Analgesic Efficacy and Safety of Tramadol/Acetaminophen Combination Tablets (Ultracet®) in Treatment of Chronic Low Back Pain: A Multicenter, Outpatient, Randomized, Double Blind, Placebo Controlled Trial

PAUL M. PELOSO, LUC FORTIN, ANDRÉ BEAULIEU, MARC KAMIN, and NORMAN R. ROSENTHAL
on Behalf of the Protocol TRP-CAN-1 Study Group

ABSTRACT. ***Objective.*** To evaluate the analgesic efficacy and safety of tramadol 37.5 mg/acetaminophen 325 mg (tramadol/APAP) combination tablets for treatment of chronic low back pain (LBP).

Methods. This 91 day, multicenter, outpatient, randomized, double blind, placebo controlled study enrolled 338 patients with chronic LBP requiring daily medication for ≥ 3 months. Patients with at least moderate pain [pain visual analog scale (VAS) with scores ≥ 40/100 mm] after washout were randomized to tramadol/APAP or placebo. After a 10 day titration, patients received 1 or 2 tablets QID. Primary outcome measure was final pain VAS score. Secondary measures included pain relief, quality of life and physical functioning, efficacy failure, and overall medication assessments.

Results. In total, 336 intent-to-treat patients received tramadol/APAP (n = 167) or placebo (n = 169). Mean baseline pain VAS score was 67.8. Intent-to-treat analysis showed significantly better mean final pain VAS scores (47.4 vs 62.9; $p < 0.001$) and mean final pain relief scores (1.8 vs 0.7; $p < 0.001$) for tramadol/APAP than for placebo. Roland Disability Questionnaire scores and physical-related subcategories of the McGill Pain Questionnaire and the Medical Outcome Study Short Form-36 Health Survey were significantly better for tramadol/APAP patients. More patients rated tramadol/APAP as "very good" or "good" than placebo (63.6 vs 25.2%; $p < 0.001$). Kaplan-Meier estimates of cumulative discontinuation rates due to efficacy failures were 22.9% (tramadol/APAP) vs 54.7% (placebo; $p < 0.001$). The most common treatment related adverse events with tramadol/APAP were nausea (12.0%), dizziness (10.8%), and constipation (10.2%). Average daily dose of tramadol/APAP was 4.2 tablets (tramadol 158 mg/APAP 1369 mg).

Conclusion. Tramadol 37.5 mg/APAP 325 mg combination tablets show efficacy in pain reduction, in measures of physical functioning and quality of life, and in overall medication assessments, with a tolerability profile comparable with other opioids used for the treatment of chronic LBP. (J Rheumatol 2004;31:2454–63)

Key Indexing Terms:
LOW BACK PAIN ANALGESIA TRAMADOL ACETAMINOPHEN

Low back pain (LBP) is a ubiquitous condition, affecting 80% to 90% of the population at some point in their lives[1]. Most patients do not receive a specific pathoanatomical diagnosis, but are diagnosed with nonspecific strains, sprains, or degenerative processes[2,3]. The most common cause of work related disability and the second most common cause of physician office visits, LBP has high impact on healthcare expenditures annually[2,4,5]. In some patients, sensitization of nociceptive pathways and neuroplastic changes in the central nervous system may perpetuate the perception of pain in the absence of ongoing tissue damage[6].

Clinical trial data suggest that centrally acting antidepressants and tramadol are effective for patients with chronic back pain[7-11]. Nonsteroidal antiinflammatory drugs appear to offer short-term symptomatic relief from acute LBP, while their effectiveness in chronic LBP is unclear[12].

From the Division of Rheumatology, Roy and Lucille Carver College of Medicine, University of Iowa Health Care, Iowa City, Iowa, USA; Institut de Physiatrie du Québec, Montréal, Québec; Centre Hospitalier Universitaire de Québec, Sainte-Foy, Québec, Canada; and Ortho-McNeil Pharmaceutical, Raritan, New Jersey, USA.

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P.M. Peloso, MD, MSc, Associate Professor of Internal Medicine, Division of Rheumatology, Roy and Lucille Carver College of Medicine, University of Iowa Health Care; L. Fortin, MD, FRCPC, MSc, Program Director of Physiatry, University of Montreal; A. Beaulieu, MD, FRCP, Professor of Medicine (Rheumatology), Faculty of Medicine, Université Laval, Quebec; M. Kamin, MD, Vice-President, Medical Affairs, Ortho Biotech; N.R. Rosenthal, MD, Vice President, Clinical Affairs, Ortho-McNeil Pharmaceutical.

Address reprint requests to Dr. P.M. Peloso, Division of Rheumatology, Roy and Lucille Carver College of Medicine, University of Iowa Health Care E330 GH, 200 Hawkins Drive, Iowa City, IA 52242.
E-mail: ppeloso@adelphia.net

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Patients may also derive benefit from nonpharmacologic interventions such as intensive exercise[13] and massage[14], although these measures are often used adjunctively. Many patients with back pain do not achieve adequate pain relief[15], and new pharmacologic solutions for such difficult to manage pain conditions are clearly needed.

A rational strategy in the pharmacologic treatment of painful conditions is to combine medications that possess different pharmacologic or pharmacokinetic characteristics and exhibit multiple analgesic mechanisms of action. Examples of augmentation of opioid analgesia, at therapeutic doses and at suboptimal doses, by aspirin, acetaminophen, and nonsteroidal antiinflammatory agents have been recognized as effective for the treatment of other forms of chronic pain[16-18]. In addition, the second step of the World Health Organization ladder for pain treatment endorses the addition of non-opioids to opioid analgesic treatments[19]. Further, combining analgesic agents may yield additive or synergistic analgesic effects[20].

The combination of tramadol and acetaminophen (Ultracet® Ortho-McNeil Pharmaceutical Inc., Raritan, NJ, USA) utilizes multiple analgesic mechanisms of action. Tramadol weakly binds to and activates μ-opioid receptors and also inhibits the reuptake of both norepinephrine and serotonin[21], but is associated with a low abuse rate and has maintained its nonscheduled classification[22]. Tramadol has demonstrated efficacy in the management of pain associated with several conditions, including chronic LBP[11,23], diabetic neuropathy[24,25], dental surgery[26,27], and osteoarthritis (OA)[28,29]. Acetaminophen, which is endorsed by the American Pain Society as a first-choice treatment for chronic pain[16], exhibits several centrally mediated mechanisms of action that may contribute to its analgesic efficacy, including inhibition of *N*-methyl-D-aspartate (NMDA) mediated or substance P mediated nitric oxide synthesis[30] and inhibition of prostaglandin-E_2 release in the spinal cord[31].

Tramadol/acetaminophen combination tablets have demonstrated analgesic efficacy for the treatment of pain associated with OA[32], fibromyalgia (FM)[33], and dental surgery[34], while a US based study suggests efficacy in the treatment of chronic LBP[35]. In previous clinical trials, the most common adverse events were nausea, headache, and constipation[27,32,36].

This randomized clinical trial, conducted in Canada, was designed to evaluate the efficacy and safety of tramadol 37.5 mg/acetaminophen 325 mg versus placebo in the treatment of patients with chronic LBP.

MATERIALS AND METHODS

Study design. This was a multicenter, outpatient, randomized, double blind, placebo controlled, parallel-group study that had a screening/washout phase and a double blind phase. Three hundred thirty-eight ambulatory patients with chronic low back pain severe enough to require daily medication for at least 3 months prior to entry were randomized. Inclusion criteria included patients over 18 years of age, with good general health. Female patients were required to either be postmenopausal for at least 1 year, incapable of becoming pregnant, or using appropriate contraceptive methods with a negative pregnancy test within 1 week of study entry. Investigators who specialize in rheumatology, pain management, or physical medicine participated at 30 centers, including university clinics and private practices.

Key exclusion criteria included use of any sedative hypnotics, short-acting analgesics, topical preparations/medications and anesthetics, or muscle relaxants for a period of less than 5 half-lives of the given medication prior to the double blind phase; use of medications that could reduce the seizure threshold within 3 weeks before the double blind phase; use of opioids or initiation of nutraceuticals within 6 weeks of the double blind phase; history of a seizure disorder, unstable medical disease, renal or hepatic dysfunction, substance abuse, inflammatory disease; and more severe pain in a location other than the lower back; or other disease states that may interfere with the interpretation of pain. Also excluded were persons who were known to have neurologic deficits in the lower extremities, tumors or infections of the spinal cord or meninges, symptomatic disk herniation, severe spinal stenosis, spondylolisthesis ≥ Grade 2, history of instability of lumbar vertebrae, as well as persons with acute vertebral fractures or who had had back surgery (except if back pain was responsive to a single surgical procedure more than 5 years prior to study enrollment). Patients could not have received treatment with tramadol within 30 days before study entry, demonstrated inability to tolerate tramadol, or had a contraindication to tramadol or acetaminophen. Physiotherapy that was started prior to the double blind phase was to be maintained throughout the study, or was otherwise not allowed.

The screening/washout phase, during which patients discontinued all pain medications, lasted up to 21 days or until the level of pain became intolerable. Patients with a pain visual analog scale (VAS) score of at least 40/100 mm (scale from 0 mm = no pain to 100 mm = extreme pain) in the low back region within the preceding 48 hours at the end of the screening/washout phase were eligible to enter the double blind phase.

The double blind phase was 91 days in duration. Patients were randomized in a 1:1 fashion to tramadol/acetaminophen or placebo, using a centrally prepared randomization scheme carried out in blocks of 8. Treatment was titrated over the initial 10 days from 1 tablet (identical-appearing tablets containing either tramadol 37.5 mg/acetaminophen 325 mg or matching placebo) at bedtime on Day 1, to 1 tablet QID on Day 10. After the initial titration phase, patients could adjust the daily dosage of study medication as needed up to a maximum of 2 tablets QID and a minimum of 3 tablets/day. Patients were evaluated on Days 1, 14, 28, 56, and 91 (final visit).

No pain medication or treatment other than the study medication was allowed during the course of the study, except for rescue medication (acetaminophen 500 mg, up to 4 tablets daily) during the first 6 days of the double blind phase, provided the patient was taking no more than 6 tablets of study medication daily. Patients experiencing pain that was not associated with the back after the first 6 days of the double blind phase were allowed to take acetaminophen at a maximum dose of 1000 mg/day for 2 consecutive days. This was allowed no more than twice for each patient during the double blind phase. Patients were allowed to continue taking prophylactic doses of aspirin (≤ 325 mg/day) for cardiovascular protection throughout the entire study period. Use of other concomitant analgesics was prohibited, and subjects were reminded of this at each study visit.

Measures. The primary efficacy measure for the assessment of tramadol/acetaminophen in the treatment of chronic LBP was the pain VAS. Using the VAS, administered at each study visit, patients indicated the amount of back pain experienced within the preceding 48 hours by marking a slash through the line of the 100 mm scale. Secondary outcomes included the pain relief rating scale, the Short-Form McGill Pain Questionnaire (SF-MPQ), Roland Disability Questionnaire (RDQ), Medical Outcome Study Short Form-36 (SF-36) Health Survey, and patient/investigator overall medication assessments.

The pain relief rating scale was administered at each study visit starting

with Day 14. Patients were to indicate the amount of back pain relief experienced relative to the no-medication screening/washout phase using a 6 point Likert scale (complete relief = 4, a lot of relief = 3, moderate relief = 2, slight relief = 1, no relief = 0, worse pain = –1).

The SF-MPQ, RDQ, and SF-36 Health Survey were administered on Day 1 and at the final visit. For the SF-MPQ, patients rated 15 pain descriptors (including sensory and affective components) on an intensity scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The sum of the intensity scale scores was calculated for the sensory components (range 0–33), the affective components (range 0–12), and the total descriptors (range 0–45). Also included was the Present Pain Intensity (PPI) index, rated on a 6 point scale of "no pain" to "excruciating pain"[37]. The RDQ is a 24 item questionnaire developed by Roland and Morris[38] that evaluates the features of health status most affected by LBP. Questions include an assessment of physical function, how well the patient feels, and the difficulty in performing activities of daily living. Each question endorsed by a subject rates one point. Scores range from 0 (no disability) to 24 (severe disability)[39,40]. In addition, a measure of "bothersomeness" has been incorporated into the questionnaire. Bothersomeness is defined by the patient's interpretation on a scale from 0 (not at all bothersome) to 10 (extremely bothersome). The SF-36 Health Survey is a 36 item survey used to evaluate the patient's physical, social, and mental well being. The survey has 36 items from which 8 scales representing concepts (such as physical functioning and social functioning) are aggregated. The only unscored item is self-reported health transition. Physical Health Summary and Mental Health Summary are aggregates of the scale. Scores were transformed to a scale of 0 to 100, a higher score indicating better quality of life, except for reported health transition, in which a higher score reflected poorer quality of life.

At the completion of the study, with patients and the investigative team still blinded to the treatment allocation, both the patient and the study investigator rated the overall therapeutic effect of the study medication on its ability to control the patient's LBP, using a 5 point scale (very good = 2, good = 1, no change = 0, poor = –1, and very poor = –2).

Statistical methods. Efficacy analyses were performed on the intent-to-treat (ITT) population, composed of all randomized patients who took at least one dose of study medication in the double blind phase and for whom at least one postrandomization efficacy measurement was available.

The primary efficacy endpoint, the pain VAS score at final visit, was analyzed using an analysis of covariance with baseline score as a covariate and treatment and center as qualitative factors. Secondary efficacy variables, including Pain Relief Rating Scores, the SF-MPQ, RDQ, and SF-36 scores, efficacy failures, and overall medication assessments by patients and investigators were analyzed. All scores were analyzed using ANOVA with score as dependent variable, treatment as a qualitative factor, and the corresponding baseline score as covariate (with the exception of the Pain Relief Rating Score, the investigator overall medication assessment, and the patient overall medication assessment, for which the baseline pain VAS score was the covariate).

Patients who discontinued from the double blind phase due to use of additional pain medication were considered efficacy failures. Kaplan-Meier estimates of the cumulative distribution of time to discontinuation due to lack of efficacy were determined. Patients who discontinued from the study due to lack of efficacy were considered events for the time-to-event analysis. The statistical significance of differences in time to discontinuation due to efficacy failure was assessed using the Cox proportional hazards regression analysis, with treatment and center as qualitative factors.

A sample size of 143 patients per group was estimated to give the study an 80% power to detect a mean difference of 10 mm on the pain VAS (0 = no pain; 100 = extreme pain), assuming that the common standard deviation would be 30 mm using a 2-group t-test with a 2-sided significance level of $\alpha = 0.05$. The sample size was set at 150 patients per group. All statistical tests of main effects were conducted at 2-sided, $\alpha = 0.05$ significance. The evaluable-for-safety population was defined as those randomized patients who took at least one dose of study medication in the double blind phase and for whom at least one safety measurement was available.

Safety. Safety was assessed by monitoring adverse events and changes from baseline in vital signs, laboratory results, and physical examinations. The evaluable-for-safety population was used for all safety analyses. Blinding was accomplished by packaging study medications to appear identical for all treatment groups and by concealing the composition and strength of the test preparations under a label mask. This study was conducted in compliance with the Declaration of Helsinki. The protocol received the approval of Ethics Review Boards at all study sites before initiation of the study. All patients gave written informed consent before being enrolled.

RESULTS

Figure 1 depicts the disposition of patients in the study. Of 338 patients randomized, 336 (99.4%) were included in the ITT population; 2 placebo patients were excluded due to a lack of post-baseline efficacy data. The evaluable-for-safety population was composed of 336 patients (99.4%), excluding 2 placebo patients for whom there were no post-baseline safety data. Of 338 patients randomized, a total of 147 (43.5%) completed the 91 day double blind phase, 86 (51.5%) in the tramadol/acetaminophen group and 61 (35.7%) in the placebo group. The most common reason for early discontinuation was insufficient pain relief; 30 (18.0%) tramadol/acetaminophen and 82 (48.0%) placebo patients discontinued for this reason. Forty-seven patients (28.1%) in the tramadol/acetaminophen group and 13 patients (7.6%) in the placebo group discontinued prematurely due to limiting adverse events. Discontinuations from the study occurred in both study arms over the course of the 3 month treatment. During the first 20 days of treatment, 30.4% of placebo patients withdrew due to any reason compared with 19.8% of tramadol/acetaminophen patients. From Days 21 through 41, an additional 22.6% of placebo patients and 12.6% of the tramadol/acetaminophen group discontinued. From Days 42 through 73, there were further withdrawals of 10.7% of placebo patients and 13.8% of tramadol/acetaminophen patients. After Day 73, there were no further withdrawals from the placebo group and 2.4% withdrawals from the drug group.

Of the 336 patients included in the ITT population, 167 patients received tramadol/acetaminophen and 169 received placebo (Figure 1). A majority of patients (94.3%) were white. The mean age was 57.5 years (range 25–82 yrs) in both groups (Table 1). At baseline the pain VAS score in the 2 treatment groups ranged from 40 to 100 mm, with mean scores of 67.9 mm in the tramadol/acetaminophen group and 67.6 mm in the placebo group (Table 1). There were no clinically meaningful differences between the 2 treatment groups for any demographic or baseline characteristic. The average daily dose was 4.2 tablets for the tramadol/acetaminophen group (tramadol 158 mg/APAP 1369 mg) and 4.1 tablets for patients treated with placebo.

Compared with placebo, the tramadol/acetaminophen group had a significantly lower final mean pain VAS score (62.9 vs 47.4 mm, respectively; $p < 0.001$; Figure 2). Patients treated with tramadol/acetaminophen exhibited significantly better final pain relief rating scores than patients

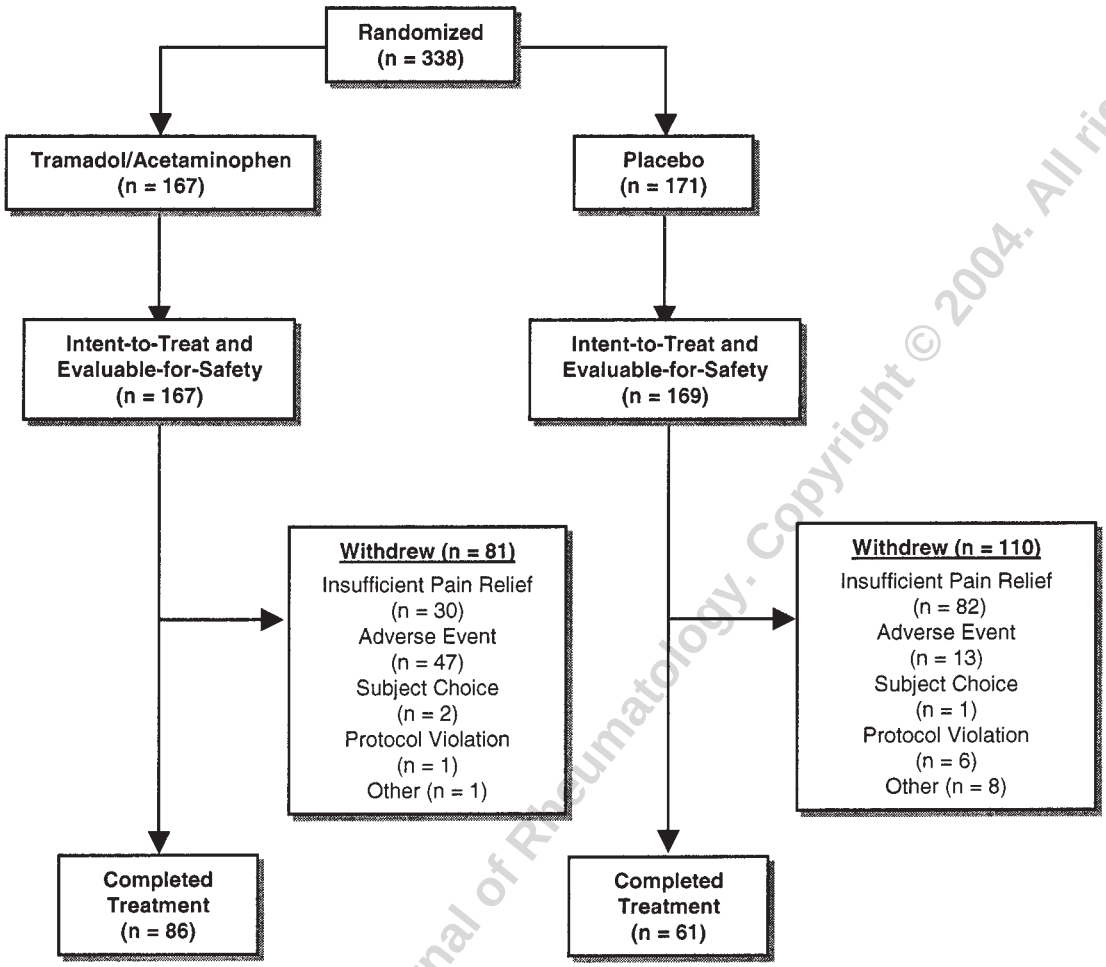

Figure 1. Patient disposition.

treated with placebo ($p < 0.001$; Table 2). A greater proportion of patients in the tramadol/acetaminophen group (65/163; 39.9%) reported final pain relief as complete or a lot, compared with patients in the placebo group (22/165; 13.3%). Conversely, a greater number of patients in the placebo group (96/165; 58.2%) reported pain relief as none or worse, compared with patients in the tramadol/acetaminophen group (37/163; 22.7%).

Table 1. Demographic and baseline characteristics.

Demographic Characteristics	Tramadol/Acetaminophen, n = 167	Placebo, n = 169	Total, n = 336
Age, yrs, mean ± SD	57.5 ± 11.47	57.5 ± 13.56	57.5 ± 12.55
Race, n (%)			
White	158 (94.6)	159 (94.1)	317 (94.3)
Black	0 (0.0)	3 (1.8)	3 (0.9)
Asian	1 (0.6)	0 (0.0)	1 (0.3)
Hispanic	1 (0.6)	1 (0.6)	2 (0.6)
Other	7 (4.2)	6 (3.6)	13 (3.9)
Sex, n (%)			
Male	60 (35.9)	66 (39.1)	126 (37.5)
Female	107 (64.1)	103 (60.9)	210 (62.5)
Baseline pain VAS, mm, mean ± SD	67.9 ± 14.95	67.6 ± 15.53	67.8 ± 15.22
Weight, kg, mean ± SD	79.6 ± 17.05	79.6 ± 17.29	79.6 ± 17.15

VAS: Visual analog scale from 1 to 100, where 0 mm = no pain, 100 mm = extreme pain.

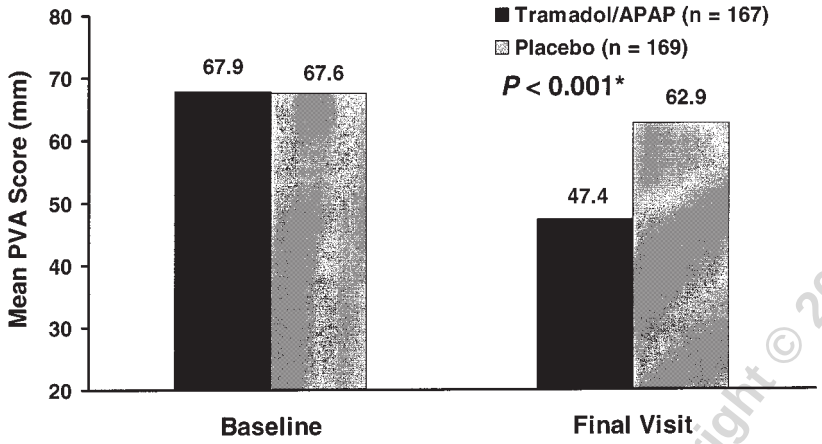

Figure 2. Pain visual analog scale scores. *Tramadol/acetaminophen (APAP) vs placebo, final visit; p value based on ANCOVA model with treatment and center as qualitative factors and baseline values as covariate.

Table 2. Clinical efficacy measures assessed at endpoints.

Endpoint	Tramadol/Acetaminophen, n = 167	Placebo, n = 169	p*
Final visit pain VAS score, mm	47.4	62.9	< 0.001
Final pain relief scores	1.8	0.7	< 0.001
Overall medication assessment scores			
Patients	0.7	–0.4	< 0.001
Investigators	0.6	–0.3	< 0.001

Pain relief scale as follows: complete relief = 4; a lot of relief = 3; moderate relief = 2; slight relief = 1; no relief = 0; worse pain = –1. * Analysis of covariance with baseline pain VAS score as covariate and treatment and center as qualitative factors.

The cumulative distribution of time to discontinuation due to lack of efficacy in the ITT population was significantly longer in the tramadol/acetaminophen group than in the placebo group ($p < 0.001$) based on Kaplan-Meier estimates (Figure 3). Differences between the treatment groups with regard to cumulative distribution of time to discontinuation due to lack of efficacy were apparent by Day 14, and at Day 84 a greater percentage in the tramadol/acetaminophen group continued (77.1%) than in the placebo group (45.4%). Overall, the tramadol/acetaminophen group had better efficacy outcomes compared with the placebo group at the final visit on the SF-36 Health Survey, SF-MPQ, RDQ, and the overall medication assessments (Table 3). For the SF-36 Health Survey, numeric improvement was seen in every subscale as well as for the Physical and Mental Component summaries. Compared with the Canadian norms for persons aged 55–65 years[41], the baseline mean values for Physical Functioning, Bodily Pain, and the Physical Component Summary were roughly 2 standard deviations below the norms and roughly one standard deviation below the norm for the Mental Health subscale, indicating poorer quality of life at the onset of the trial. At the final visit, significant treatment group differences were detected for the Physical Functioning ($p = 0.017$), Bodily Pain ($p < 0.001$), and Mental Health ($p = 0.023$) subscales, as well as the Physical Component Summary ($p = 0.018$). Patients treated with tramadol/acetaminophen exhibited a significantly greater change in the SF-MPQ from baseline to the final visit on the Sensory Component score ($p = 0.009$), Present Pain Index ($p < 0.001$), and Total Score ($p = 0.011$). Patients treated with tramadol/acetaminophen exhibited a significantly greater change from baseline on the Bothersomeness subscale of the Roland Disability Questionnaire ($p < 0.001$), as well as the Total Score ($p = 0.043$). A greater proportion of patients provided an overall medical assessment of very good or good in the tramadol/acetaminophen group (63.6%) than in the placebo group (25.2%; $p < 0.001$), and the mean overall medication assessment score for both patients and investigators was significantly better for the tramadol/acetaminophen group than placebo ($p < 0.001$; Table 3).

The evaluable-for-safety population was used for all safety analyses. In the tramadol/acetaminophen group, the most common treatment related adverse events were nausea, dizziness, constipation, and somnolence (Table 4). The most

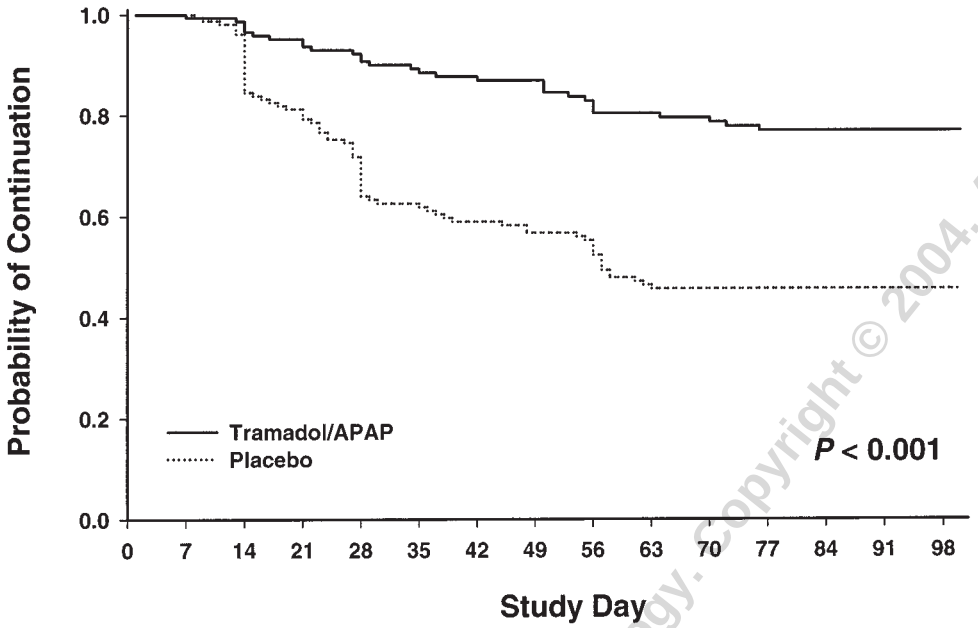

Figure 3. Time to discontinuation due to lack of efficacy. The final Kaplan-Meier estimate of cumulative discontinuation rate due to lack of efficacy was 22.9% for the tramadol/APAP group and 54.7% for the placebo group after 84 days of therapy (p value computed using the Cox proportional hazards regression analysis with treatment and center as qualitative factors).

common treatment related adverse events in the placebo group were headache, nausea, somnolence, and constipation. No serious adverse event was considered by the investigator to be related to study medication. There were no patient deaths reported during this study. There were no clinically significant changes in mean values for serum chemistry, hematology or urine laboratory tests, or vital signs in either group.

DISCUSSION

This multicenter, randomized, double blind, placebo controlled, parallel-group study was designed to assess the efficacy and safety of the combination tablet tramadol 37.5 mg/acetaminophen 325 mg in the treatment of chronic low back pain. Treatment with tramadol 37.5 mg/acetaminophen 325 mg was associated with a significant reduction in pain (pain VAS scores) and significantly better pain relief compared with treatment with placebo, as well as significantly longer time to discontinuation due to lack of efficacy. This favorable clinical response was also shown by significant improvements within the Physical Component Summary and Bodily Pain subscore of the SF-36. Further, both patients and investigators assessed tramadol 37.5 mg/acetaminophen 325 mg as superior to placebo. The patient responses to the Roland Disability Questionnaire indicated that tramadol/acetaminophen treatment brought statistically significant improvement in the actions affected by LBP.

The clinical significance of these results is supported by our categorical responder analysis that found 48.5% of the tramadol/acetaminophen group compared with 20.7% of the placebo group had ≥ 30% reduction in pain VAS score ($p < 0.001$). In a recent study of clinically meaningful changes in pain intensity across diverse pain syndromes, a decrease of 30% in pain intensity was considered to be clinically meaningful[42]. In addition, 36.5% of the tramadol/acetaminophen group and 16% of the placebo group had ≥ 50% reduction in pain VAS score ($p < 0.001$). The number needed to treat (NNT), another measure of the clinical importance of the treatment effects[43], is defined as the number of patients needed to be treated with the agent in order to show benefit over placebo for one additional patient. For pain reduction ≥ 30%, the tramadol/acetaminophen NNT is 4 (95% CI 3–6) and for ≥ 50% reduction, the tramadol/acetaminophen NNT is 5 (95% CI 4–9). Although the confidence intervals are relatively wide, these NNT values are consistent with a moderate to large treatment effect size. Making valid comparisons between the results of this study and previous studies of chronic low back is difficult due to the variability of clinical trial designs. The authors encourage the use of NNT analyses in reporting results of clinical trials to allow for meaningful comparisons of analgesics studied in the treatment of chronic LBP. This trial replicates a previously reported chronic LBP study of similar design using this combination medication[35]. In addition, a 4 week randomized clinical trial of patients with chronic low back and/or hip pain found that tramadol/acetaminophen tablets had efficacy comparable to codeine/acetaminophen tablets[36]. In

Table 3. Clinical efficacy measures assessed by change from baseline.

Measure/Category	Treatment	n	Baseline, mean ± SD	Final Visit, mean ± SD	Change, mean ± SD	p*
SF-MPQ						
Sensory component	Tr/APAP	164	15.8 ± 7.2	11.3 ± 7.8	–4.5 ± 8.8	0.009
	Placebo	161	15.0 ± 7.1	13.1 ± 8.4	–1.9 ± 6.9	
Affective component	Tr/APAP	164	5.7 ± 3.4	4.1 ± 3.6	–1.6 ± 3.9	0.064
	Placebo	161	5.0 ± 3.6	4.5 ± 3.7	–0.6 ± 3.2	
Total score	Tr/APAP	164	21.5 ± 10.0	15.5 ± 10.8	–6.1 ± 12.0	0.011
	Placebo	161	20.0 ± 10.2	17.5 ± 11.6	–2.5 ± 9.2	
Present pain index	Tr/APAP	162	2.9 ± 1.0	2.0 ± 1.2	–1.0 ± 1.2	< 0.001
	Placebo	159	2.7 ± 1.0	2.3 ± 1.2	–0.4 ± 1.2	
RDQ						
Total score	Tr/APAP	164	15.2 ± 4.2	12.8 ± 5.9	–2.4 ± 4.7	0.043
	Placebo	163	15.0 ± 4.8	13.7 ± 5.7	–1.3 ± 3.9	
Bothersomeness	Tr/APAP	156	7.3 ± 1.5	5.8 ± 2.6	–1.5 ± 2.6	< 0.001
	Placebo	157	7.1 ± 1.8	6.8 ± 2.5	–0.3 ± 2.0	
SF-36†						
Physical Functioning	Tr/APAP	164	37.1 ± 21.9	44.8 ± 25.7	7.7 ± 20.7	0.017
	Placebo	163	38.7 ± 22.4	41.0 ± 26.2	2.3 ± 17.8	
Role-Physical	Tr/APAP	164	18.4 ± 28.8	27.3 ± 38.6	8.8 ± 35.6	0.419
	Placebo	163	17.2 ± 26.9	23.5 ± 33.5	6.3 ± 32.0	
Bodily Pain	Tr/APAP	164	29.3 ± 13.7	40.5 ± 21.4	11.2 ± 22.0	< 0.001
	Placebo	163	32.6 ± 14.8	34.1 ± 18.2	1.6 ± 17.6	
General health	Tr/APAP	163	61.0 ± 19.2	61.4 ± 19.8	0.3 ± 14.6	0.449
	Placebo	163	57.9 ± 22.0	57.9 ± 21.1	0.1 ± 13.7	
Vitality	Tr/APAP	164	38.5 ± 18.5	44.5 ± 20.9	6.0 ± 20.7	0.140
	Placebo	163	41.2 ± 19.4	43.2 ± 20.2	2.0 ± 16.5	
Social functioning	Tr/APAP	164	55.8 ± 25.5	60.4 ± 24.8	4.6 ± 25.4	0.611
	Placebo	163	59.7 ± 25.7	61.1 ± 25.9	1.5 ± 23.8	
Role-emotional	Tr/APAP	164	52.4 ± 42.9	56.5 ± 42.8	4.1 ± 41.4	0.587
	Placebo	163	54.2 ± 43.8	55.2 ± 43.2	1.0 ± 39.1	
Mental health	Tr/APAP	164	65.5 ± 17.9	67.8 ± 19.6	2.3 ± 15.6	0.023
	Placebo	163	67.1 ± 20.6	65.2 ± 21.0	–2.0 ± 15.1	
Reported health transition	Tr/APAP	164	60.4 ± 24.6	51.8 ± 24.9	–8.5 ± 28.7	0.403
	Placebo	163	60.4 ± 22.9	54.0 ± 23.2	–6.4 ± 26.0	
Physical component summary	Tr/APAP	163	29.7 ± 7.2	33.2 ± 10.0	3.5 ± 8.4	0.018
	Placebo	163	29.6 ± 7.7	31.1 ± 9.0	1.5 ± 7.1	
Mental component summary	Tr/APAP	163	46.9 ± 10.6	47.6 ± 11.3	0.8 ± 9.3	0.372
	Placebo	163	48.1 ± 11.9	47.5 ± 11.6	–0.5 ± 9.2	

SF-MPQ: Short Form McGill Pain Questionnaire; RDQ: Roland Disability Questionnaire; SF-36: SF-36 Health Survey; Tr/APAP: tramadol/acetaminophen. * Analysis of covariance with baseline scores as covariate and treatment and center as qualitative factors. † Scores are transformed to 0 to 100 scale, with higher scores indicating better quality of life, except for Reported Health Transition, for which lower scores indicate better quality of life.

other chronic pain studies, tramadol/acetaminophen has been shown to be effective and safe for the treatment of FM[33] and as add-on therapy to COX-2 for OA[44].

In our study, the percentage of patients who withdrew due to limiting adverse events in the drug treatment group was 28%, compared with 8% withdrawals from the placebo group. The withdrawal rate in this trial is similar to those previously reported for patients with FM receiving the combination medication in a 3 month trial (21%)[33] and in another 3 month LBP trial of tramadol/acetaminophen (18%)[35]. For comparison, in a 4 week study of combination hydrocodone and ibuprofen for treatment of chronic pain (46% had back pain), the discontinuations due to adverse events were 26.1% (15 mg hydrocodone/400 mg ibuprofen)[45]. In a retrospective opioid analysis, discontinuation due to adverse event rates as high as 29% have been reported[46].

Clearly, additional treatment options are needed for chronic pain conditions. A recent survey by the American Pain Society[47] indicated that chronic pain sufferers may simply give up on medical assistance, feeling that there is nothing that can be done to alleviate their pain. In addition to pain relief, treatment with tramadol 37.5 mg/acetaminophen 325 mg was associated with improved quality of life (measured by the SF-36) as well as with improvements in emotional and mental health (by SF-MPQ); this suggests that tramadol/acetaminophen may be an effective therapeu-

Table 4. Adverse events with ≥ 2% incidence by relationship to study medication.

Adverse Event	Tramadol/Acetaminophen, n = 167		Placebo, n = 169	
	Related* n (%)	Unrelated n (%)	Related* n (%)	Unrelated n (%)
Nausea	20 (12.0)	22 (13.2)	3 (1.8)	7 (4.1)
Dizziness	18 (10.8)	12 (7.2)	1 (0.6)	11 (6.5)
Constipation	17 (10.2)	20 (12.0)	2 (1.2)	11 (6.5)
Somnolence	15 (9.0)	13 (7.8)	3 (1.8)	2 (1.2)
Headache	11 (6.6)	36 (21.6)	7 (4.1)	30 (17.8)
Dry mouth	11 (6.6)	13 (7.8)	0 (0.0)	6 (3.6)
Vomiting	10 (6.0)	9 (5.4)	0 (0.0)	4 (2.4)
Anorexia	6 (3.6)	5 (3.0)	0 (0.0)	3 (1.8)
Increased sweating	6 (3.6)	8 (4.8)	0 (0.0)	1 (0.6)
Hot flushes	4 (2.4)	7 (4.2)	0 (0.0)	1 (0.6)

* Relationship to study medication was judged probable or very likely by the investigator.

tic agent for management of chronic LBP. Further, the combination tramadol/acetaminophen tablet was associated with improved functioning, as indicated by the RDQ results, which address clinically meaningful issues such as difficulty in walking; needing assistance in performing daily activities; limitations to standing, bending, or kneeling; a loss of appetite or sleep; and tendency to stay in bed or at home. The quality of life factors from the RDQ complement the physical functioning and social functioning assessments reported on the SF-36. For patients with chronic LBP, benefits in all of these areas may lead to more normal activities at work and at home. When factored together, the facets of pain relief described in this study, which include the alleviation of pain, the increases in the multidimensional analyses of physical and mental well being, and the benefits reported for activities of daily living, suggest that this combination medication can show clinically meaningful effectiveness in the real-world setting for treatment of chronic LBP.

In spite of the high methodological quality of this study, the broad range of outcome measures used, and the clinically important benefits seen, this study has limitations. A more homogeneous back pain sample was extracted from the larger clinical population of back pain sufferers by use of inclusion and exclusion criteria. For example, the study excluded patients with neurologic deficits in the lower extremities. Thus a study of patients with specific neurologic deficits, such as herniated disc, with this combination tablet would be needed to extend these findings to a broader population of back pain patients seen in clinical practice. A limitation of this study is the absence of a systematic approach to characterizing LBP in this study population (e.g., the use of the Quebec Task Force Classification[48]). Instead, patients were selected using a functional definition of LBP based on duration, location, and severity of pain as well as the absence of neurologic deficits in the lower extremities. The generalizability of this study might have been enhanced if a standardized classification system for characterizing LBP had been used. Cointerventions, some specifically allowed and some specifically excluded, may have influenced the subject's perception of pain or the control of pain during therapy. Also, the sample size of this study limits the ability to assess differences in serious adverse events between treatment groups. A test of the maintenance of the blinding was not conducted in this study. Testing the adequacy of blinding will improve the quality and interpretation of placebo controlled trials and should be considered an integral part of clinical trial design. Unmeasured endpoints include return-to-work and sick leave. Future studies using these endpoints are warranted to corroborate the positive findings from the patient based questionnaires used. Future clinical evaluations of tramadol/acetaminophen should compare this drug with other drugs or evaluate this drug as add-on therapy to other active treatments. In addition, the management of longterm problems often includes pharmacologic treatment and physical therapies, and the incremental benefits of nonpharmacologic interventions were not assessed in this study.

Our study showed moderate benefits over the course of a 3 month treatment with tramadol/acetaminophen for patients with chronic LBP. The combination tablets are effective across a wide range of clinical measures, including pain and patient and physician overall assessment, as well as physical functioning and health related quality of life. In addition, the combination was safe and showed a discontinuation rate due to adverse events comparable with other opioids used in the treatment of chronic pain. Tramadol/acetaminophen should be considered as an option for the treatment of chronic low back pain.

APPENDIX

Members of the TRP-CAN-1 Study Group included: J.D. Adachi, MD, Hamilton, ON; T.P. Anastassiades, MD, PhD, Kingston, ON; P.A. Baer, MD, Toronto, ON; R.P. Baker, MD, Richmond, BC; A. Beaulieu, MD, Sainte-Foy, QC;

M.J. Bell, MD, Hamilton, ON; W.G. Bensen, MD, Hamilton, ON; G. Boire, MD, Fleurimont, QC; A.A.M. Bookman, MD, Toronto, ON; J.M.G. Canvin, MD, Winnipeg, MB; A.A. Cividino, MD, Hamilton, ON; K.A. Davis, MD, Ottawa, ON; M.A. Fitzcharles, MD, Montreal, QC; L. Fortin, MD, Montreal, QC; A.S. Gordon, MD, Toronto, ON; L.E. Hart, MD, Hamilton, ON; A.V. Jovaisas, MD, Ottawa, ON; D.A. Kumbhare, MD, Hamilton, ON; T.G. McCarthy, MD, Winnipeg, MB; T.C. Monchesky, MD, Courtice, ON; W.P. Olszynski, MD, PhD, Saskatoon, SK; P.M. Peloso, MD, MSc, Saskatoon, SK; S.J. Pillersdorf, MD, Guelph, ON; J. Rodrigues, MD, Windsor, ON; E.M. Sellers, MD, PhD, Toronto, ON; K. Shojania, MD, Richmond, BC; J.C. Thorne, MD, Newmarket, ON; M. Willans, MD, Sarnia, ON; A.J. Yorke, MD, Surrey, BC; M. Zummer, MD, Montreal, QC.

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