Safety and Efficacy of Two Doses of Tandospirone Citrate for Generalized Anxiety Disorder: A Multicenter Randomized Controlled Trial

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Research Article

Keywords: Generalized anxiety disorder, tandospirone, randomized controlled trial, Safety, Efficacy

Posted Date: October 5th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-800448/v1

Abstract

Background

This study aimed to determine the safety and efficacy of different doses of tandospirone to treat generalized anxiety disorder (GAD).

Methods

This parallel randomized controlled trial involved patients with GAD from eight centers in China between 01/2012 and 09/2018. Patients were randomly assigned to 60 mg/day and 30 mg/day groups. The primary endpoint was the overall response rate at the end of week 6. The secondary endpoints included significant response rate, change in Hamilton Anxiety Scale (HAMA) total score, HAMA subscale score, Hamilton Depression Scale-17 (HAMD-17), and adverse drug reactions.

Results

No significant difference was found in the overall response rate (65.7% vs 58.4%, $P > 0.05$) between 60 mg/day and 30 mg/day groups. The significant response rate (34.3% vs 22.6%, $P = 0.032$) was better in the 60 mg/day group. The reduction in HAMA total score, somatic anxiety factor, cardiovascular symptom factor, gastrointestinal symptom factor, and HAMD-17 score were better in the 60 mg/day group (all $P < 0.05$). The incidence of dizziness and gastrointestinal reactions of the 60 mg/day group was higher than that of the 30 mg/day group. However, there was no significant difference in the proportion of withdrawal due to adverse events.

Conclusions

For GAD treatment, the overall response rate of high-dose tandospirone was similar to that of low-dose tandospirone. The safety in the two groups was tolerable. Patients with good compliance might benefit from a high-dose regimen.

Trial registration:

The trial registration no. was NCT01614041(07/06/2012).

Background

Generalized anxiety disorder (GAD) is a subtype of anxiety disorder characterized by psychological anxiety and various somatic symptoms [1], severely affecting health and quality of life. GAD is common

in China [2], where the lifetime prevalence is 0.3% [3]. Patients with GAD often complain of gastrointestinal and somatic symptoms such as headache [4], both of which are often misdiagnosed. The proportion of patients receiving systemic treatment with anxiolytic drugs does not exceed 8.5% in China [5]. Thus, anxiolytic treatment has become a focus of basic research and clinical practice.

Pharmacotherapy is the first-line option for GAD treatment, with a response rate ranging from 60–75% [6]. A meta-analysis of 89 studies enrolling 25,441 patients with GAD compared the efficacy of 22 anxiolytic drugs [7]. The safety and efficacy varied among medications; however, the sample sizes of some studies limited the validity of their conclusions. Forty-six percent of patients with GAD discontinued the treatment within 3.7 months after receiving medication for various reasons such as drug intolerance [8], which was one reason for the smaller proportion of systemic treatment in patients with GAD. Medications studied in these meta-analyses omitted tandospirone.

Tandospirone citrate is a partial agonist of the 5-HT_{1A} receptor [9, 10], which selectively binds to the 5-HT_{1A} receptor in the brain. The anti-anxiety effect is exerted by inhibiting the activities of the 5-HT_{1A} system via selectively stimulating the 5-HT_{1A} receptor widely distributed in these sites. The action sites are primarily in the limbic system, including the hippocampus and amygdala, and the raphe nucleus projecting 5-HT_{1A} nerves. The receptor pharmacology of tandospirone is relatively simple. It has a smaller effect on D_2 compared with 5-HT_{1A} receptor partial agonist buspirone (another common anti-anxiety agent) [10]. A multicenter, open-label study of various tandospirone doses showed that the anxiolytic effect of tandospirone was 67.4% with good tolerance [11].

Rat experiments demonstrated that the anti-anxiety effect of tandospirone significantly correlated with its concentration in plasma and brain after 0.5 h, without increases in corresponding side effects [12]. Therefore, it was speculated that a higher dose of tandospirone would achieve sufficient blood concentrations and reduce anxiety more effectively. A clinical study on GAD, mixed anxiety-depression demonstrated that the higher dose of tandospirone had a good anti-anxiety effect without severe side effects [13]; however, that study only included 23 cases.

Therefore, this multicenter, randomized, parallel-group controlled trial was designed to assess the anti-anxiety effect of tandospirone at various doses and provide an evidence basis for the pharmacological treatment of GAD.

Methods

Study design and participants

This multicenter, randomized, parallel-group controlled trial recruited patients with GAD from eight hospitals (5 sites from Shanghai, Beijing, Guangdong province, Henan province) between January 2012 and September 2018.

The inclusion criteria were as follows: (1) inpatients or outpatients; (2) DSM-IV criteria for GAD; (3) aged 18–65 years; (4) Hamilton Anxiety Scale (HAMA) score of screening and baseline of ≥17; and (5) administration of SSRI, SNRI, and NASSA agreeing to discontinue and elute for 2 weeks.

The exclusion criteria were as follows: (1) severe suicidal tendencies; (2) score of item 6 in HAMA≥3; (3) Hamilton Depression Scale (HAMD) score ≥21 at screening; (4) baseline HAMA score reduction rate ≥25% compared with screening; (5) anxiety disorder secondary to other mental or physical diseases; (6) lactation, pregnancy, or possibility of becoming pregnant during the trial; (7) severe or unstable heart, liver, kidney, endocrine, blood, respiratory, and other medical diseases, or history of abnormal blood thyroid-stimulating hormone level; (8) history of epilepsy, except for childhood febrile convulsions; or (9) currently using benzodiazepines to treat anxiety.

This study was approved and supervised by the ethics committee of Tongji Hospital of Tongji University [Approval No. (Tong) Lun Shen No. (117)]. Written informed consent was signed by all patients. The trial registration no. was NCT01614041, the date of registration was June 7, 2012.

Randomization and intervention

Patients were randomized 1:1 into 60 mg/day and 30 mg/day groups using the stratified block randomization (the stratification factor was central).

Patients with GAD were given tandospirone 20 mg three times per day (60 mg/day group) or 10 mg three times per day (30 mg/day group) for six consecutive weeks and were followed up at weeks 0, 1, 2, 4, and 6.

Endpoints

The primary endpoint was the overall response rate at week 6. The secondary endpoints included significant response rate and recovery rate at week 6 and the change in HAMD-17, HAMA total score, and HAMA subscale score (somatic anxiety factor, psychic anxiety factor, fear symptom factor, insomnia symptom factor, memory symptom factor, cardiovascular symptom factor, and gastrointestinal symptom factor) from baseline till week 6.

The overall response rate was defined as the percentage of patients with a decrease in HAMA total score ≥50% relative to baseline. The significant response rate was defined as the percentage of patients with a decrease in HAMA total score ≥75% relative to baseline. The recovery was defined as a HAMA score of ≤7.

Safety

Adverse reaction reports were used for safety evaluation. The frequency and number of adverse reactions and adverse reactions leading to withdrawal were counted. The incidence of adverse reactions was calculated.

Calculation of sample size

Two-sided tests were used to calculate effectiveness, with $\alpha = 0.05$ and $\beta = 0.2$ (power = 80%). According to the literature [11], the overall response rate of tandospirone in the low-dose group was estimated to be 67% after 6 weeks of treatment. It was estimated that the high-dose group would be 15% better than the low-dose group in the present study. Based on the ratio of 1:1, the sample size of each group was calculated as 133 patents. Given loss to follow-up, 150 patients were enrolled in each group from a total of 300 patients.

Statistical analysis

SAS 9.4 (SAS Institute Inc., NC, USA) and SPSS 20.0 software (IBM Corp., NY, USA) were used for statistical analysis. Continuous data were tested with the Kolmogorov–Smirnov test for normal distribution. Normally distributed continuous data were expressed as means ± standard deviation. Categorical data were expressed as *n* (%). Normally distributed continuous data were tested using the Student *t* test. Categorical data were analyzed using the chi-square test or Fisher's exact test. All statistical tests were performed using two-sided tests, with $P<0.05$ considered statistically significant.

Full analytical set (FAS) includes qualified patients and those lost to follow-up but does not include excluded patients. When the primary efficacy indicators were missing, the previous results were carried forward according to an intention-to-treat analysis.

Per-protocol analysis (PPS) refers to the set of patients that met the inclusion criteria, did not meet the exclusion criteria, and completed the treatment plan, that is, patients that met the trial plan with good compliance and completed the case report form requirements.

Safety set (SS) refers to the actual data of patients who received at least one treatment with safety index records. The missing values of safety were not carried forward.

The endpoints were analyzed using FAS and PPS. Adverse events were analyzed using SS.

Results

Patient characteristics and disposition

Due to the difficulty in recruiting patients, 280 patients were screened at the baseline visit and 274 were randomly assigned to the study treatments (Fig. 1). The majority who did not pass the screening (four of six) did not meet the study entry criteria, and two patients met the exclusion criteria. Of the 274 patients, 137 were randomly assigned to 60 mg/day and 30 mg/day groups, respectively. Further, 129 and 132 patients in the 60 mg/day and 30 mg/day groups, respectively, completed the study (Fig. 1).

Baseline demographic and clinical characteristics are summarized in Table 1. HAMA somatic anxiety factor score, HAMA cardiovascular symptom factor score, HAMA gastrointestinal symptom factor score,

and HAMD-17 score were higher in the 60 mg/day group (all $P < 0.05$).

Table 1
Demographic and clinical characteristics of patients with generalized anxiety disorder

	60 mg/day (*N* = 137)	**30 mg/day (*N* = 137)**	***P***
Age, year, mean ± SD	40.3 ± 13.0	41.5 ± 12.7	0.435
Sex, *n* (%)			0.536
Male	51 (37.2)	56 (40.9)	
Female	86 (62.8)	81 (59.1)	
Married, *n* (%)			0.042
Single*	30 (21.9)	22 (16.1)	
Married	107 (78.1)	108 (78.8)	
Education, *n* (%)			0.637
Primary school	10 (7.3)	8 (5.9)	
Middle school or above	127 (92.7)	128 (94.1)	
Total HAMA score, mean ± SD	31.6 ± 12.01	29.4 ± 11.47	0.13
Psychic anxiety factor	15.9 ± 6.0	15.3 ± 5.7	0.356
Somatic anxiety factor	15.6 ± 6.4	14.1 ± 6.2	**0.048**
Fear symptom factor	2.2 ± 1.36	2.2 ± 1.21	0.851
Insomnia symptom factor	2.6 ± 1.12	2.4 ± 1.10	0.232
Memory symptom factor	2.2 ± 1.27	2.0 ± 1.33	0.151
Cardiovascular symptom factor	2.5 ± 0.92	2.2 ± 0.97	**0.031**
Gastrointestinal symptom factor	2.2 ± 1.15	1.8 ± 1.11	**0.019**
CGI-S, mean ± SD	4.8 ± 1.1	4.6 ± 0.8	0.127
HAMD-17 score, mean ± SD	13.0 ± 3.2	12.1 ± 2.7	**0.01**

*Single state included those who were divorced or widowed. The education degree of one participant in the common-dose group was missed. #Chi-square test.

Efficacy

In the FAS, the overall response rate (65.7% vs 58.4%, $P > 0.05$) and recovery rate (41.6% vs 39.4%, $P = 0.712$) at week 6 were similar in both groups. The significant response rate (34.3% vs 22.6%, $P = 0.032$) at week 6 were numerically higher in the 60 mg/day group than in the 30 mg/day group. Relative to baseline, the reduction in HAMA total score was 17.84 ± 6.89 in the 60 mg/day group versus 15.77 ± 5.74 for the 30 mg/day group ($P = 0.007$). Relative to baseline, the reduction in HAMA somatic anxiety factors was 8.93 ± 3.88 in the 60 mg/day group versus 7.38 ± 3.28 in the 30 mg/day group ($P < 0.001$). The reduction in HAMA the psychic anxiety factors was 8.91 ± 3.51 in the 60 mg/day group versus 8.39 ± 3.21 in the 30 mg/day group ($P = 0.197$). The reduction in the fear symptom factor was 1.26 ± 0.88 in the 60 mg/day group versus 1.26 ± 0.81 in the 30 mg/day group ($P = 0.943$). The reduction in the insomina symptom factor was 1.39 ± 0.86 in the 60 mg/day group versus 1.31 ± 0.80 in the 30 mg/day group ($P = 0.468$). The reduction in the cardiovascular symptom factor was 1.35 ± 0.81 in the 60 mg/day group versus 1.03 ± 0.80 in the 30 mg/day group ($P = 0.001$). The reduction in the gastrointestinal symptom factor was 1.25 ± 0.80 in the 60 mg/day group versus 1.01 ± 0.79 in the 30 mg/day group ($P = 0.013$). HAMD-17 analysis revealed that after 6 weeks of treatment, the total score change in HAMD was 7.95 ± 3.55 in the 60 mg/day group and 6.68 ± 3.10 in the 30 mg/day group, the difference was statistically significant ($P = 0.002$) (Table 2).

Table 2
Primary and secondary endpoints in week 6 in full-analysis population

	60 mg/day (*N* = 137)	**30 mg/day (*N* = 137)**	**P**
Overall response rate, *n* (%) (primary endpoint)	90 (65.7)	80 (58.4)	>0.05
Significant response rate, *n* (%)	47 (34.3)	31 (22.6)	**0.032**
Recovery rate, n (%)	57 (41.6)	54 (39.4)	0.712
Change in the HAMA total score, mean ± SD	−17.84 ± 6.89	−15.77 ± 5.74	**0.007**
Change in the somatic anxiety factor	−8.93 ± 3.88	−7.38 ± 3.28	**<0.001**
Change in the psychic anxiety factor	−8.91 ± 3.51	−8.39 ± 3.21	0.197
Change in the fear symptom factor	−1.26 ± 0.88	−1.26 ± 0.81	0.943
Change in the insomnia symptom factor	−1.39 ± 0.86	−1.31 ± 0.80	0.468
Change in the memory symptom factor	−1.31 ± 0.85	−1.12 ± 0.83	0.063
Change in the cardiovascular symptom factor	−1.35 ± 0.81	−1.03 ± 0.80	**0.001**
Change in the gastrointestinal symptom factor	−1.25 ± 0.80	−1.01 ± 0.79	**0.013**
Change in the HAMD-17 score, mean ± SD	−7.95 ± 3.55	−6.68 ± 3.10	**0.002**

PPS showed that the overall response rate in week 6 of the 60 mg/day group was higher in the 60 mg/day group than in the 30 mg/day group (69.0% vs 57.3%. $P = 0.0498$). The significant response rate

at week 6 (35.7% vs 20.6%, $P = 0.007$) was significantly improved in the 60 mg/day group than in the 30 mg/day group. The recovery rate at week 6 (43.4% vs 38.2%, $P = 0.390$) was not significantly different. The reduction from baseline in HAMA total score was 18.64 ± 5.99 in the 60 mg/day group and 15.79 ± 5.80 in the 30 mg/day group ($P < 0.001$). The reduction from baseline in the HAMA somatic anxiety factor was 9.30 ± 3.53 in the 60 mg/day group and 7.37 ± 3.24 in the 30 mg/day group ($P < 0.001$). The reduction from baseline in HAMA psychic anxiety factor was 9.34 ± 3.05 in the 60 mg/day group and 8.41 ± 3.25 in the 30 mg/day group ($P = 0.018$). The reduction from baseline in HAMA fear symptom factor was 1.32 ± 0.86 in the 60 mg/day group and 1.25 ± 0.82 in the 30 mg/day group ($P = 0.526$). The reduction from baseline in HAMA insomnia symptom factor was 1.45 ± 0.83 in the 60 mg/day group and 1.32 ± 0.79 in the 30 mg/day group ($P = 0.199$). The reduction from baseline in HAMA memory symptom factor was 1.37 ± 0.81 in the 60 mg/day group and 1.11 ± 0.83 in the 30 mg/day group ($P = 0.012$). The reduction from baseline in HAMA cardiovascular symptom factor was 1.41 ± 0.79 in the 60 mg/day group and 1.00 ± 0.79 in the 30 mg/day group ($P < 0.001$). The reduction from baseline in HAMA gastrointestinal symptom factor was 1.29 ± 0.79 in the 60 mg/day group and 1.01 ± 0.80 in the 30 mg/day group ($P = 0.005$). After 6 weeks of treatment, the score changes in HAMD-17 were different in the 60 mg/day and 30 mg/day groups (8.01 ± 3.49 vs 6.66 ± 3.13, $P = 0.001$) (Table 3).

Table 3
Primary and secondary endpoints in week 6 in per-protocol population

	60 mg/day (*N* = 137)	**30 mg/day (*N* = 137)**	***P***
Overall response rate, *n* (%) (primary endpoint)	89 (69.0)	75 (57.3)	**0.0498**
Significant response rate, *n* (%)	46 (35.7)	27 (20.6)	**0.007**
Recovery rate, *n* (%)	56 (43.4)	50 (38.2)	0.390
Change in the HAMA total score, mean ± SD	−18.64 ± 5.99	−15.79 ± 5.80	**<0.001**
Change in the somatic anxiety factor	−9.30 ± 3.53	−7.37 ± 3.24	**<0.001**
Change in the psychic anxiety factor	−9.34 ± 3.05	−8.41 ± 3.25	**0.018**
Change in the fear symptom factor	−1.32 ± 0.86	−1.25 ± 0.82	0.526
Change in the insomnia symptom factor	−1.45 ± 0.83	−1.32 ± 0.79	0.199
Change in the memory symptom factor	−1.37 ± 0.81	−1.11 ± 0.83	**0.012**
Change in the cardiovascular symptom factor	−1.41 ± 0.79	−1.00 ± 0.79	**<0.001**
Change in the gastrointestinal symptom factor	−1.29 ± 0.79	−1.01 ± 0.80	**0.005**
Change in the HAMD-17 score, mean ± SD	−8.01 ± 3.49	−6.66 ± 3.13	**0.001**

Adverse Drug Reactions

A total of 32 patients had adverse drug reactions. The incidence was 23.4% in the 60 mg/day group. A total of 16 patients (11.7%) had adverse reactions in the 30 mg/day group (P = 0.011). Common adverse reactions occurred in the nervous and gastrointestinal systems. Further, 18 patients (13.1%) in the 60 mg/day group and 3 patients (2.2%) in the 30 mg/day group had adverse nervous system reactions. The most common adverse nervous system reaction was dizziness, occurring in 12 patients (8.8%) in the 60 mg/day group that lasted for a median of 10 days (range 1–25 days) without any change in the therapeutic dose. It resolved spontaneously. There was one patient in the 30 mg/day group (0.7%) whose symptoms resolved after 5 days. The incidence of dizziness was statistically different between the groups (Table 4).

Table 4
Treatment-emergent adverse reactions in patients with generalized anxiety disorder

	60 mg/day (*N* = 137)	**30 mg/day (*N* = 137)**	***P***
Adverse reactions	32 (23.4)	16 (11.7)	**0.011**
Withdrawal	3 (2.2)	1 (0.7)	0.622
Nervous system reactions	18 (13.1)	3 (2.2)	**<0.001**
Dizziness	12 (8.8)	1 (0.7)	**0.002**
Abdominal discomfort	7 (5.1)	1 (0.7)	0.066*
Nausea	6 (4.4)	4 (2.9)	0.519
Headache	5 (3.6)	0 (0)	0.060*
Scalp numbness	3 (2.2)	2 (1.5)	1.000*
Drowsiness	2 (1.5)	3 (2.2)	1.000*
Sweating	3 (2.2)	1 (0.7)	0.622*
Palpitations	2 (1.5)	2 (1.5)	1.000
Loss of appetite	2 (1.5)	0 (0)	0.498*
Constipation	1 (0.7)	1 (0.7)	1.000*
Greasy food be disgusted	1 (0.7)	0 (0)	1.000*
Diarrhea	0 (0)	1 (0.7)	1.000*
Vomiting	0 (0)	1 (0.7)	1.000*
Increased libido	1 (0.7)	0 (0)	1.000*
Agitation	1 (0.7)	0 (0)	1.000*
Pruritus	0 (0)	1 (0.7)	1.000*
Limbs fever	1 (0.7)	0 (0)	1.000*
Fatigue	1 (0.7)	0 (0)	1.000*
Chest tightness	1 (0.7)	0 (0)	1.000*

*Fisher exact test.

Also, 18 (13.1%) patients in the 60 mg/day group and 5 (3.6%) in the 30 mg/day group developed adverse gastrointestinal disorders. All resolved spontaneously. Common adverse reactions included abdominal discomfort and nausea, and no statistically significant difference in incidence was found between the groups.

Three participants in the 60 mg/day group withdrew because of adverse reactions, including epigastric discomfort (resolved at the time of withdrawal), dizziness (resolved after withdrawal), and early awakening (resolved after withdrawal). One patient in the 30 mg/day group withdrew because of feelings of burnout (relieved after withdrawal). All patients experienced no serious adverse events.

Discussion

GAD is more common in the community and general hospitals [4]. Treatment requires a greater emphasis on efficacy and tolerability [14]. Tandospirone is an effective drug for GAD treatment [15]; nevertheless, few evidence-based studies have explored its efficacy. One study involved a variable-dose single arm [11], while another study's sample size was only 14 in the 60 mg/day group and 9 in the 30 mg/day group [14]. A review of the literature revealed that the present study was the first with a large sample size to systematically determine the safety and efficacy of 60 mg/day tandospirone to treat GAD. The main finding was that the overall response rate of 60 mg/day and 30 mg/day tandospirone was 65.7% and 58.4%, respectively. No significant difference was observed in the full-analysis population between the two groups. However, a statistically significant difference in the overall response rate was found in the per-protocol population between the two groups.

A meta-analysis showed that the best efficacy of common medications for anxiety disorder ranged from 54.5–67.7% [16]. For example, the effective rate of 10–20 mg/day escitalopram and sertraline for GAD was 68% [17] and 63% [18] or 59.2% [19], respectively. According to FAS, the effective rate of 30 mg/day and 60 mg/day tandospirone for GAD treatment for 6 weeks was 58.4% and 65.7%, respectively. The HAMD-17 analysis suggested that tandospirone had better efficacy for depressive symptoms of GAD. The efficacy of 20 mg and 40 mg paroxetine to treat GAD was compared, the effective rate was 62% and 68%, with cure rates of 30% and 36%, respectively, using a cure standard of HAMA≤7 [20]. These results suggested that the high dose might have better efficacy, consistent with the suggestion that GAD required a larger therapeutic dose. The present study also showed that the effectiveness rate and marked effectiveness rate of 60 mg/day tandospirone for GAD treatment were similar to those of 40 mg/day paroxetine.

Both 30 mg/day and 60 mg/day tandospirone effectively improved anxiety symptoms in patients with GAD. Although core symptoms of GAD are anxiety and worry, patients with GAD also show gastrointestinal symptoms, palpitations, shortness of breath, chest distress, headache, muscle tension, and fatigue. They are often treated in general hospitals for these complaints. Pediatric GAD can present with recurrent abdominal pain that limits school attendance. Medications that can improve the physical symptoms more effectively may be more acceptable to such patients to establish confidence in long-

course treatment. SSRIs such as sertraline are more effective than placebo for treating psychic anxiety [19]. Venlafaxine, which has a similar efficacy for somatic anxiety and psychiatric anxiety symptoms [21], has relatively poor tolerability. Benzodiazepines have better efficacy for somatic anxiety than for psychiatric anxiety [22]. Because of their side effects and addiction risks, multiple consensuses and guidelines list benzodiazepines as second- or even third-line anxiolytics [23]. This has led to the search for safer and more effective GAD treatments for somatic anxiety symptoms. The present study suggested that 60 mg/day tandospirone might improve the somatic anxiety subscale compared with 30 mg/day tandospirone, regardless of FAS or PPS.

The findings suggested that 60 mg/day tandospirone could more significantly improve cardiovascular and gastrointestinal symptoms in patients with GAD. This might be due to two reasons. First, cardiovascular and gastrointestinal symptoms are important clinical manifestations in patients with GAD, as is the case for somatic anxiety. With greater improvement in anxiety symptoms, cardiovascular and gastrointestinal symptoms are more significantly relieved. Second, it is the good receptor selectivity of tandospirone that mainly binds to the 5-HT_{1A} receptor other than dopamine [10]. The effects of tandospirone on the gastrointestinal tract, heart, and blood vessels are relatively less, reflecting the relationship between the pharmacological advantages of the single tandospirone receptor and the better efficacy of high dose on somatic anxiety, particularly gastrointestinal and cardiovascular symptoms. Thus, the high dose had better efficacy on the somatic anxiety subscale, suggesting that tandospirone had exceptional effects in patients with somatic anxiety symptoms.

In the per-protocol population, both primary and secondary endpoints showed better efficacy of high-dose tandospirone. This indicated that patients with good compliance might benefit from a high-dose regimen.

The present study found that tandospirone treatment was well tolerated. The adverse drug reactions were similar to those of other antidepressants that acted on the 5-HT system to treat anxiety disorders and depression, primarily dizziness and gastrointestinal reaction [24]. Among the adverse drug reactions, only dizziness was significantly increased in the high-dose group, one patient withdrew from the study for this reason. Although a higher proportion of adverse reactions occurred in the high-dose group than in the low-dose group (23.4% vs 11.7%, respectively), the high dose did not increase the proportion of withdrawals from the trial significantly, suggesting the safety of the high-dose treatment. A placebo-controlled study on the use of duloxetine to treat GAD reported at least one adverse event in the duloxetine and placebo groups, with incidences of 60.2% and 44.1%, respectively [25]. It suggested that a high dose of tandospirone increased the risk of adverse effects (but not significantly) with good tolerance [26].

The present study had some limitations, including short follow-up time, no blinding, no placebo-controlled group, and number of the patients less than the sample size, all of which limited the generalization of the conclusions.

Conclusions

The safety and efficacy of high-dose tandospirone were similar to those of low-dose tandospirone. The patients with good compliance might benefit from a high-dose regimen. More efficacy and safety data of different doses of tandospirone in patients with GAD need to be collected in real-world clinical practice.

List Of Abbreviations

FAS, full analytical set

GAD, generalized anxiety disorder

HAMA, Hamilton Anxiety Scale

HAMD, Hamilton Depression Scale

PPS, per-protocol analysis

SS, safety set

Declarations

Ethics approval and consent to participate

This study was approved and supervised by the ethics committee of Tongji Hospital of Tongji University [Approval No. (Tong) Lun Shen No. (117)]. Written informed consent was signed by all patients. The trial registration no. was NCT01614041, the date of registration was June 7, 2012. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Written informed consent was signed by all patients.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors confirm that there are no conflicts of interest.

Funding

This work was supported by Psychosomatic Medicine Project of Key Developing Disciplines of Shanghai Municipal Health Commission (2019ZB0202), Three-Year Initiative Plan for Strengthening Public Health System Construction in Shanghai (GWV-10.2-XD29), Projects of Shanghai health and Family Planning Commission (201740007). We also wish to thank Sumitomo Pharmaceuticals (Suzhou) Co., Ltd for funding support (No. DSPC-SED-1101). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

WY Wu, HY Zhang, SX Shi and JL Ji contributed to the study concept, design, analysis, and interpretation. QW Li, HY Zhang, GZ Lin, SX Shi, YL Zhang, JL Ji, J Yao and WY Wu contributed to data acquisition, and data analysis and interpretation. All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted.

Acknowledgements

This work was supported by Psychosomatic Medicine Project of Key Developing Disciplines of Shanghai Municipal Health Commission (2019ZB0202), Three-Year Initiative Plan for Strengthening Public Health System Construction in Shanghai (GWV-10.2-XD29), Projects of Shanghai health and Family Planning Commission (201740007). We also wish to thank Sumitomo Pharmaceuticals (Suzhou) Co., Ltd for funding support (No. DSPC-SED-1101).

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Figures

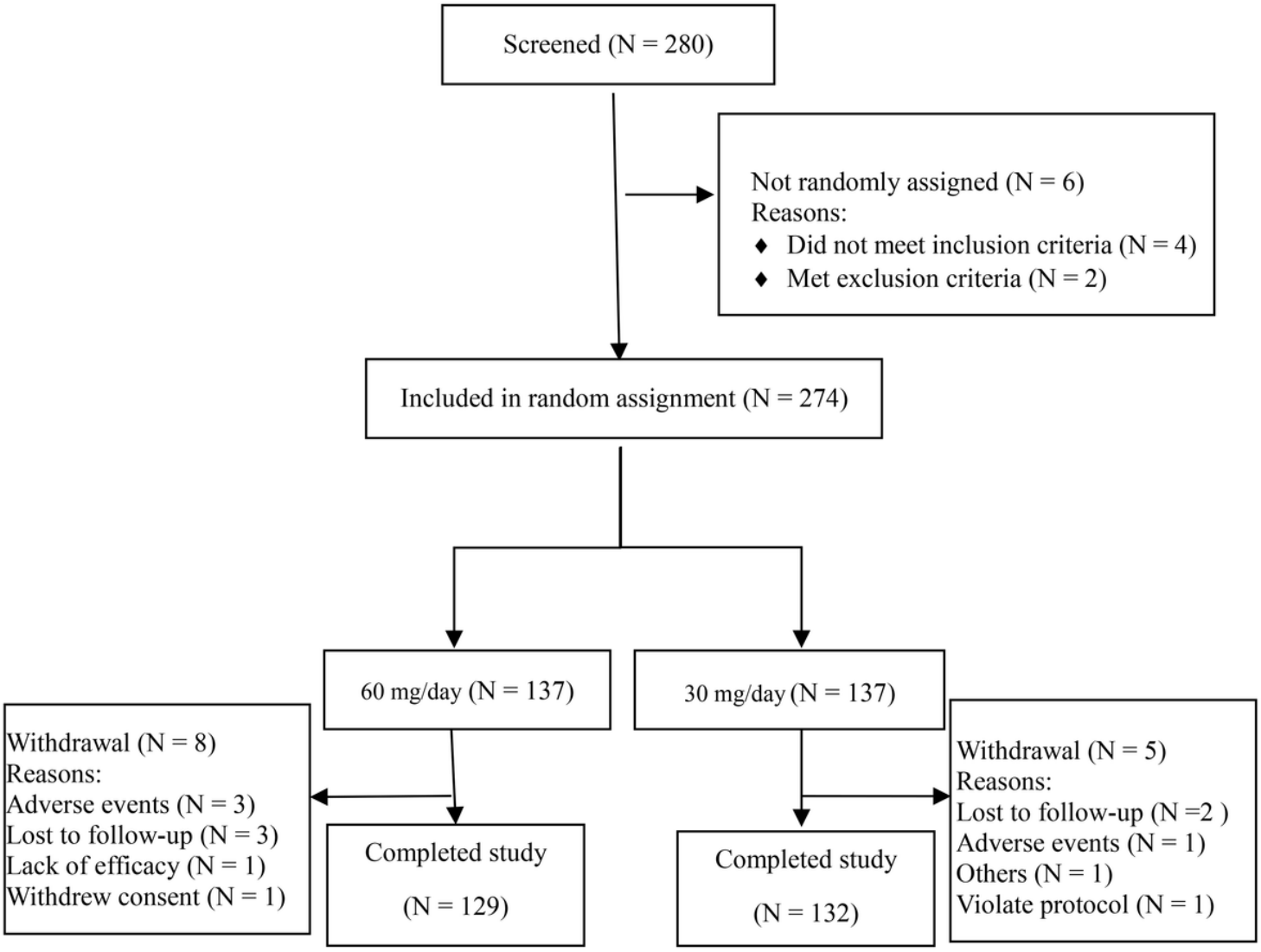

Figure 1

Flow chart.