Extended-release Trazodone in Major Depressive Disorder: A Randomized, Double-blind, Placebo-controlled Study

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ABSTRACT

Objective: To investigate the efficacy, safety, and clinical benefit of a once-daily formulation of trazodone (Trazodone Contramid® OAD) in the treatment of major depressive disorder.

Design/Participants: In this double-blind study, 412 patients with major depressive disorder (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria) were randomized 1:1 to receive either Trazodone Contramid OAD (150 to 375mg) or placebo. Treatment was titrated over two weeks to each individual optimal dose. Patients then continued six weeks of treatment; further dose adjustments were allowed based on efficacy and tolerability.

Measurements: The primary end point was change in the 17-item Hamilton Depression Rating Scale total score from baseline to last study visit. Secondary end points included Hamilton Depression Rating Scale responders/remitters, change in Montgomery-Åsberg Depression Rating Scale, Clinician and Patient Global Improvement Scales, and quality of sleep.

Results: From the end of titration to the end of the six-week treatment period, the mean maximum daily dose of the intent-to-treat population was 310mg for the active group and 355mg for the placebo group. There was a statistically significant difference

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between trazodone and placebo on the mean HAMD-17 score (-11.4 vs. -9.3, P=0.012). A significant difference was present as early as Week 1 and was maintained at all subsequent study visits. Many secondary end points supported these findings, including improvements in quality of sleep. The most frequent adverse events were the same for both the treatment and placebo groups: headache and somnolence. There were no serious adverse events that were considered related to treatment. There were no clinically significant electrocardiogram or laboratory abnormalities.

Conclusions: The trazodone Contramid formulation was more effective than placebo in major depressive disorder and was well tolerated.

INTRODUCTION

Trazodone is a triazolopyridine-derived antidepressant that acts by means of serotonin-2A and -2C (5HT2A/2C) receptor antagonism and through serotonin reuptake inhibition.[1,2] It belongs to a distinct class of antidepressants referred to as serotonin-2 antagonist/reuptake inhibitors (SARIs). Trazodone has moderate histamine-1 (H_1) receptor antagonism and possesses some anxiolytic and hypnotic properties.[3,4]

Since its introduction 40 years ago as an atypical antidepressant with unique pharmacological properties, trazodone's antidepressant equivalence to other drug classes is demonstrated in several comparative studies, including those with the tricyclic antidepressants amitriptyline and imipramine;[4] the selective serotonin reuptake inhibitors (SSRIs) fluoxetine,[5,6] paroxetine,[7] sertraline,[8] citalopram, and escitalopram;[9] the serotonin-norepinephrine reuptake inhibitors (SNRIs) venlafaxine[10] and mirtazapine;[9] and the norepinephrine and dopamine reuptake inhibitor bupropion.[11]

The sedative effects of immediate-release formulations of trazodone limit its dosing as an antidepressant.[1,10] Immediate-release trazodone is primarily prescribed as a hypnotic at doses ranging from 50 to 200mg.[1,12] At these low doses, immediate-release formulations achieve plasma concentrations that are sufficient to exploit sedating effects secondary to 5HT2A and H_1 receptor antagonism, but are not sustained sufficiently to induce an antidepressant effect.[3,13] To achieve an antidepressant effect, higher daily dosages must be maintained if they are to adequately inhibit the 5HT2A and 5HT2C receptors and block the serotonin transporter.[3]

The sedating effects of trazodone may also be beneficial to patients with insomnia associated with MDD. Insomnia is a risk factor for the onset and relapse of MDD and an independent predictor for treatment failure, while its treatment may increase remission rates.[3,14,15] Trazodone administered as a single dose at bedtime may mitigate adverse effects associated with immediate-release trazodone.[16] However, current immediate-release formulations of trazodone recommend administration as divided daily doses.[17] No once-daily, controlled-release formulations exist for trazodone, while most other antidepressants are available as once-daily formulations. It is possible that a formulation that controls the release of trazodone over 24 hours may optimize its antidepressant efficacy while improving sleep in patients with MDD. These factors collectively provide a rationale for examining once-daily formulations of trazodone as a monotherapy for patients with MDD.

Trazodone Contramid® once-a day (OAD) is an extended-release, once-daily formulation of trazodone HCl developed by Labopharm Inc. (Laval, Québec, Canada). Trazodone Contramid OAD (TCOAD) is designed to optimize the antidepressant efficacy of trazodone. Contramid is a cross-linked, high-amylose starch excipient that provides controlled release of trazodone over an extended period.[18] TCOAD is available as 150 and 300mg trazodone HCl scored caplets to provide flexibility in dosing, and exhibits linear pharmacokinetics over doses ranging from 75 to 375mg. Administration of 300mg TCOAD provides equivalent steady-state exposure to 100mg immediate-release trazodone administered three times a day, yet with a 42-percent lower mean maximum plasma concentration (1812 vs. 3118ng/mL; Labopharm Inc., data on file).

The objective of this randomized, double-blind, phase III study was to investigate the efficacy and tolerability of TCOAD in patients with MDD.

METHODS

Patient selection. Patients included in this study were men and women, 18 years of age or older, who fulfilled the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for primary MDD, even in the presence of another nonexcluded Axis I disorder. Patients were required to have the current episode of MDD for a minimum of one month, whether diagnosed with a single episode or recurrent episodes. Eligible patients had to have dysphoria for most days over the previous four weeks and a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of at least 26 at screening and baseline. Patients' MADRS scores were used as an entry criterion rather than the 17-item Hamilton Depression Rating Scale (HAMD-17) score to reduce the potential for investigator bias on the primary end point when evaluating patients for inclusion in the study.

Patients with *DSM-IV* MDD specifiers, such as catatonic features, postpartum onset, and/or seasonal patterns, were excluded from the study. Other exclusion criteria consisted of patients with generalized anxiety disorder, panic disorder, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, eating disorder, bipolar disorder, alcohol/substance abuse or dependence (caffeine and nicotine allowed), any psychotic disorder, depression secondary to stroke, cancer, or other severe medical illnesses, psychotherapy at the time of enrollment, or high suicide risk. Patients were also excluded if, within the previous three weeks, they were treated with monoamine oxidase inhibitors or during the study used

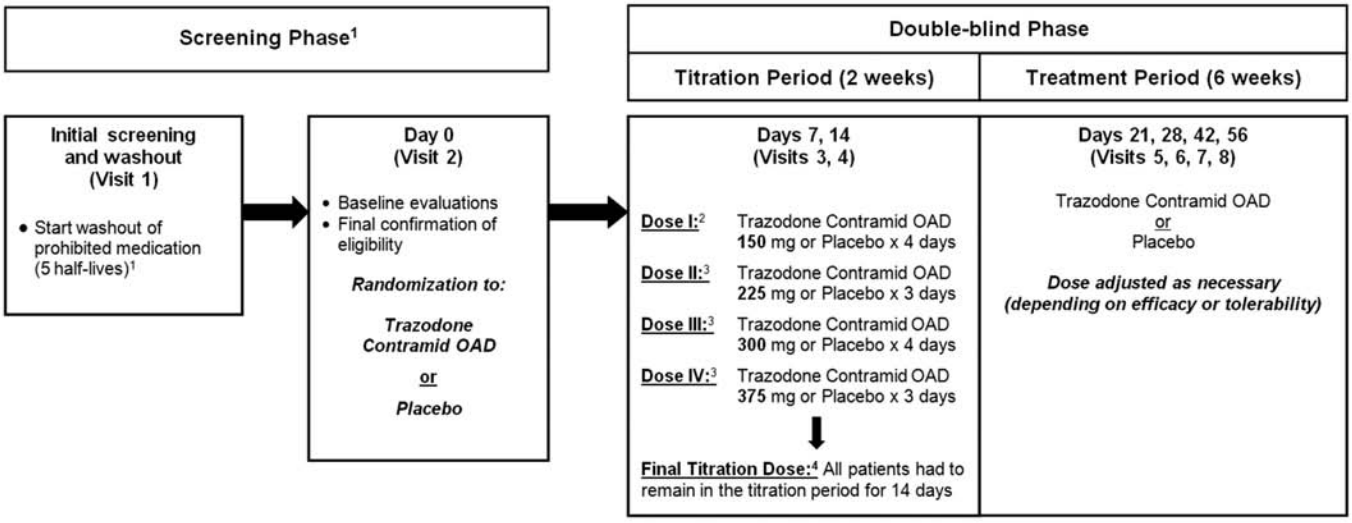


FIGURE 1. Study design
1. The number of days in the screening phase was determined by washout time of patient's previous medications.
2. Patients who could not tolerate the 150 mg dose had to exit the study.
3. Patients who could not tolerate the next dose after trying it for at least 2 days could decrease to the previous dose. In rare cases, if the patient was unable to tolerate the higher dose after trying it for at least 1 day, the dose could be decreased to the previous level. Patients were allowed to decrease their dose only once during the titration period.
4. Patients had to stay at the final titration dose until the end of titration.

antipsychotics, protease inhibitors, or any concomitant medications causing QT or PR prolongation.

Study design. This double-blind, randomized, placebo-controlled, two-arm, multicenter study (Labopharm protocol 04ACL3-001) evaluated the efficacy and safety of TCOAD (150, 225, 300, 375mg daily) versus placebo for the treatment of MDD. The study was conducted from May 2007 to November 2007 at 38 active centers in the USA and Canada. The protocol conformed to the International Conference on Harmonisation—Good Clinical Practice (ICH-GCP) guidelines and was conducted in compliance with the Declaration of Helsinki.

During the first screening visit, patients provided informed consent and underwent an initial screening for inclusion (Figure 1). The screening visit included the informed consent procedure and assessment for the *DSM-IV* criteria for MDD (confirmed by the Mini International Neuropsychiatric Interview), the MADRS, concurrent medications, a medical history, a physical examination, vital signs, hematology and blood chemistry analyses, urinalysis, and a 12-lead electrocardiogram (ECG). ECGs were performed at the study centers and interpreted centrally by an independent bioanalytic firm (Covance Cardiac Safety Services, Reno, Nevada) by a panel of cardiologists blind to the patients' treatment statuses.

In addition to the medications listed in the exclusion criteria, use of antidepressants other than the study medication (including herbal preparations), sedatives, and hypnotics were not permitted during the study. Patients had to be off all prohibited medications for at least five half lives prior to randomization at baseline. Baseline (Visit 2) assessments included the MADRS, HAMD-17, Clinical Global Impression—Severity of Illness (CGI-S), quality of sleep measures, and vital signs. Patients who met eligibility criteria were then randomized to either the TCOAD or placebo treatment arms.

Each randomized patient was registered into the Fisher Automated Clinical Trial System (FACTS), which tracked patient enrollment status and managed randomization, study medication inventory, resupply, and distribution to each participating site.

Over the first two weeks of the double-blind phase, patients' doses were titrated every 3 to 4 days by 75mg increments from a starting dose of 150mg to a maximum daily dose of 375mg. At each dosing step, if a dose was not well tolerated after two days, patients had the option to decrease to the previous dose. On Days 4 and 9 of titration, patients were contacted by telephone to assess their progress and to assist in deciding whether to decrease the dose of study medication. Patients were allowed to decrease their dosage only once during the titration period. Once the optimal daily dose was selected, patients remained at that dose until the beginning of the six-week treatment period, after which the dose could be adjusted based on efficacy or tolerability. Rescue medications for the treatment of MDD symptoms were not allowed during the study.

Patients were instructed to take their medication once daily at bedtime. To maintain blinding, the active drug and placebo were identical in appearance.

Study assessments. Efficacy and safety evaluations were done at baseline (Day 0), at Days 7 and 14 (titration period visits), and at Days 21, 28, 42, and 56 (treatment period visits). For each visit to the clinic, a "visit window" of plus or minus three days was allowed, with the exception

of the last study visit and evaluations performed following discontinuation, for which a plus or minus one-week visit window was permitted.

The primary end point was the change in the HAMD-17 total score from baseline to the last study visit (Day 56 or following discontinuation). Secondary end points consisted of 13 measures: HAMD-17 responders, defined as patients with a decrease of 50 percent or more from baseline to last visit on the HAMD-17 total score; HAMD-17 remitters, defined as patients who achieved a HAMD-17 total score of 7 or less; change in HAMD-17 depressed mood item from baseline; change in MADRS total score from baseline to the last study visit; Clinical Global Impression—Improvement of Illness (CGI-I) responders, defined as patients assessed by investigators as "much improved" or "very much improved" at the last study visit; Patient Global Impression—Improvement of Illness (PGI-I) responders, defined as patients who reported being "much improved" or "very much improved" at the last study visit; change in CGI-S from baseline; CGI-I at the last study visit; PGI-I at the last study visit; and discontinuations due to lack of efficacy. The final secondary end point assessed quality of sleep across three parameters—overall quality of sleep, trouble falling asleep, and awakening during the night—using patient-rated, four-point Likert scale: overall quality of sleep had the possible response options of "excellent", "good," "fair," and "very poor;" trouble falling asleep and awakening during the night had the possible response options of "never," "rarely," "frequently," and "always."

At each visit, patients' concomitant medications and adverse events were recorded. Body weight, hematology, blood chemistry, urinalysis, physical examination, and a standard supine, 12-lead ECG were recorded at the last study visit. All AEs and SAEs were followed to resolution, until the condition stabilized or until the patient was lost to followup.

Statistical analyses. Safety analyses were performed on the safety (intent-to-treat [ITT]) population, which was defined as patients who were randomized to the study medication at baseline. Efficacy analyses were performed on the modified ITT population and per protocol (PP) populations. The modified ITT population was defined as all randomized patients who received at least one dosage of the double-blinded study medication, and at least one post-baseline HAMD-17 assessment. The PP population was defined as all randomized patients who completed the study, had no major protocol violations, and had a HAMD-17 rating at the end of the study. End-of-study scores for post-randomization missing data in the modified ITT population were derived using the last observation carried forward (LOCF) data imputation. The observed cases (OC) dataset included only the observations that occurred within the allowed visit window.

The primary efficacy end point (change in HAMD-17 from baseline) was compared between the treatment groups using an analysis of covariance (ANCOVA), with treatment, study center, and baseline as covariates. A mixed-model repeated-measures (MMRM) analysis using an unstructured covariance matrix was used as a sensitivity analysis to support the primary efficacy end point LOCF analysis results. The overall difference over time between the two treatment groups for the primary efficacy end point was tested using a mixed linear model for repeated measures with treatment and study center as factors, study week as the time point, and baseline HAMD-17 total score as a covariate. Only assessments from the treatment period were incorporated into the repeated measurement model.

To achieve 90 percent power to detect a 3.0 unit absolute mean change in the HAMD-17 total score from baseline, a sample size of 133 patients in each treatment group was needed to complete the study; this assumed a common standard deviation of 7.5 with a two-group, two-tailed t test with significance set at P=0.05. Assuming a discontinuation rate of 30 percent, an enrollment of 190 patients in each treatment group was required.

For the categorical secondary end points—responders and remitters in HAMD-17, CGI-I, and PGI-I scores—a Cochran-Mantel-Haenszel test, adjusted for site, was used to test for statistically significant differences between treatment groups. A Fisher's exact test was used to test for statistically significant differences between groups for the percentage of patients who discontinued due to lack of efficacy and for significant differences in the distribution of responses for each of the three quality of sleep Likert-type items at each visit. For the continuous secondary end points, change from baseline in the HAMD-17 depressed mood item (item 1), change from baseline in MADRS, and CGI-S, a two-way (treatment, time), repeated-measures ANCOVA was used to assess whether the mean response profile over the treatment period differed significantly between the two groups.

RESULTS

Patient characteristics. Of 574 patients screened, a total of 412 patients were randomized to receive either TCOAD (n=206) or placebo (n=206). There were no remarkable differences between the treatment groups with respect to gender, age, or ethnicity. One hundred and five of 412 patients (25.5%; TCOAD, n=62; placebo, n=43) prematurely discontinued the study (Figure 2); six patients (1.5%) discontinued without receiving at least one dose of study medication. Of the 406 patients who received at least one dose of study medication (202 patients in the TCOAD group; 204 patients in the placebo group), the most frequent reasons for discontinuation were AEs (TCOAD, n=25; placebo, n=6), patients lost to followup (TCOAD, n=11; placebo, n=15), and patient requests (TCOAD, n=11; placebo, n=9). The modified ITT population contained all 406 patients that comprised the safety population. The PP population contained a total of 298 patients (TCOAD, n=136; placebo, n=162).

Baseline characteristics are

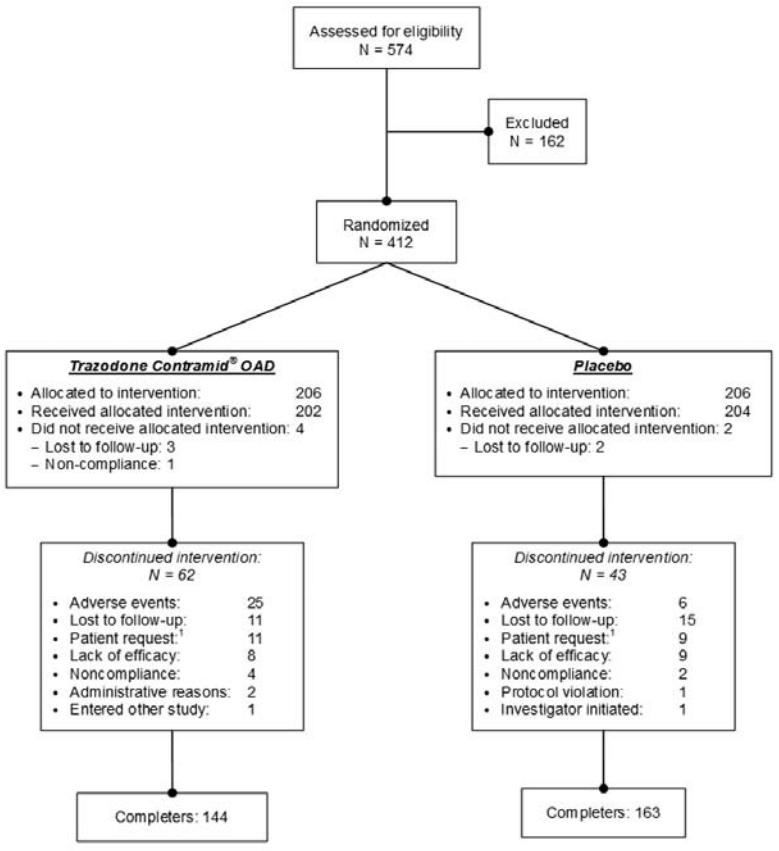


FIGURE 2. Study flowchart
[1]Patient requests included reasons for discontinuation other than adverse events or lack of efficacy.

presented in Table 1. The mean age of the modified ITT population was 43.9 (SD: 13.1) years; 260 of 406 (64.0%) were female, and 279 of 406 (68.7%) were Caucasian. There were no remarkable differences between treatment groups with respect to demographics, depression history, baseline depression parameters (HAMD-17, MADRS, and CGI-S) or baseline quality of sleep parameters (overall quality of sleep, trouble falling asleep, awakening during the night). On average, randomized patients had one (SD: 1.1) previous depressive episode over the 24 months prior to study entry (Table 2); the overall mean duration of the current episode was 14.7 (SD: 31.0) months.

In total, 88 of 406 of the randomized patients (21.7%) took medication within the 30 days prior to taking the study medication. The most commonly used medications, regardless of treatment group, were antidepressants (TCOAD: 11/202, 5.4%; placebo: 18/204, 8.8%). Other medications taken by patients in the safety population in the 30 days prior to the study included anxiolytics (14/406 patients, 3.4%), nonsteroidal anti-inflammatory drugs (8 patients, 2.0%), hypnotics and sedatives (13 patients, 3.2%), opioids (8 patients, 2.0%) and other analgesics and antipyretics (14 patients, 3.4%).

Dosing and exposure. At the end of the two-week titration period, 108 of 177 patients (61.0%) in the TCOAD group and 168 of 194 patients (86.6%) receiving placebo required the highest available dosage of 375mg once-daily (dose level IV, Figure 1). The mean maximum daily dosage of the safety population from the end of titration to the end of the six-week treatment period was 310mg (SD: 81mg) for the TCOAD group and 355mg (SD: 50mg) for patients on placebo. Over the total course of the study (titration and treatment period combined), the mean number of days of therapy was 51.6 (SD: 12.8) days for the active treatment and 46.8 (SD: 17.6) days for placebo. The distribution of daily dosages for patients at the end of titration is summarized in Table 3.

Antidepressant efficacy. The mean HAMD-17 total scores at baseline were 23.2 (SD: 4.2) and 22.4 (SD: 4.4) for patients randomized to TCOAD and placebo, respectively (Table 1). The corresponding mean scores at the last study visit (LOCF) were 11.8 (SD: 8.0) for the active treatment group and 13.2 (SD: 8.1) for placebo. Consequently, the primary end point of this study—the change in the HAMD-17 total score from baseline to the last study visit—decreased by an average of 11.4 (SD: 8.2) in the TCOAD group versus 9.3 (SD: 7.9) in the placebo group. This difference was found to be statistically significant in favor of the TCOAD group (P=0.012, Table 4). The corresponding percentage of change in the HAMD-17 total score was 49 percent in the TCOAD group and 41 percent in the placebo group. The statistical significance achieved with the LOCF analyses were confirmed by the MMRM sensitivity analysis, which also achieved statistical significance (P=0.006, Table 4).

The antidepressant efficacy of the active treatment group was further supported by the change from baseline in the HAMD-17 total score at each post-randomized visit; these results demonstrated a significantly greater improvement in the mean HAMD-17 total score in the TCOAD group compared with placebo by the first week of the double-blind phase (Day 7 of titration, mean [SD]: 5.6 [5.2] vs. 3.9 [4.8], respectively; P=0.005, LOCF). The significantly greater differences were maintained throughout the study (Figure 3). To assess the average antidepressant efficacy throughout treatment, an ANCOVA of the time-weighted average (TWA) of the HAMD-17 total scores at each study visit during the six week treatment period was performed. These results

demonstrated a significantly greater decrease in absolute mean improvement in the HAMD-17 total score from baseline for the TCOAD compared with placebo (11.0 [SD: 7.2] vs. 8.6 [SD: 6.8], respectively; *P*=0.002). A summary of the primary and secondary efficacy results is presented in Table 4.

The majority of the secondary efficacy end points at the last study visit (Day 56) showed statistically significant better outcomes for patients receiving TCOAD than those receiving placebo, which held across both the modified ITT and PP populations (Table 4). There was a higher percentage of HAMD-17 responders and a greater decrease in the change from baseline in the HAMD-17 depressed mood item (item 1), CGI-S, and MADRS total score. The results of the HAMD-17 responder analysis demonstrated that there were more responders in the active treatment group than in placebo by the end of the titration period (*P*=0.008, LOCF). The significantly greater number of HAMD-17 responders was maintained until the end of the treatment period (Figure 3b).

At the last study visit, the number of HAMD-17 remitters and percentages of CGI-I and PGI-I responders in patients receiving TCOAD were not statistically different (LOCF) compared with placebo. However, the mean percentages of HAMD-17 remitters in the modified ITT and PP populations were significantly higher for patients in the TCOAD group than placebo during all other treatment period assessment days (Figure 3c). Moreover, the PGI-I in the active treatment group was significantly different from placebo for the PP population (*P*=0.033): 114 of 133 patients (85.7%) receiving TCOAD were "improved" (minimally, much, or very much) compared with 120 of 160 (75.0%) receiving placebo.

Quality of sleep. At the end of the study, the patients from the modified ITT/ LOCF dataset in the TCOAD group had statistically significant improvements compared with placebo in all quality of sleep parameters; the differences in the quality of sleep questionnaire response distributions also achieved statistical significance in the PP population, except for overall quality of sleep. Improvements in quality of sleep were quantified by assessing the proportion of patients with more favorable responses on the Likert scales at the end of the study. To illustrate, 121 of 201 patients (60.2%) in the modified ITT population receiving TCOAD reported having either "excellent" or "good" overall quality of sleep compared with 92 of 204 patients (45.1%) receiving placebo; 150 of 201 patients (74.6%) receiving active treatment also reported "never" or "rarely" having trouble falling asleep compared with 122 of 204 patients (59.8%) receiving placebo. Likewise, 140 of 201 patients (69.7%) in the active treatment group reported "never" or "rarely" awakening during the night compared with 111 of 204 (54.4%) in the placebo group.

The response distributions for all quality of sleep parameters throughout the study are illustrated in Figure 4. Specifically, there was a trend toward a greater proportion of patients receiving TCOAD reporting "excellent" or "good" overall quality of sleep (Figure 4a), "never" or "rarely" trouble falling asleep (Figure 4b), and "never" or "rarely" experiencing awakening during the night (Figure 4c). Moreover, some of the improvements in the quality of sleep were associated with a rapid onset: the overall quality of sleep (Figure 4a) and awakening during the night (Figure 4c) response distributions showed statistically significant shifts to better responses in

TABLE 1. Baseline characteristics of randomized patients.

	TCOAD (N=202)	PLACEBO (N=204)	*P* VALUE
DEMOGRAPHICS			
Gender (n)			> 0.99
Male	73 (36.1%)	73 (35.8%)	
Female	129 (63.9%)	131 (64.2%)	
Age (years)			
Mean (SD)	43.8 (12.8)	44.0 (13.5)	0.87
Ethnic origin (n)	Caucasian: 139 (68.8%) Black: 41 (20.3%) Asian: 4 (2.0%) Other: 18 (8.9%)	Caucasian: 140 (68.6%) Black: 44 (21.6%) Asian: 3 (1.5%) Other: 17 (8.3%)	0.97
CLINICAL CHARACTERISTICS			
HAMD-17 total score [mean (SD)]	23.2 (4.2)	22.4 (4.4)	0.08
MADRS total score [mean (SD)]	32.6 (4.1)	31.9 (4.3)	0.21
Clinical global impression, severity of illness (n)	Mildly ill: 0 Moderately ill: 95 (47.0%) Markedly ill: 104 (51.5%) Severely ill: 3 (1.5%)	Mildly ill: 1 (0.5%) Moderately ill: 115 (56.4%) Markedly ill: 85 (41.7%) Severely ill: 3 (1.5%)	0.13
Overall quality of sleep (n)	Excellent: 2 (1.0%) Good: 13 (6.4%) Fair: 91 (45.0%) Very poor: 96 (47.5%)	Excellent: 3 (1.5%) Good: 17 (8.3%) Fair: 85 (41.7%) Very poor: 99 (48.5%)	0.8
Trouble falling asleep (n)	Never: 15 (7.4%) Rarely: 25 (12.4%) Frequently: 98 (48.5%) Always: 64 (31.7%)	Never: 18 (8.8%) Rarely: 37 (18.1%) Frequently: 90 (44.1%) Always: 59 (28.9%)	0.37
Awakening during the night (n)	Never: 6 (3.0%) Rarely: 26 (12.9%) Frequently: 90 (44.6%) Always: 80 (39.6%)	Never: 6 (2.9%) Rarely: 28 (13.7%) Frequently: 90 (44.1%) Always: 80 (39.2%)	> 0.99

TCOAD=Trazodone Contramid OAD

TABLE 2. Depression history of the modified ITT population.

	TCOAD (N=202)	PLACEBO (N=204)	*P* VALUE
DURATION OF CURRENT EPISODE (MONTHS)			
Mean (SD)	14.3 (38.0)	15.0 (22.2)	0.55
PREVIOUS EPISODES IN THE LAST 24 MONTHS			
Mean number of previous episodes in the last 24 months[2]			
n	166	173	
Mean (SD)	1.0 (0.9)	1.1 (1.2)	0.40
Number of patients with previous episodes in the last 24 months[2]			
n	166	173	
Patients with 0 episode	54 (32.5%)	53 (30.6%)	0.80
Patients with 1 episode	67 (40.4%)	76 (43.9%)	
Patients with 2 episodes	36 (21.7%)	35 (20.2%)	
Patients with 3 episodes or more	9 (5.4%)	9 (5.2%)	

1 *P* values were calculated using Fisher's exact test for categorical variables and ANOVA with pooled site and treatment as categorical factors for continuous variables.
2 Data were based on the total number of patients with complete records; 31 patients had missing records in the placebo group and 36 patients had missing records in the active treatment group.

TCOAD=Trazodone Contramid OAD

TABLE 3. Final dose level at the end of the titration period (safety population)

	TCOAD	PLACEBO
150mg/day	24 patients	5 patients
225mg/day	18 patients	8 patients
300mg/day	27 patients	13 patients
375mg/day	108 patients	168 patients

TCOAD=Trazodone Contramid OAD

TABLE 4. Primary and secondary antidepressant efficacy outcomes at end of study (56 days post randomization)

	MODIFIED ITT POPULATION		PP POPULATION	
	TCOAD	PLACEBO	TCOAD	PLACEBO
PRIMARY END POINT				
Change in HAMD-17 total score from baseline				
N (modified ITT/ LOCF; PP/OC)	202	204	135	162
Mean (SD)	-11.4 (8.2)	-9.3 (7.9)	-13.0 (8.0)	-10.4 (7.8)
95% CI	-12.3, -10.1	-10.3, -8.2	-14.1, -11.5	-11.7, -9.4
P value†	0.012		0.009	
MMRM analysis				
N (OC)	141	163	N/A	N/A
MMRM estimate	-11.1	-8.9	N/A	N/A
95% CI	-14.2, -8.1	-11.8, -5.9	N/A	N/A
P value	0.006		N/A	
SECONDARY END POINTS				
Changes from baseline to last study visit				
Change in HAMD-17 depressed mood item				
N (modified ITT/ LOCF; PP/OC)	202	204	135	162
Mean (SD)	-1.6 (1.3)	-1.3 (1.2)	-1.9 (1.3)	-1.5 (1.2)
P value†	0.030		0.009	
Change in MADRS total score				
N (OC)	178	182	134	160
Mean (SD)	-16.6 (11.3)	-14.1 (11.9)	-18.7 (10.8)	-15.5 (11.6)
P value†	0.036		0.010	

TCOAD=Trazodone Contramid OAD

patients receiving TCOAD by Day 7 of the titration phase. These significant differences were maintained throughout most days of the treatment period.

Safety and tolerability. TCOAD was relatively well tolerated. AEs were the primary reason for withdrawal in patients receiving active treatment. There were 25 of 202 patients (12.4%) in the TCOAD group and six of 204 patients (2.9%) in the placebo group who discontinued due to AEs (Figure 2). The most commonly reported reasons for discontinuations due to AEs in the TCOAD group were dizziness (7 patients), sedation (5 patients), and somnolence (3 patients).

During the course of the study, 345 of 406 patients (85.0%) in the safety population (181 on TCOAD; 164 on placebo) reported at least one AE. AEs reported by five percent or more patients are presented in Table 5. The most common (≥10%) were headache, somnolence, dry mouth, dizziness, nausea, sedation, fatigue, and diarrhea. Overall, the intensity of AEs experienced by patients on TCOAD was mild to moderate in the majority of cases and similar to placebo (TCOAD: 148/202, 73.3%; placebo: 148/204, 72.5%). Only one patient treated with TCOAD reported anxiety during the study compared with five receiving placebo (TCOAD: 1/202, 0.5%; placebo: 5/204, 2.5%). There were no notable changes in vital signs (blood pressure, respiratory rate, pulse) or body weight in either treatment group during the study. No ECG abnormalities occurring during the trial were considered clinically

significant. Although some patients exhibited ECG waveforms that fluctuated between normal and abnormal in both groups, the general review of the data did not reveal a consistent signal of repolarization abnormalities associated with trazodone at the doses that were administered in the trial.

Five patients experienced at least one SAE during the study or within 30 days after the last dose (3 patients in the TCOAD group; 2 patients in the placebo group). One patient receiving placebo died; despite appropriate followup, the family did not consent to the release of the autopsy results, and the exact cause of death is unknown. None of the SAEs were judged to be related to the study medication.

The incidence of sexual dysfunction in patients on TCOAD (10/202, 4.9%; placebo: 5/204, 2.5%) was unusually low for an antidepressant. In the TCOAD group, the most common sexual dysfunction was decreased libido, which occurred in three patients; collectively, ejaculation dysfunctions (comprising ejaculation delay, disorder, or failure) occurred in three patients. Table 6 summarizes the incidence of sexual dysfunction in the safety population. No instances of priapism occurred during the study.

The mean time to onset and median duration of the most common AEs are presented in Table 7. The mean time to onset of the most common AEs in patients treated with TCOAD ranged from 6 to 10 days, except for diarrhea (17 days) and back pain (26 days). In the placebo group, the mean time to onset of the most common AEs ranged from 9 to 13 days except for diarrhea (17 days), constipation (17 days), and back pain (23 days). In the TCOAD group, the time to onset for sedation ranged from 1 to 21 days (mean: 6 days); the time to onset for somnolence ranged from 1 to 37 days (mean: 8 days).

Data on duration of AEs were not normally distributed; thus, the median durations are presented. The median duration of the most common AEs (≥10%) in patients receiving TCOAD ranged from 4 to 9 days (Table 7) except for dry mouth (27 days, placebo: 22.5 days), sedation (12.5 days, placebo: 18 days), and fatigue (23 days; placebo: 19 days). Although the duration was prolonged in some patients, this did not generally lead patients to discontinue the study.

TABLE 4, CONTINUED. Primary and secondary antidepressant efficacy outcomes at end of study (56 days post randomization)

	MODIFIED ITT POPULATION		PP POPULATION	
	TCOAD	**PLACEBO**	**TCOAD**	**PLACEBO**
Change in CGI-S from baseline				
N (modified ITT/ LOCF; PP/OC)	202	204	135	162
Mean (SD)	-1.7 (1.4)	-1.4 (1.4)	-2.0 (1.3)	-1.6 (1.4)
P value†	0.036		0.017	
Responders and remitters at last study visit				
HAMD-17 responders				
N (modified ITT/ LOCF; PP/OC)	202	204	136	162
Responders, n	109 (54.0%)	84 (41.2%)	84 (62.2%)	77 (47.5%)
P value†	0.003		0.006	
HAMD-17 remitters				
N (modified ITT/ LOCF; PP/OC)	202	204	136	162
Remitters, n	72 (35.6%)	65 (31.9%)	59 (43.7%)	62 (38.3%)
P value†	0.22		0.26	
CGI-I responders				
Last study visit, N	180	183	133	160
Responders, n	96 (53.3%)	89 (48.6%)	84 (62.7%)	87 (54.4%)
P value‡	0.22		0.066	
PGI-I responders				
Last study visit, N	176	183	133	160
Responders, n	90 (51.1%)	80 (43.7%)	76 (57.1%)	77 (48.1%)
P value‡	0.15		0.15	
Improvement of illness				
CGI-I (n)				
Last study visit, N	178	182	134	160
Very much improved	52 (29.2%)	57 (31.3%)	46 (34.3%)	56 (35.0%)
Much improved	44 (24.7%)	32 (17.6%)	38 (28.4%)	31 (19.4%)
Minimally improved	43 (24.2%)	42 (23.1%)	33 (24.6%)	37 (23.1%)
No change	33 (18.5%)	45 (24.7%)	16 (11.9%)	34 (21.3%)
Minimally worse	4 (2.2%)	2 (1.1%)	—	—
Much worse	1 (0.6%)	3 (1.6%)	1 (0.7%)	2 (1.3%)
Very much worse	1 (0.6%)	1 (0.5%)	—	—
P value‡	0.22		0.066	

TCOAD=Trazodone Contramid OAD

DISCUSSION

This is the first large, randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of a once-daily, extended-release

TABLE 4, CONTINUED. Primary and secondary antidepressant efficacy outcomes at end of study (56 days post randomization)

	MODIFIED ITT POPULATION		PP POPULATION	
	TCOAD	PLACEBO	TCOAD	PLACEBO
PGI-I (n)				
Last study visit, N	176	183	133	160
Very much improved	35 (19.9%)	34 (18.6%)	32 (24.1%)	34 (21.3%)
Much improved	55 (31.3%)	46 (25.1%)	44 (33.1%)	43 (26.9%)
Minimally improved	48 (27.3%)	48 (26.2%)	38 (28.6%)	43 (26.9%)
No change	31 (17.6%)	39 (21.3%)	17 (12.8%)	33 (20.6%)
Minimally worse	3 (1.7%)	10 (5.5%)	1 (0.8%)	5 (3.1%)
Much worse	3 (1.7%)	3 (1.6%)	1 (0.8%)	1 (0.6%)
Very much worse	1 (0.6%)	3 (1.6%)	—	1 (0.6%)
P value‡	0.084		0.033	
Discontinuations due to lack of efficacy				
Safety population, N	202	204	N/A	N/A
Discontinuations due to lack of efficacy, n	8 (4.0%)	9 (4.4%)	N/A	N/A
P value§	> 0.99		—	

LOCF, last observation carried forward; OC, observed cases; MMRM, mixed-model repeated-measures
† ANCOVA
‡ Cochran-Mantel-Haenszel test
§ Fisher's exact test
N/A: Not applicable
TCOAD=Trazodone Contramid OAD

formulation of trazodone HCl (TCOAD) in patients with MDD. Following the two-week titration period, patients receiving TCOAD maintained a mean maximum daily dosage of 310mg during the six-week treatment period. Following eight weeks of treatment, the result of primary efficacy end point analyses demonstrated a consistent statistical superiority of TCOAD therapy over placebo. This was accompanied by statistically significant improvements in 7 of 13 secondary efficacy end points in the active treatment group compared with placebo for both the modified ITT and PP populations. TCOAD was also well-tolerated: the majority of AEs were mild to moderate in intensity, occurred during titration, and transient for most patients.

Antidepressant efficacy. Following eight weeks of treatment, there was a statistically significant greater decrease in the mean HAMD-17 total score in the TCOAD group from baseline (-11.4) than placebo (-9.3). The statistical significance achieved by the modified ITT population (P=0.012) was also achieved in the PP population analyses (P=0.009). This outcome was supported by four secondary efficacy outcomes: active treatment demonstrated in a significantly greater decrease from baseline than placebo in the mean HAMD-17 mood item, the mean MADRS score, the mean CGI-S score, and the number of HAMD-17 responders (Table 4). These results are consistent with a large body of evidence demonstrating the efficacy of other trazodone formulations in the treatment of MDD.[6–8,10,11,19–21]

A noteworthy supplement to these analyses was the inclusion of an MMRM sensitivity analysis. The MMRM sensitivity analysis imputes missing data with a likelihood-based estimation of patient responses derived from the patient population data. Analyses of covariance using this form of imputation provide lower and more consistent type I error rates than results obtained from analyses with LOCF imputed data.[22] The results of the MMRM analysis on the decrease in the HAMD-17 total score from baseline affirmed the statistical significance achieved by the LOCF- and OC-based analyses (P=0.006, Table 4), thereby demonstrating a consistent statistically superiority of TCOAD over placebo on the primary efficacy end point.

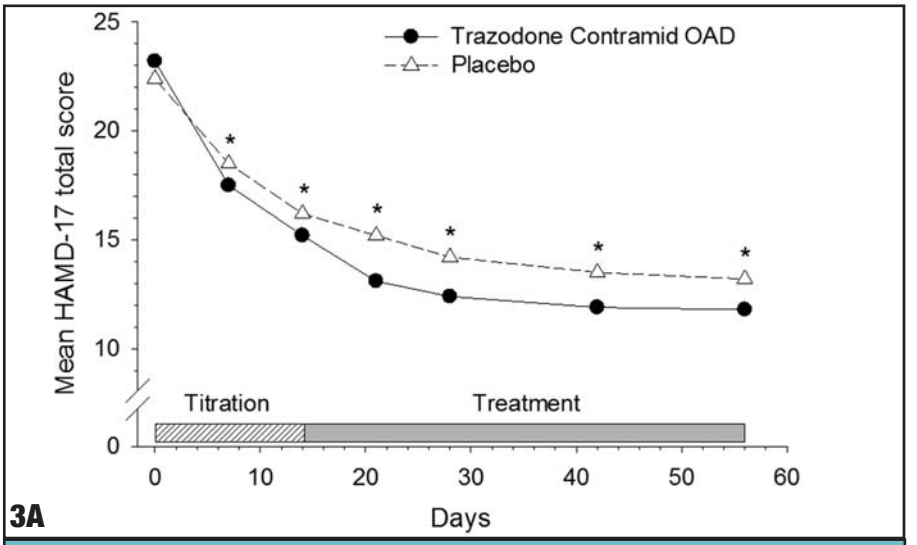
While all significantly improved secondary end points in the modified ITT population were also demonstrated in the PP population, other secondary end points, such as the PGI-I and CGI-I (Table 4), exhibited notable differences. Statistical significance was not achieved for both these end points in the modified ITT population (LOCF), yet the PP population analysis achieved significance for the PGI-I (P=0.033, OC) and approached significance for the CGI-I (P=0.066, OC). With these end points, LOCF imputation may have contributed to decreasing the proportion of patients reporting their improvement of illness (i.e., PGI-I) as "very much improved" and "much improved" (TCOAD: LOCF, 90/176 [51.1%], OC, 76/133 [57.1%]; placebo: LOCF, 80/183 [43.7%]; OC, 77/160 [48.1%]). A similar decrease between the two analyses was also observed for the CGI-I, which had a noticeable effect on the P values (modified ITT population, P=0.22; PP population, P=0.07).

Efficacy during the double-blind phase. The clinical relevance of early improvements in HAMD-17 scores was illustrated in patients with MDD receiving mirtazapine or paroxetine therapy.[23] Szegedi et al[23] showed that an early improvement in HAMD-17 scores, defined as a reduction of at least 20 percent within two weeks of treatment, was a highly sensitive predictor of a later stable response and remission.[23] The improvement in the mean HAMD-17 score observed after the first week of therapy corresponded to a relative decrease of 24 percent from baseline in patients receiving TCOAD versus 18 percent decrease in the placebo group (Figure 3a). Early

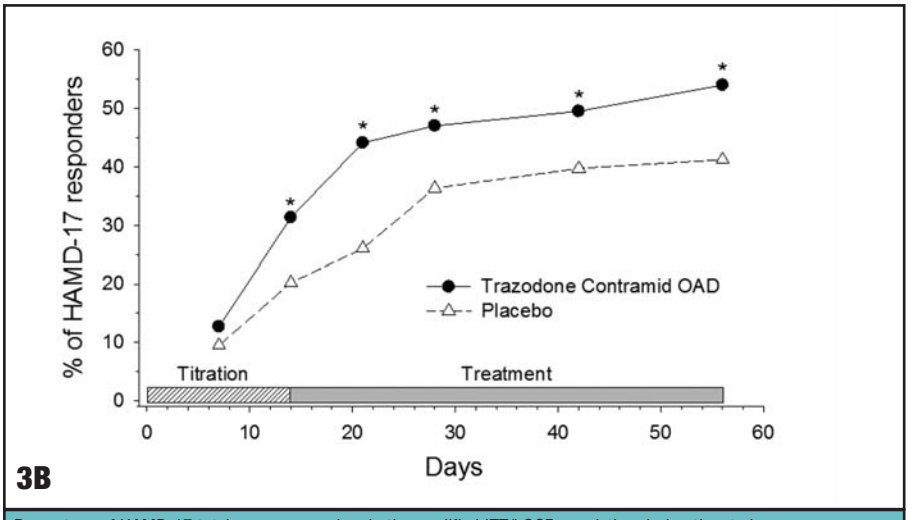
improvements in patients receiving TCOAD—that is, those that occurred within the first two weeks of the double-blind phase—were further characterized by a significantly greater number of HAMD-17 responders than placebo (Figure 3b). While the number of HAMD-17 remitters receiving active treatment (72/202, 35.6%) was not significantly different from placebo at the end of the study (due to an unexpected increase in the percentage of remitters in placebo group from Day 42 to Day 56) there were significantly more remitters in the TCOAD group for all other assessments during the treatment period (Figure 3c).

Quality of sleep. TCOAD significantly improves quality of sleep in patients with MDD (Figure 4). It is well known that trazodone improves sleep quality in both depressed and nondepressed patients.[24] For example, in a double-blind, four-week, multicenter study with depressed inpatients, Brooks et al[25] demonstrated that 100 to 400mg/day of immediate-release trazodone, given either as a single night-time or thrice daily dosage, significantly improved sleep variables (onset, satisfaction, and duration) compared with placebo. Studies further show that trazodone is more effective than various comparators in improving sleep as assessed by the HAMD sleep disturbance factor.[7,8,10,11,26]

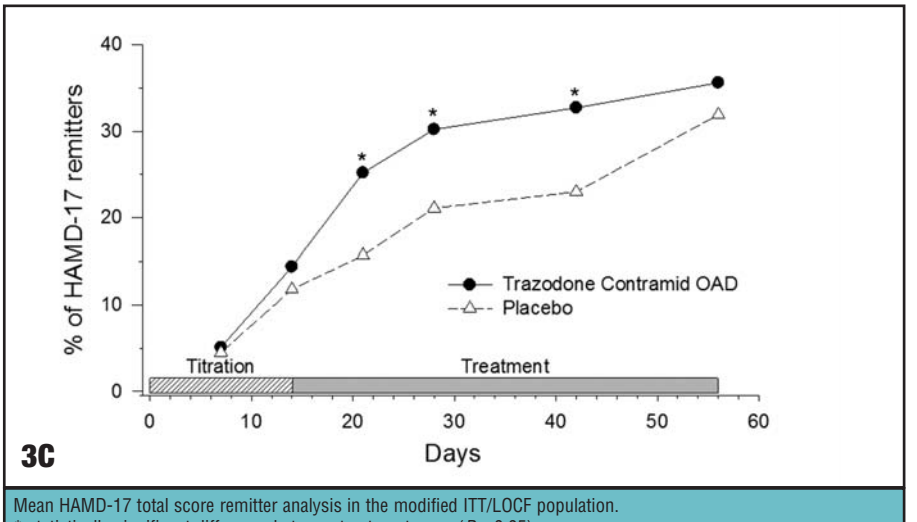
The clinical utility of targeting insomnia in patients with MDD, which is reported in more than 90 percent of patients, in part arises from its predictive association for the onset and relapse of MDD.[4,14,27,28] Indeed, the persistence of insomnia in patients with major depression can serve as a marker of treatment failure in commonly administered treatments such as SSRIs.[14] Moreover, recent evidence suggests treatment of insomnia may contribute to improvement in nonsleep depressive symptoms.[28] In the present study, the prevalence of insomnia at baseline was representative of the overall prevalence of insomnia in patients with MDD. A patient was classified as having insomnia if either his or her baseline HAMD item 4 (early



Mean HAMD-17 total scores in the modified ITT/LOCF population.
* statistically significant difference between groups ($P < 0.05$).

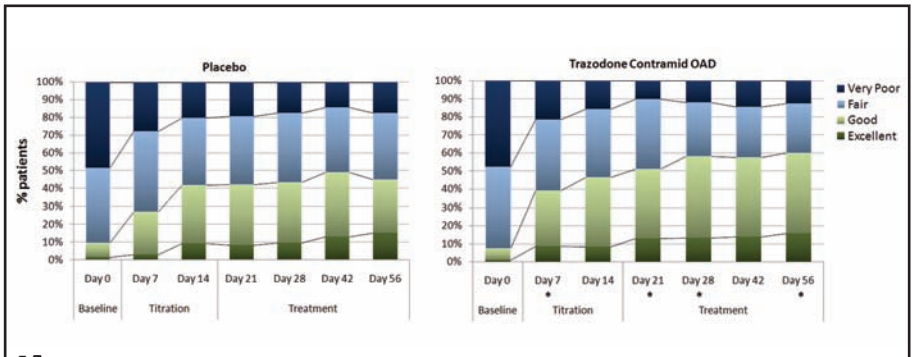


Percentage of HAMD-17 total score responders in the modified ITT/LOCF population during the study.
* statistically significant treatment-by-time interaction ($P < 0.05$).



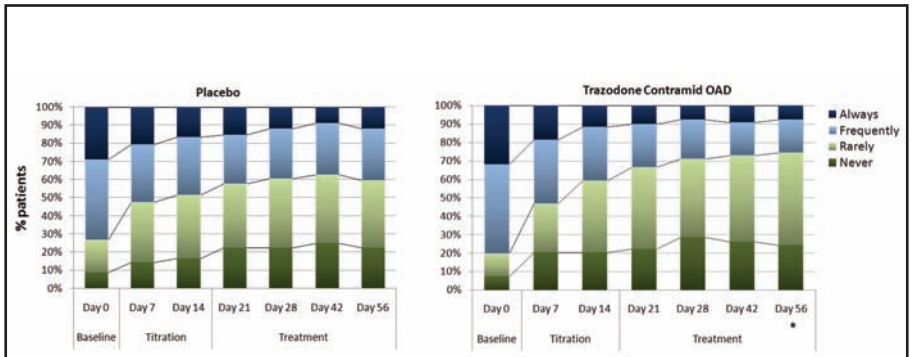
Mean HAMD-17 total score remitter analysis in the modified ITT/LOCF population.
* statistically significant difference between treatment arms ($P < 0.05$).

FIGURES 3A–C. HAMD-17 outcomes



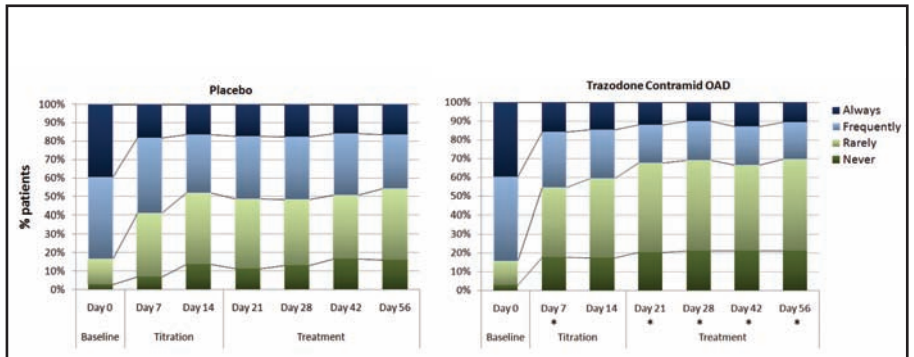
4A

"Overall quality of sleep" questionnaire response distributions



4B

"Trouble falling asleep" questionnaire response distributions



4C

"Awakening during the night" questionnaire response distributions

FIGURE 4. Distribution of responses for quality of sleep measures of the modified ITT/LOCF population.

*response distribution significantly different from placebo, $P<0.05$.

TABLE 5. Incidence of treatment emergent adverse events reported by ≥5% of patients (n)

PREFERRED TERM	TCOAD (N=202)	PLACEBO (N=204)
Headache	67 (33.2%)	55 (27.0%)
Somnolence†	63 (31.2%)	32 (15.7%)
Dry mouth	51 (25.2%)	26 (12.7%)
Dizziness	50 (24.8%)	25 (12.3%)
Nausea	42 (20.8%)	26 (12.7%)
Sedation†	34 (16.8%)	7 (3.4%)
Fatigue	30 (14.9%)	17 (8.3%)
Diarrhea	19 (9.4%)	23 (11.3%)
Constipation	16 (7.9%)	4 (2.0%)
Back pain	11 (5.4%)	7 (3.4%)
Vision blurred	11 (5.4%)	—

† Note: Sedation and somnolence were recorded as separate preferred terms. To ensure proper classification within each category, each reported case of somnolence and sedation was followed-up and confirmed by the investigator.

TCOAD=Trazodone Contramid OAD

insomnia), item 5 (middle insomnia), or item 6 (insomnia late) scores was 2 or greater or the sum of the three insomnia item scores was 4 or greater. Based on these criteria, 379 of 406 patients (93.3%) in the safety population (TCOAD, 191; placebo, 188) had insomnia at baseline. This corresponded closely with the proportion of patients who report having "fair" or "very poor" overall quality of sleep at baseline (371/406 [91.4%]; Table 1). Patients receiving active treatment demonstrated significant improvements in all three quality of sleep end points, with an improvement by the first week of therapy in "overall quality of sleep" (Figure 4a) and "awakening during the night" (Figure 4c).

Safety and tolerability. The incidence of the AEs reported in the present study were typical of those found with other formulations of trazodone.[6–8,11,17,21,29,30] Moreover, TCOAD was well tolerated: most AEs were mild to moderate in intensity and led to few discontinuations. Of the 25 patients who discontinued in the active treatment group due to AEs, the most common reasons were dizziness, sedation, and somnolence typically associated with trazodone. When the time course of these AEs was examined in the safety population (Table 7), these effects were found to have an early onset and were transient for most patients. Specifically, dizziness had a mean onset of 6.7 days and a median duration of four days; somnolence, a mean onset of 7.6 days and a median duration of nine days; and sedation, a mean onset of 6.1 days and a median duration of 12.5 days. Although the duration was prolonged

in some patients, it did not lead to many discontinuations. In total, 15 of 202 patients (7.4%) discontinued due to these AEs—only eight patients (4.0%) receiving TCOAD discontinued because of sedation or somnolence. The low discontinuation rates combined with the improved quality of sleep in patients receiving active treatment speaks to the notion that the antidepressant efficacy achieved with a mean daily dosage of 310mg of TCOAD was accompanied by beneficial rather than intolerable or unacceptable sedative effects.

AEs of particular concern are those related to weight gain and sexual dysfunction, which are among the most prevalent reasons for discontinuation of antidepressant therapy.[31,32] In this study, there were no significant changes in body weight in either treatment group. While trazodone is not associated with the sexual adverse events observed with SSRIs or SNRIs,[33–35] rare sexual adverse effects have occurred. The occurrence of priapism in men can lead to permanent impairment of erectile function or impotence.[17] However, the incidence of this event in men treated with trazodone is rare (1 in 1,000 to 1 in 10,000)[36] and was not observed in this study. The sexual side effects of trazodone also include increased libido and hypersexual behavior.[37,38] These sexual side effects of trazodone have led to its study as a potential treatment for erectile dysfunction[39,40] and as a treatment for SSRI-related sexual dysfunction.[41] The mean age of our study population (44 years) suggests that the patients were generally sexual active. The low rate of sexual dysfunction reported in patients receiving TCOAD (4.9% vs. 2.5% for placebo, Table 6) combined with its antidepressant efficacy and the purported benefits of some sexual side effects of trazodone suggest TCOAD may be of interest for patients with MDD who have previously experienced sexually related AEs on SSRIs or SNRIs.

TABLE 6. Incidence of sexually related adverse events in the safety population (n)

PREFERRED TERM	TCOAD (N=202)	PLACEBO (N=204)
Ejaculation delayed	2	0
Ejaculation disorder	1	0
Ejaculation failure	0	1
Erectile dysfunction	2	1
Libido decreased	3	2
Orgasm abnormal	1	0
Penile pain	0	1
Premature ejaculation	0	1
Sexual dysfunction	1	0
TOTAL	**10 events in 10 patients (4.9%)**	**6 events in 5 patients (2.5%)**

TCOAD=Trazodone Contramid OAD

TABLE 7. Mean time to onset and median duration of treatment emergent adverse events reported by ≥5% of patients

	TIME TO ONSET, DAYS [MEAN (SD)]		DURATION, DAYS [MEDIAN (IQR)]	
PREFERRED TERM	TCOAD (N=202)	PLACEBO (N=204)	TCOAD (N=202)	PLACEBO (N=204)
Headache	9.8 (10.3)	9.6 (9.4)	4 (1, 14)	3 (1, 15)
Somnolence	7.6 (7.0)	9.7 (10.5)	9 (4, 22)	4.5 (3, 11)
Dry mouth	6.1 (6.0)	9.8 (13.3)	27 (12, 46)	22.5 (5, 44)
Dizziness	6.7 (5.6)	11.2 (8.0)	4 (2, 17)	2 (1, 10)
Nausea	9.6 (8.8)	9.2 (8.1)	3 (1, 7)	2 (1, 7)
Sedation	6.1 (5.9)	5.9 (3.7)	12.5 (6, 27)	18 (3, 32)
Fatigue	7.9 (7.5)	13.3 (15.2)	23 (10, 53)	19 (8, 23)
Diarrhea	16.5 (13.2)	16.8 (14.1)	3 (1, 7)	3 (1, 5)
Constipation	7.2 (7.0)	17.3 (15.4)	7 (3, 29.5)	14.5 (6.5, 19)
Back pain	26.0 (18.7)	22.9 (22.0)	4 (1, 14)	3 (1, 4)
Vision blurred	8.6 (5.1)	—	20 (2, 23)	—

TCOAD=Trazodone Contramid OAD

CONCLUSION

The results of this large, randomized, double-blind study show that TCOAD—at a mean maximum daily dosage of 310mg—demonstrated a significantly greater improvement in the HAMD-17 primary efficacy end point over placebo. The efficacy was further supported by significant improvements in 7 of 13 secondary end points, including HAMD-17 responders, MADRS score, and quality of sleep. The antidepressant efficacy, improvements in quality of sleep, lack of sexual dysfunction, and the low incidence of anxiety in patients receiving TCOAD may be related to the antagonism of 5HT2A/2C and H_1 receptors by trazodone.[3] Although TCOAD was associated with serotonergic and histamine-related AEs typical of those associated with trazodone, this once-daily, extended-release formulation was associated with AEs that were well tolerated and transient for most patients. We conclude that TCOAD at the recommended daily dosage of 300mg appeared to be an appropriate monotherapy for patients with MDD.

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