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Efficacy and Safety of Prolonged-Release Trazodone in Major Depressive Disorder: A Multicenter, Randomized, Double-Blind, Flexible-Dose Trial

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Key Words

Major depressive disorder · Trazodone · Serotonin-2 antagonist/reuptake inhibitor · Placebo-controlled trial · Hamilton Depression Rating Scale

Abstract

Objective: To investigate the efficacy, safety, and clinical benefit of prolonged-release trazodone (Trittico) in the treatment of major depressive disorder (MDD). ***Methods:*** In this study, 363 Chinese patients with MDD were randomized 1:1 to receive either prolonged-release trazodone (150–450 mg) or placebo treatment for 6 weeks. The primary efficacy measurement was the change of the 17-item Hamilton Depression Rating Scale (HAMD-17) total score from baseline to the end of the study. The secondary efficacy measurements were the response and remission rates, the Clinical Global Impression – Improvement of Illness (CGI-I) score at the end of the study, and the change of the HAMD-14 total score and quality of sleep [evaluated by the Pittsburgh Sleep Quality Index (PSQI) scale] during the study period. ***Results:*** The mean maximum daily dose was 273.11 mg for the trazodone group and 290.92 mg for the placebo group. At the end of the study, there was a significant difference between the two groups in the HAMD-17 change score (trazodone vs. placebo: –11.07 vs. –8.29, $p < 0.001$). Trazodone showed advantages at 1 week of treatment, and the effect lasted until the end of the study (week 6). The response and remission rates of the trazodone group were significantly higher than those in the placebo group (response rate: 59.6 vs. 37.2%, $p < 0.001$; remission rate: 35.5 vs. 22.2%, $p = 0.005$). The majority of the adverse reactions of trazodone were mild to moderate, and the most frequent adverse reactions (≥5%) were dizziness, dry mouth, somnolence, and nausea. ***Conclusions:*** Prolonged-release trazodone was more effective than placebo in MDD and was well tolerated.

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Introduction

Major depressive disorder (MDD), also referred to as major depression or unipolar depression, is a common psychiatric disorder characterized by depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. The 2010 Global Burden of Disease (GBD) study identified depressive disorders as a leading cause of burden. They are also a contributor of burden allocated to suicide and ischemic heart disease [1]. Although electroconvulsive therapy, psychotherapy, and some other therapies can be used in the treatment of MDD, antidepressants are the primary choice due to their efficacy in relieving depressed mood, accompanied anxiety, and somatic symptoms.

Trazodone is a triazolopyridine derivative effective in the treatment of depressive disorders, including depression accompanied by anxiety and sleep disorders. It is an inhibitor of serotonin reuptake and an antagonist at 5-HT2A and 5-HT2C receptors, a moderately to highly potent α-adrenoceptor antagonist, and has moderate antihistaminergic activity [2, 3]. Unlike other antipsychiatric drugs, trazodone is not contraindicated for glaucoma and urination disorders [4]. Since there is no anticholinergic activity, trazodone also has no effect on cardiac function like tricyclic antidepressant [3]. Trazodone Trittico is a prolonged-release formulation of trazodone hydrochloride. It is equally effective as the conventional formulation [5, 6] and is available as 75- and 150-mg trazodone hydrochloride caplets to provide flexibility in dosing. The prolonged-release trazodone formulation further improved treatment compliance in treatment doses and decreased peak plasma concentrations and dosing frequency compared with conventional trazodone.

Prolonged-release trazodone is equally effective as some selective serotonin reuptake inhibitors, but has less adverse effects on sleep. In a double-blind study [7], patients were randomized to receive either prolonged-release trazodone at 150–450 mg/day (n = 55) or paroxetine at 20–40 mg/day (n = 53) during a treatment period of 6 weeks. Trazodone was found to be equally effective as paroxetine at reducing symptoms of depression, and in both groups there were >85% responders and >65% remitters. Although the onset of efficacy was faster for patients treated with paroxetine, sleep disorders were significantly less evident for patients in the trazodone group at the end of the study. In another study of prolonged-release trazodone at 150–450 mg/day (n = 62) versus sertraline at 20–40 mg/day (n = 60), trazodone and sertraline were equally effective in reducing depressive symptoms and in promoting remission, and had similar onset times. However, sleep disturbances were significantly less evident for patients receiving trazodone at the study end point [8].

In China, prolonged-release trazodone is a new antidepressant for treating MDD and is not widely used in the clinic. The efficacy and safety of prolonged-release trazodone for Chinese patients with MDD are also unclear. Therefore, we designed this study to compare prolonged-release trazodone and placebo in Chinese MDD patients.

Methods

Study Design

This 6-week, multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of prolonged-release trazodone versus placebo for the treatment of MDD. The sample size was calculated according to the Drug Registration Regulation of The People's Republic of China, which requires 100 patients per group in order to achieve sufficient power. To achieve 90% power to detect a 3.0-unit absolute mean change in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score from baseline, a sample size of 151 patients in each treatment group was needed to complete the study; this assumed a common standard deviation of 8.0 with a two-group, two-tailed t test with significance set at $p = 0.05$. Assuming a discontinuation rate of 20%, an enrollment of 189 patients in each treatment group was required.

Participants

Inpatients and outpatients were recruited if they met the following criteria: (1) age 18–65 years; (2) a diagnosis of MDD as defined in Axis I of the Diagnostic and Statistical Manual of Mental Disorders, ed 4, Text Revision (DSM-IV-TR), and (3) a total score at the HAMD-17 of ≥18. Patients were excluded if they met DSM-IV-TR Axis I criteria for any other mental disorder except anxiety disorders, which sometimes have depression as comorbidity. Further exclusion criteria were a history of severe drug allergy or hypersensitivity, other serious illness or sequela of serious illness, fluoxetine within 5 weeks prior to inclusion, and/or inability to comply with the protocol in the investigators' opinion. Patients were also excluded if they seriously tended to commit suicide. Patients who had joined any other clinical trial or who received oral antipsychotic drugs, monoamine oxidase inhibitors, protease inhibitors, any concomitant medications causing QT or PR prolongation, or electroconvulsive therapy within 30 days prior to initiation of the study were also excluded. Women who were pregnant or breastfeeding were also excluded.

The study was conducted from December 2011 to December 2013 at 13 psychiatric hospitals in China. The study protocol was approved by the ethics committees at each center and was carried out in accordance with the Guideline for Good Clinical Practice and the Declaration of Helsinki. All medication was free to enrolled participants. All patients and their caregivers provided written informed consent before enrollment. Our experiments comply with the current laws of China.

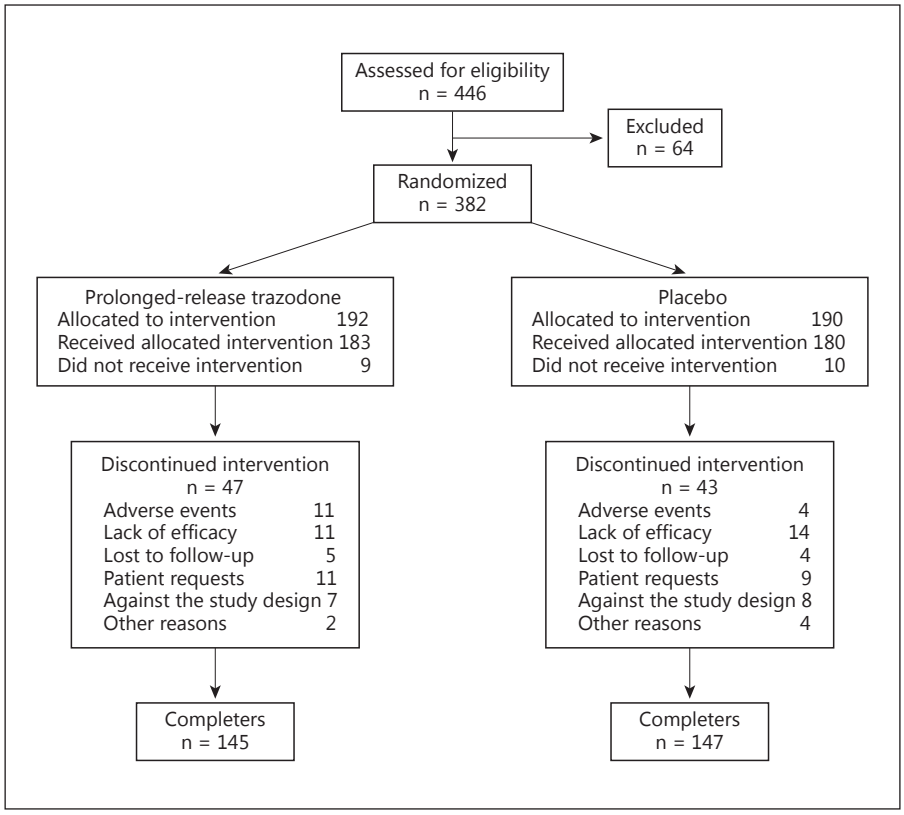

Fig. 1. Flow chart of the study.

Randomization to Treatment Conditions

Participants were randomized (without restriction or stratification) through a computer-generated table to one of the two treatments in blocks of four to ensure approximately equal numbers in the two treatment groups. Assignment (randomization) was determined after the patients completed all assessments. To ensure concealment of the randomization, which was conducted independently of the investigators by a research pharmacist at a separate facility, medication was provided in coded packages (75 mg prolonged-release trazodone and 75 mg mock trazodone, or 150 mg prolonged-release trazodone and 150 mg mock trazodone). Prolonged-release trazodone and mock trazodone were identical in appearance, taste, and odor.

Study Procedure

The study comprised a screening and washout phase and a double-blind active treatment phase. Patients were evaluated at screening (visit 1, day –7), baseline (visit 2, day 0), and on days 7, 14, 21, and 42 of treatment (visits 3, 4, 5, and 6, respectively). Patients went through a 1- to 7-day placebo washout period and were randomly assigned to receive prolonged-release trazodone or placebo treatment for 6 weeks. Trazodone was titrated over 1 week to the recommended dose (150 mg twice daily). Patients first received 75 mg trazodone or placebo in the evening on days 0–3 and two caplets of 75 mg trazodone or placebo in the evening on days 4–7. After 1 week of dose titration, patients continued to take 150 mg trazodone or placebo twice daily. Patients considered to be nonresponders after 3 weeks of treatment (Clinical Global Impression – Global Improvement score >3) were treated with an increased dosage of trazodone or placebo (450 mg/day).

Assessment of Compliance

Most patients were accompanied by their caregivers at each visit, and the treatment was supervised by the caregivers. Compliance was assessed by the investigators by counting the remaining medications at each visit. Compliance was considered good if a patient took 80% of the medications.

Assessments of Efficacy and Safety

The primary efficacy measurement was the change in the HAMD-17 total score from baseline to the end of the study period. The secondary efficacy measurements were response and remission rates, the distribution of Clinical Global Impression – Severity of illness (CGI-S) and Clinical Global Impression – Improvement of Illness (CGI-I) responders at the end of the study, and the change of the HAMD-14 total score and quality of sleep [evaluated by the Pittsburgh Sleep Quality Index (PSQI) scale] from baseline to the end of the study period. Response was defined as a change in the HAMD-17 total score of ≥50% and remission as a HAMD-17 total score ≤7. CGI-I responders were defined as patients assessed by investigators as 'minimally improved', 'much improved', or 'very much improved' at the last study visit.

All investigators were trained to use the study scales and passed the test of consistency. At the first visit, information regarding sociodemographic and medical and psychiatric history was collected. Results of laboratory examinations (routine examination of

Table 1. Baseline sociodemographic details and clinical characteristics

Characteristics	Prolonged-release trazodone (n = 183)	Placebo (n = 180)	χ^2/F	p value
Mean age ± SD, years	39.5±12.7	38.3±12.2	0.775	0.891
Gender, n (%)				
Female	113 (61.7)	110 (61.1)	0.0187	0.891
Male	70 (38.3)	70 (38.9)		
Mean weight ± SD, kg	60.2±11.9	60.0±9.8	0.027	0.869
Mean breath ± SD, time/min	18.8±1.2	18.8±1.2	0.343	0.559
Mean heart rate ± SD, beats/min	75.6±7.8	74.7±8.6	1.314	0.252
Mean systolic blood pressure ± SD, mm Hg	113.6±12.5	113.3±11.3	0.023	0.878
Mean diastolic blood pressure ± SD, mm Hg	73.8±7.8	73.5±7.9	0.035	0.851
Mean HAMD-17 score ± SD	21.6±2.8	21.9±3.4	1.045	0.307
Mean HAMD-14 score ± SD	16.5±5.5	17.0±5.6	0.626	0.429
Mean PSQI score ± SD	12.6±3.7	12.9±4.3	0.707	0.401

blood and urine, hepatic and renal function, and fasting blood sugar) were obtained at baseline and week 6. An electrocardiogram was done at baseline and on weeks 2 and 6. At each visit, physical and neurological examinations were performed, and blood pressure and weight were recorded. The investigators also recorded the number of medications taken and the adverse events (AEs), which were reported by the patients or caregivers at each visit. If a patient withdrew from the study for any reason, the date and reason were recorded and the last visit was considered the final visit.

Statistical Analysis

Statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, N.C., USA). Continuous variables were described using means (standard deviation, SD), whereas categorical variables were reported using frequencies and percentages. Efficacy analysis was conducted in the intent-to-treat (ITT) and per-protocol (PP) populations. The ITT population was defined as all patients who received ≥1 dose of medication and had data available from ≥1 valid post-baseline efficacy 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. The last observation carried forward (LOCF) method of replacing missing values was adopted to take potential differences in discontinuation rates into account. Using either parametric (analysis of covariance, ANCOVA) or nonparametric (Cochran-Mantel-Haenszel) testing, continuous baseline data were compared between the groups. The χ^2 test or Fisher's exact test, when appropriate, was used to ensure comparability of baseline qualitative data between the groups. Changes (HAMD-17 total score, HAMD-14 total score, and PQSI score) from baseline to the end of the study were analyzed using ANCOVA, with treatment and treatment center as factors, baseline HAMD-17 total score as covariate, and by considering the interaction between treatment and treatment center. If this interaction was not statistically significant at 0.10, it was removed from the model. Between-group comparisons of responder and remitter rate, GCI-S, GCI-I, and tolerability comparisons were performed using χ^2 test or Fisher's exact test.

Results

Patient Characteristics

Of 446 patients screened, a total of 382 patients were randomized to receive either prolonged-release trazodone (n = 192) or placebo (n = 190). Ninety patients (prolonged-release trazodone, n = 47; placebo, n = 43) discontinued the study, and finally, 292 patients (prolonged-release trazodone, n = 145; placebo, n = 147) completed the trial (fig. 1). No significant differences were found between the groups regarding the rate of discontinuation (p = 0.671). The ITT population contained all 363 patients that comprised the safety population. The PP population consisted of a total of 332 patients (prolonged-release trazodone, n = 185; placebo, n = 181).

No significant differences were found between the groups in baseline sociodemographic details and clinical characteristics (table 1). The average maximum dose of prolonged-release trazodone was 273.11 mg/day compared with placebo 290.92 mg/day, and significant differences were found between the groups (p < 0.001). The number of patients who needed an increase in their dosage in the prolonged-release trazodone group (n = 23) was less than that in the placebo group (n = 47), and significant differences were found between the groups (p = 0.001).

Efficacy

Change in the HAMD-17 Total Score

The mean HAMD-17 total scores at baseline were 21.6 (SD 2.8) and 21.9 (SD 3.4) for patients randomized to the prolonged-release trazodone and placebo groups, respec-

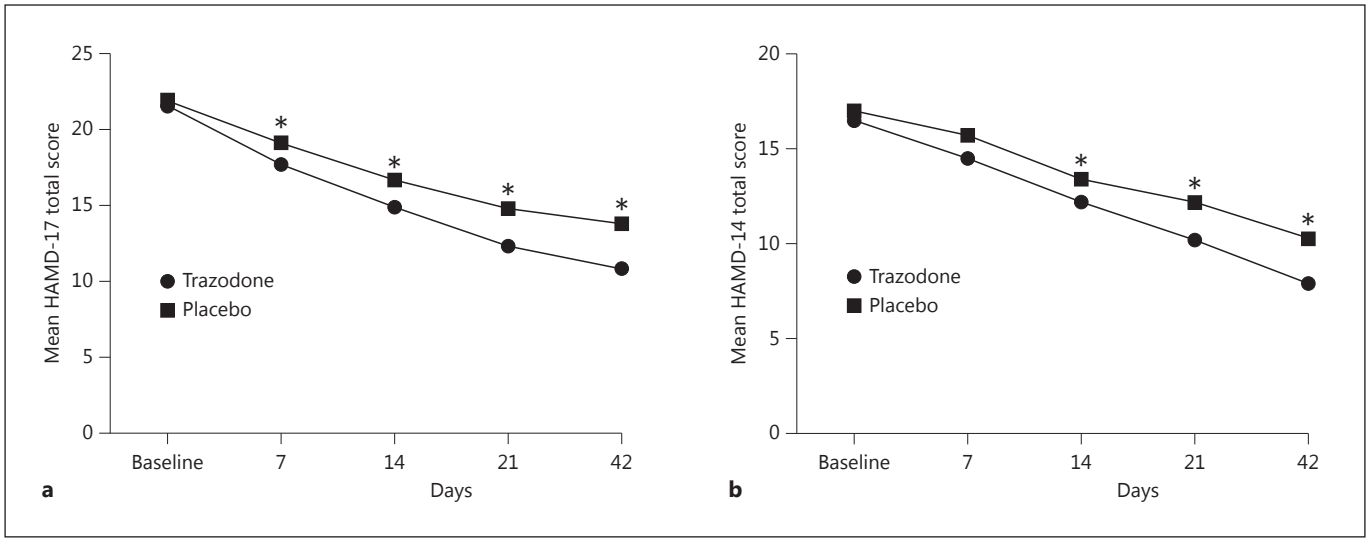

Fig. 2. Mean HAMD-17 (**a**) and HAMD-14 (**b**) total scores in the ITT/LOCF population. * Statistically significant difference between the groups ($p < 0.05$).

tively. The corresponding mean scores at the last study visit (LOCF) were 10.8 (SD 6.4) for the active treatment group and 13.8 (SD 6.9) for the placebo group. Consequently, the change in the HAMD-17 total score from baseline to the last study visit decreased by an average of 11.07 (SD 6.5) in the prolonged-release trazodone group versus 8.29 (SD 6.5) in the placebo group. This difference was found to be statistically significant in favor of the prolonged-release trazodone group ($p < 0.001$) and was still statistically significant after correcting for treatment center and baseline values ($p < 0.05$). The corresponding percentage of change in the HAMD-17 total score was 51% in the prolonged-release trazodone group and 38% in the placebo group.

The antidepressant efficacy in the active treatment group was further supported by the change from baseline in the HAMD-17 total score at each post-randomized visit; there was a significantly greater improvement in the mean HAMD-17 total score in the prolonged-release trazodone group compared with the placebo group at 1, 2, 3, and 6 weeks of the double-blind phase (all $p < 0.05$) (fig. 2a).

Change in the HAMD-14 Total Score

The change in the HAMD-14 total score from baseline to the last study visit decreased by an average of 8.89 (SD 5.2) in the prolonged-release group versus 6.66 (SD 5.3) in the placebo group (fig. 2b). This difference was found to be statistically significant in favor of the prolonged-release trazodone group ($p = 0.005$) and was still statistically significant after correcting for treatment center and baseline values ($p < 0.05$). The corresponding percentage of change in the HAMD-14 total score was 54% in the prolonged-release trazodone group and 39% in the placebo group.

Response and Remission Rates

Response rates were 59.6% (109/183) versus 37.2% (67/180) in the prolonged-release trazodone versus placebo groups, and significant differences were found between the groups ($p < 0.001$). Remission rates in the prolonged-release trazodone group were also significantly higher than in the placebo group [35.5% (65/183) vs. 22.2% (40/180), $p = 0.005$]. The response rates of the dose-up (450 mg/day) patients were 30.4 versus 27.7% in the prolonged-release trazodone versus placebo groups, and no significant between-group differences were found ($p = 0.811$). The remission rate of the dose-up (450 mg/day) patients were 26.1 versus 12.8% in the prolonged-release trazodone versus placebo groups, and no significant between-group differences were found ($p = 0.168$).

Severity of Illness (CGI-S)

Evaluation of the CGI-S showed that there was a statistically significant difference between the groups at the last visit ($p = 0.004$) (fig. 3a). At baseline, the large majority of patients (trazodone 148/183, 80.9%; placebo 143/180, 79.4%) were considered to be moderately or

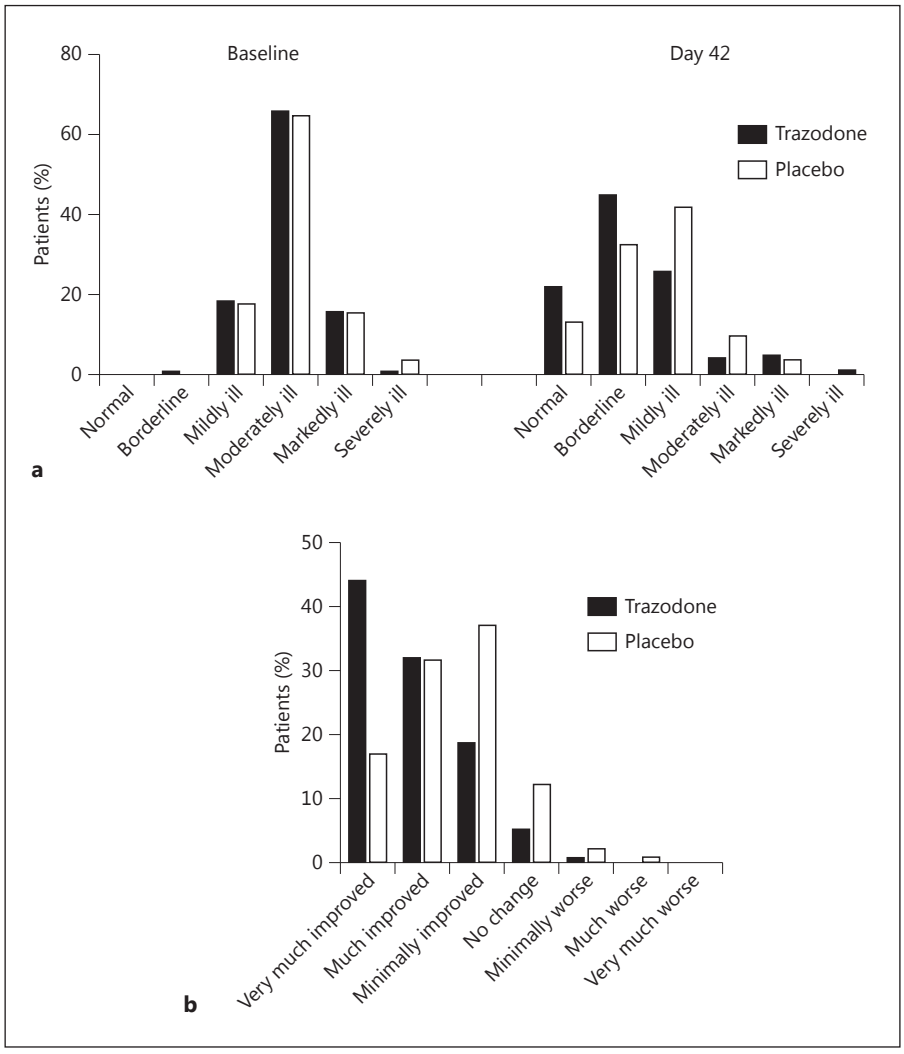

Fig. 3. a CGI-S at baseline and on day 42 in the ITT/LOCF population. **b** CGI-I on day 42 in the ITT/LOCF population.

markedly ill, and only 1 patient in the trazodone group was considered to be borderline. By the end of the study, >80% in either group were considered to be normal or borderline or mildly ill (trazodone 144/157, 91.7%; placebo 129/149, 86.6%), and more patients in the trazodone group were considered to be normal (trazodone 34/157, 21.7%; placebo 19/149, 12.8%).

Improvement of Illness (CGI-I) Responders

At the last study visit, the percentage of CGI-I responders among patients receiving prolonged-release trazodone was statistically different (LOCF) compared with that among the placebo group ($p < 0.001$); 148 of 157 patients (94.3%) receiving prolonged-release trazodone were 'improved' (minimally, much, or very much) compared with 127 of 149 (85.2%) receiving placebo (fig. 3b).

Quality of Sleep

The PSQI total score from baseline to the last study visit was decreased by an average of 6.4 (SD 4.1) in the prolonged-release trazodone group versus 4.5 (SD 4.3) in the placebo group, and this difference was found to be statistically significant in favor of the prolonged-release trazodone group ($p < 0.001$).

Safety and Tolerability

During the course of the study, 156 of 366 patients in the safety population reported 241 cases of AEs. Significant differences were found between the prolonged-release trazodone and placebo groups [100 (54.1%) vs. 56 (30.9%), $p < 0.001$]. AEs ≥5% are presented in table 2: the most frequent AEs (except dizziness and somnolence) were the same for both the treatment and placebo groups

Table 2. AEs during the 6-week treatment

AEs	Prolonged-release trazodone (n = 185)	Placebo (n = 181)	χ^2	p value
Dizziness	37 (20)	13 (7.2)	12.744	0.000
Dry mouth	20 (10.8)	13 (7.2)	1.468	0.226
Somnolence	20 (10.8)	2 (1.1)	15.255	0.000
Nausea	11 (5.9)	5 (2.8)	2.218	0.136
Headache	10 (5.4)	4 (2.2)	2.539	0.111

Values are expressed as n (%). AEs >5% are shown; some patients experienced >1 AE.

(table 2). Overall, the intensity of AEs experienced by patients on prolonged-release trazodone was mild to moderate in the majority of cases. Only 1 patient in the prolonged-release trazodone group experienced a severe AE during the study. One patient treated with prolonged-release trazodone reported an increase in depressive symptoms after 14 days of treatment, and the HAMD-17 total score increased by 4 after 2 weeks of treatment (the baseline score was 27). Considering that the increase in depressive symptoms may be associated with prolonged-release trazodone, the dose of prolonged-release trazodone was reduced gradually and stopped at 20 days. Then, the patient was treated with duloxetine. After a divided dose formulation of 80 mg duloxetine for 24 days and six electroshock therapies within this period, his symptoms improved.

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.

Discussion

Our multicenter, randomized, double-blind, placebo-controlled study compared the efficacy and safety of prolonged-release trazodone and placebo in Chinese MDD patients. The result of the primary end point analyses demonstrated a statistical superiority of prolonged-release trazodone over placebo. All secondary end points also demonstrated a statistical superiority of prolonged-release trazodone over placebo. In addition, all significantly improved end points in the ITT population were also demonstrated in the PP population. Prolonged-release trazodone was well tolerated: the intensity of AEs was mild to moderate in the majority of cases.

Following 6 weeks of treatment, there was a statistically significant greater decrease in the mean HAMD-17 total score in the prolonged-release trazodone group than in the placebo group. The statistical significance achieved by the modified ITT population was also achieved in the PP population analyses. These results are consistent with a large amount of evidence demonstrating the efficacy of other trazodone formulations in the treatment of MDD [6–9]. The HAMD-17 total score of the prolonged-release trazodone group at baseline in our study was consistent with that reported from two similar European multicenters, double-blind, randomized trials [7, 8], but the changes in HAMD-17 total score from baseline to the end of the study as well as response and remission rates (–11.07, 59.6, and 35.5%, respectively) were lower than in the other two studies (–14.6, 87.3, and 69.1%, respectively; –12.9, 74.2, and 59.7%, respectively). Maybe this is due to the average daily dose of prolonged-release trazodone (273.11 mg) in our study that was below the average daily dose of the other two studies (305 and 297 mg). Compared with another prolonged-release trazodone formulation, a once-a-day formulation (TzCOAD, Oleptro™) [9], both formulations responded in the first week. The number of HAMD-17 remitters was similar, but our study had more HAMD-17 responders than Sheehan et al.'s [9] study (59.6 vs. 54.0%). The standard effect size analysis of a previously published randomized study showed that the HAMD items with the greatest improvement were insomnia (late –0.24), feelings of guilt (–0.24), and depressed mood (–0.23), and the antidepressant efficacy was independent of the baseline severity of insomnia and of the improvement in insomnia [10].

Prolonged-release trazodone responded in the first week and showed an early improvement in HAMD-17 scores. The proportion of patients in the prolonged-release trazodone group who needed an increase in their dose after 3 weeks of treatment was less than that in the placebo group (12.6 vs. 26.1%). At the same time, 26.1% of patients who needed an increase in their dose after 3 weeks of treatment in the prolonged-release trazodone group showed remission at the end of the study. Therefore, for patients who do not remit at 3 weeks of treatment an increase to a 450-mg dose should be considered.

This study indicates that trazodone obviously improves sleep quality compared with placebo; this result is consistent with previous studies [9]. Besides, sleep disturbances were significantly less evident for patients who re-

ceived trazodone treatment compared with sertraline and paroxetine [7, 8]. It is well known that a low dose (25–100 mg) of trazodone has therapeutic activity as a hypnotic [11]. Wichniak et al. [12] compared the effectiveness of trazodone treatment in patients with primary insomnia with and without prior history of hypnotics use. They found that trazodone improves sleep quality and daytime functioning independently of a prior history of hypnotics use. In addition, trazodone was observed by Kaynak et al. [13] to be effective in the treatment of antidepressant-associated insomnia. Zavesicka et al. [14] observed that trazodone improved the results of cognitive behavior therapy of primary insomnia in nondepressed patients. It significantly increased the slow-wave sleep duration compared with cognitive behavior therapy treatment only. Accordingly, trazodone may be a therapeutic choice in the treatment of patients with major depression showing prevalent sleep disturbances.

Prolonged-release trazodone was well tolerated: most AEs were mild to moderate in intensity and led to few discontinuations, and this corresponds with other studies [7–9]. Eleven (6.0%) patients in the prolonged-release trazodone group and 4 (2.2%) patients in the placebo group discontinued due to AEs such as somnolence and dizziness. In other studies, patients treated with prolonged-release trazodone discontinued due to AEs such as dizziness, sedation, and somnolence [9] and anxiety, insomnia, and tremor [8].

In summary, as depression treatment has a placebo effect, in this experiment we adopted a double-blind, placebo-controlled randomized (1:1) design. The results show that the efficacy index of the placebo group at the end of the study improved from baseline, and the difference was statistically significant, but there was less improvement in the prolonged-release trazodone group, which further proves that prolonged-release trazodone is superior to placebo treatment. Prolonged-release trazodone showed improvement at 1 week of treatment, which lasted until the end of the study (week 6). Moreover, it can be said that gradually increasing the dosage regimen showed good security, and the majority of adverse reactions were mild to moderate (≥5%), which included dizziness, dry mouth, somnolence, and nausea.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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