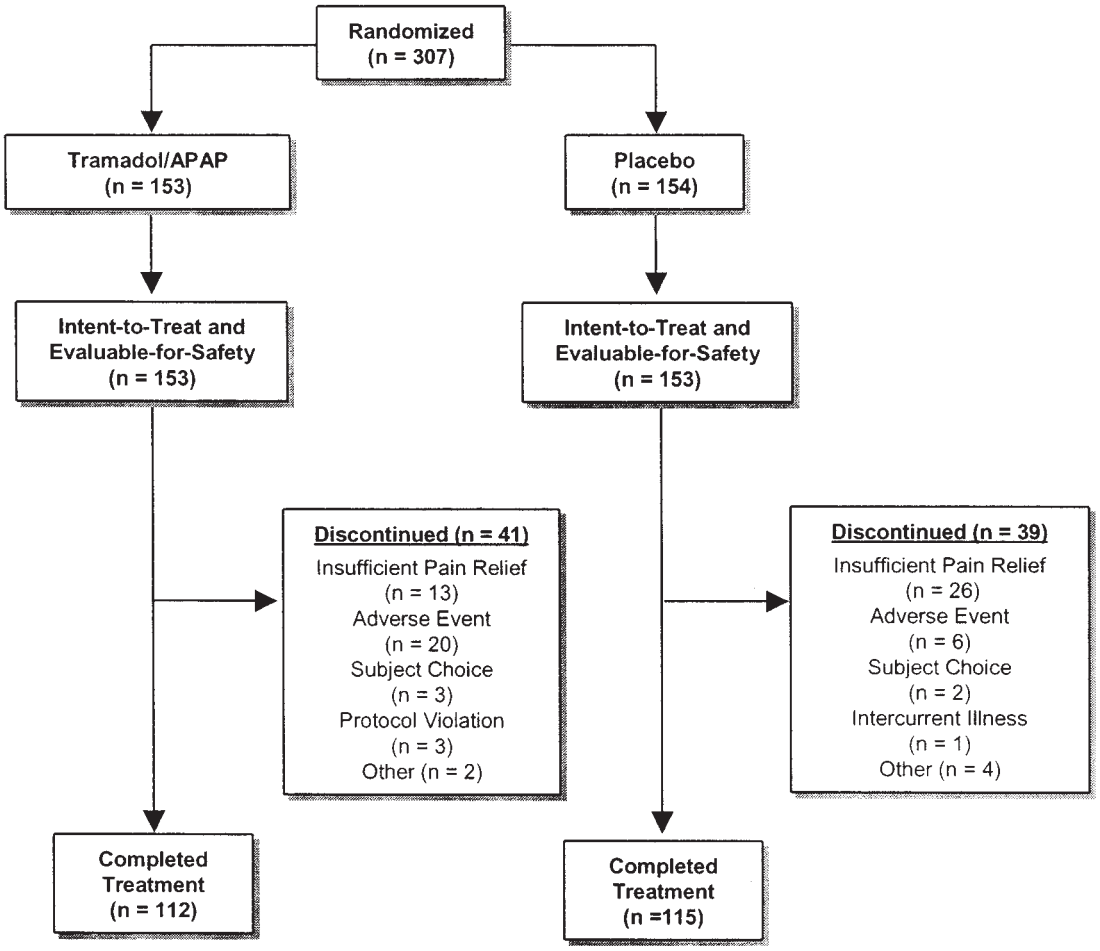

Figure 1. Subject disposition.

Table 1. Summary of demographic and baseline characteristics (intent-to-treat population).

Characteristic	Tramadol/APAP, n = 153	Placebo, n = 153	Total, n = 306
Age, yrs, mean (± SD)	60.1 (± 9.08)	61.8 (± 8.84)	61.0 (± 8.99)
< 65, n (%)	99 (64.7)	89 (58.2)	188 (61.4)
≥ 65, n (%)	54 (35.3)	64 (41.8)	118 (38.6)
Race, n (%)			
White	130 (85.0)	133 (86.9)	263 (85.9)
Black	22 (14.4)	19 (12.4)	41 (13.4)
Asian	1 (0.7)	1 (0.7)	2 (0.7)
Sex, n (%)			
Male	53 (34.6)	44 (28.8)	97 (31.7)
Female	100 (65.4)	109 (71.2)	209 (68.3)
Target joint, n (%)			
Knee	125 (81.7)	112 (73.2)	237 (77.5)
Right	69 (45.1)	61 (39.9)	130 (42.5)
Left	56 (36.6)	51 (33.3)	107 (35.0)
Hip	28 (18.3)	41 (26.8)	69 (22.5)
Right	12 (7.8)	26 (17.0)	38 (12.4)
Left	16 (10.5)	15 (9.8)	31 (10.1)

Table 2. Summary of efficacy measures. Data presented as mean ± SD except where noted. P values were computed to compare final tramadol/APAP measures to final placebo measures, except for SF-36 Health Survey scores, where mean changes from baseline for tramadol/APAP group were compared with mean changes from baseline for the placebo group.

Measure	Tramadol/APAP, n = 153 Baseline	Placebo, n = 153 Baseline	Tramadol/APAP, n = 153 Final	Placebo, n = 153 Final	p
Mean VAS scale score*	69.0 ± 12.52	69.5 ± 13.17	41.5 ± 26.00	48.3 ± 26.63	0.025
Pain relief rating score**	—	—	2.0 ± 1.18	1.6 ± 1.21	0.002
WOMAC Score***					
Amount of pain	5.4 ± 1.42	5.7 ± 1.59	3.8 ± 1.91	4.2 ± 1.84	0.263
Stiffness	6.0 ± 1.65	6.3 ± 1.77	4.4 ± 2.05	4.9 ± 1.92	0.056
Physical function	5.6 ± 1.51	5.9 ± 1.53	3.9 ± 1.84	4.5 ± 1.86	0.049
Overall	5.6 ± 1.38	5.9 ± 1.47	4.0 ± 1.81	4.4 ± 1.73	0.086
SF-36 Health Survey score†					
Physical functioning	30.4 ± 19.33	28.7 ± 18.50	41.3 ± 25.32	36.8 ± 22.13	0.113
Role-physical	24.4 ± 32.73	22.0 ± 32.75	46.8 ± 40.96	35.6 ± 37.46	0.010
Bodily pain	33.3 ± 13.36	29.9 ± 13.59	48.2 ± 20.68	43.8 ± 19.74	0.254
General health	64.4 ± 19.41	64.0 ± 18.99	65.1 ± 20.22	66.9 ± 19.11	0.244
Vitality	46.3 ± 20.95	43.2 ± 20.60	50.6 ± 21.27	48.9 ± 21.60	0.972
Social functioning	63.8 ± 23.27	60.3 ± 27.47	72.6 ± 25.06	68.1 ± 25.52	0.231
Role-emotional	62.3 ± 40.63	58.5 ± 43.55	70.8 ± 38.80	63.3 ± 43.75	0.123
Mental health	74.2 ± 16.98	73.4 ± 17.43	77.1 ± 17.94	75.6 ± 18.33	0.508
Reported health transition	53.0 ± 22.00	57.0 ± 24.15	42.2 ± 23.66	46.8 ± 23.30	0.184
Physical component summary	28.4 ± 7.52	27.8 ± 6.71	34.0 ± 10.23	32.6 ± 8.78	0.276
Mental component summary	52.6 ± 10.35	51.6 ± 10.89	53.5 ± 10.09	52.6 ± 11.02	0.579
Subjects' overall assessment††	—	—	0.8 ± 1.08	0.4 ± 1.19	0.005
Investigators' overall assessment††	—	—	0.8 ± 1.07	0.4 ± 1.19	0.001
Cumulative distribution of time to discontinuation due to lack of efficacy, %#	—	—	8.9	17.7	0.016
Proportion of subjects discontinuing due to lack of efficacy, n (%)	—	—	13 (8.5)	26 (17.0)	0.029

* 100 mm scale, where no pain = 0 to extreme pain = 100. ** Likert scale, where complete relief = 4, a lot = 3, moderate = 2, slight = 1, none = 0, worse = –1. *** The normalized range is 0–10 for each WOMAC category, lower scores indicating better improvement. Only those subjects with both baseline and final values are included. † SF-36 Health Survey scores are transformed to a 0–100 scale, a higher score indicating better quality of life, except for Reported Health Transition, where a higher score indicates a diminished quality of life. Only those subjects with both baseline and final values are included. †† Likert scale, where very good = 2, good = 1, no change = 0, poor = –1, very poor = –2. # Kaplan-Meier estimates after 84 days of therapy.

for the tramadol/APAP group (p = 0.002), with a greater proportion of subjects reporting pain relief as "complete" (4.6% vs 0.7%) or "a lot" (37.8% vs 26.5%) compared with those receiving placebo. Pain relief scores improved consistently across 4 time periods (Days 2–20, 21–41, 42–73, and > Day 73) in the tramadol/APAP group (1.7, 1.9, 2.0, 2.2, respectively), while the scores in the placebo group reached a plateau (1.3, 1.8, 1.7, 1.9). The cumulative distribution of time to discontinuation due to lack of efficacy was significantly earlier for placebo (p = 0.016). The proportion of subjects discontinuing treatment due to lack of efficacy was twice as large in the placebo group (17.0%) compared with the tramadol/APAP group (8.5%; p = 0.029).

Tramadol/APAP received higher ratings on overall assessment by both subjects (p = 0.005) and investigators (p = 0.001). Roughly two-thirds of subjects (67.8%) and investigators (71.1%) assessed tramadol/APAP as "Good" or "Very Good," compared with 54.3% of subject ratings and 54.0% of investigator ratings from the placebo group.

The mean baseline WOMAC scores for each category (Amount of Pain, Stiffness, Physical Function, Overall) were similar for both treatment groups (Table 2). Subjects in the tramadol/APAP group had a significantly improved (lower) mean final WOMAC score for Physical Function compared with the placebo group (3.9 and 4.5, respectively; p = 0.049). Subjects in the tramadol/APAP group had improved mean final WOMAC scores compared with placebo for Stiffness and Overall, which approached statistical significance (p = 0.056 and p = 0.086, respectively). Mean final WOMAC scores for the Amount of Pain were not statistically significant between treatment groups.

Quality-of-life measures on the SF-36 Health Survey showed greater numerical improvements for the tramadol/APAP group than for placebo in Physical Functioning, Bodily Pain, Social Functioning, Role-Emotional, Mental Health, Reported Health Transition, and Physical Component Summary (Table 2). A significant treatment-group difference was detected for the Role-Physical subscale (p = 0.010).

The mean tramadol/APAP dose was 4.1 tablets (154 mg tramadol/1332 mg APAP). A total of 306 participants (n = 153 tramadol/APAP, n = 153 placebo) were evaluable for safety. Discontinuations due to adverse events occurred in 13.1% of tramadol/APAP subjects and 3.9% of placebo subjects, with the greatest incidence for nausea (3.9%), constipation (2.6%), dizziness (2.0%), and somnolence (2.0%) in the tramadol/APAP group, while no treatment-limiting adverse event had incidence ≥ 1% in the placebo group. In the tramadol/APAP group, the most common treatment-related adverse events were somnolence, nausea, and constipation, while dizziness was the most common treatment-related adverse event in the placebo group (Table 3). No serious adverse event occurred that was considered related to the study medication.

Table 3. Adverse events with ≥ 1.0% incidence by relationship to study medication.

	Tramadol/APAP, n = 153		Placebo, n = 153	
	Related*, n (%)	Unrelated, n (%)	Related*, n (%)	Unrelated, n (%)
Adverse Event				
Somnolence	10 (6.5)	8 (5.2)	1 (0.7)	0 (0.0)
Nausea	7 (4.6)	16 (10.5)	1 (0.7)	6 (3.9)
Constipation	5 (3.3)	15 (9.8)	0 (0.0)	5 (3.3)
Fatigue	4 (2.6)	6 (3.9)	0 (0.0)	2 (1.3)
Vomiting	2 (1.3)	2 (1.3)	0 (0.0)	0 (0.0)
Dizziness	1 (0.7)	9 (5.9)	2 (1.3)	2 (1.3)

* Relationship to study medication was judged Probable or Very Likely by the investigator.

DISCUSSION

Results from this study support the use of tramadol 37.5 mg/APAP 325 mg combination tablets as adjunctive therapy for OA pain when COX-2-selective NSAID therapy alone is insufficient. The final mean VAS scores as well as the pain relief rating scores were significantly lower for subjects treated with tramadol/APAP in combination with a COX-2 NSAID, as compared with subjects treated with placebo and a COX-2 NSAID. The clinical significance of these findings is supported by secondary outcomes that measured physical functioning, quality of life, and efficacy failure (rate and probability of discontinuation), as well as by the outcomes from the subject/investigator assessment. In addition, the favorable VAS categorical responder rate is consistent with a clinically meaningful response as described by Farrar, *et al*[29]. Further, the treatment effect size in our study is comparable to that seen in some monotherapy trials of COX-2 NSAID[30]. In contrast to WOMAC stiffness and physical function and the SF-36 Role-Physical scales, which showed statistically significant improvements, the WOMAC pain score and SF-36 bodily pain score showed numerical but not statistical improvement. This might have occurred as a result of instrument limitations including inadequate sensitivity or specificity[31].

The ACR recommends pharmacologic and nonpharmacologic adjunctive therapies for management of hip or knee OA. The pharmacologic recommendations for the management of hip and knee OA include NSAID, COX-2 NSAID, or APAP for mild to moderate pain, tramadol for moderate to severe pain, and opioids for severe pain. The ACR also states that a combination of complementary analgesic agents or substitution of an alternative pharmacologic agent should be considered for subjects who do not receive adequate relief from monotherapy. However, only one NSAID should be used at any given time, except for the use of a cardioprotective dose of aspirin[17]. Acetaminophen plus an opioid were among the adjunctive pharmacologic options reviewed for the management of OA[32], and combined treatment with

acetaminophen and naproxen was reported to be more effective in reducing pain than naproxen alone. A recent add-on study of painful OA flare showed tramadol/APAP to significantly reduce daily pain intensity (from 2.4 to 1.3 on a 4-point scale) and to improve physical function and overall OA symptoms in subjects whose pain was not adequately controlled by nonselective NSAID or COX-2 NSAID therapy[23].

In addition to assessing the effect of tramadol/APAP as add-on therapy for pain, several functional domains were assessed in this study by the WOMAC Index and SF-36 Health Survey. In a separate study of OA subjects undergoing comprehensive in-subject rehabilitation interventions, comparison of scores from WOMAC and the SF-36 Health Survey found that the most responsive subscore was the pain scale for both instruments, while the physical function improvement scale was more limited, and stiffness was the least responsive subscore. Although the responsiveness of the functional improvement scale was limited, this was detected better by WOMAC than by SF-36[33]. These findings were confirmed in our study of symptomatic OA subjects. The WOMAC physical function subscore showed statistically significant differences between treatments with tramadol/APAP and placebo (3.9 vs 4.5; $p = 0.049$), and the differences in the stiffness subscore (4.4 vs 4.9; $p = 0.056$) and overall subscore (4.0 vs 4.4; $p = 0.086$) approached statistical significance. The magnitude of the changes for the WOMAC pain, physical function, and stiffness scores seen here (16, 17, and 16, respectively, on a normalized 0–100 scale) are likely to be clinically relevant, based on previous estimates of the minimal perceptible clinical improvement using WOMAC measurements for these same scores (9.7, 9.3, and 10.0, respectively, on a 0–100 mm scale)[34].

The effectiveness of tramadol/APAP as add-on therapy for subjects experiencing inadequate pain relief from ongoing COX-2 NSAID therapy shown here reinforces our previous study indicating that tramadol/APAP is effective and well tolerated as add-on therapy in subjects with acute flare of OA pain inadequately controlled by NSAID[23]. In particular, many subjects can attain "a lot" or "complete" pain relief with the addition of tramadol/APAP. The results of the present study reinforce earlier findings[23,35,36] that tramadol/APAP is generally well tolerated by subjects. It was well tolerated as an add-on medication for OA subjects taking celecoxib or rofecoxib, and the most common adverse events were similar to those observed in previous tramadol/APAP studies. There was no evidence of abuse or withdrawal, and no seizures in this study of 307 subjects. The abuse potential with tramadol, an unscheduled medication in the United States, is limited and mainly confined to persons with a history of substance abuse[37]. Tramadol/APAP has shown better tolerability than some opioids in previous evaluations. A lower incidence of constipation (11% vs 21%) and somnolence (17% vs 24%) was found for subjects with chronic low back pain and/or OA receiving tramadol/APAP compared with those receiving codeine/APAP[36]. Similarly, subjects treated with tramadol/APAP following arthroscopic surgery reported lower incidence of constipation (0% vs 11%) and vomiting (8% vs 16%) than those in the codeine/APAP group[38]. In a single-dose comparison of analgesics after oral surgery, the tramadol/APAP group showed reductions of about half for vomiting (12% vs 30%) and nausea (18% vs 36%) compared with the hydrocodone/APAP group[36].

These results indicate that tramadol 37.5 mg/APAP 325 mg combination tablets can be safely added to ongoing COX-2 NSAID therapy for patients with OA and that this combination therapy provides increased analgesic effect. Given the need for alternative analgesics that offer low potential risk for abuse and improved tolerability, these combination tablets provide a useful analgesic choice for clinicians.

APPENDIX

Members of the CAPSS-114 Study Group include J.R. Caldwell, MD, Gainesville, Florida; R.G. Cesearec, MD, Wauwatosa, Wisconsin; G.B. DeLashmet Jr, MD, Jackson, Mississippi; G. Divittorio, MD, Mobile, Alabama; R.D. Emkey, MD, FACP, FACR, Wyomissing, Pennsylvania; S. Fallahi, MD, FACP, Montgomery, Alabama; H.S.E. Fung, MD, FRCPC, FACR, Waco, Texas; L.I. Gilderman, DO, Pembroke Pines, Florida; O.S. Gluck, MD, FACP, FACR, Phoenix, Arizona (replaced by): J. Tesser, MD, Phoenix, Arizona; A.L. Goldman, MD, Milwaukee, Wisconsin; W.L. Gray, MD, Spokane, Washington; M. Greenwald, MD, Rancho Mirage, California; R. Hymowitz, MD, Medford, New Jersey; A.A. Kashif, MD, Charlotte, North Carolina; M.I. Keller, MD, San Diego, California; M.D. Kohen, MD, South Daytona, Florida; L.V. Larsen, MD, PhD, Salt Lake City, Utah; T.W. Littlejohn III, MD, Winston-Salem, North Carolina; S.H. Lourie, MD, Lanham, Maryland; J.D. McKay, DO, FACR, FACOI, Tulsa, Oklahoma; R.B. Nett Jr, MD, RPh, San Antonio, Texas; G.A. Pyke, MD, Longwood, Florida; R.J. Rapoport, MD, FACR, Fall River, Massachusetts; A.J. Razzetti, MD, DeLand, Florida; B.S. Samuels, MD, Dover, New Hampshire; P.A. Saxe, MD, FACP, PA, Delray Beach, Florida; T.L. Shlotzhauer, MD, Rochester, New York; and H.L. Staley, MD, Indianapolis, Indiana.

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