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Effects of tandospirone augmentation in major depressive disorder patients with high anxiety: A multicenter, randomized, parallel-controlled, open-label study

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ABSTRACT

Background: High levels of anxiety symptoms are common in individuals with major depressive disorder (MDD). Adjunctive anxiolytics are widely used in such patients; however, only a few studies have examined the strategy using tandospirone. This study aimed to evaluate the efficacy and safety of adjunctive tandospirone in individuals with MDD and high level of anxiety symptoms.

Methods: A multicenter, randomized, parallel-controlled, open-label study was conducted to evaluate the efficacy and safety of tandospirone coupled with selective serotonin reuptake inhibitors (SSRIs) in patients with MDD and high level of anxiety symptoms. Two hundred and forty-five patients fulfilling the DSM-IV-TR criteria for MDD were randomly assigned to 6 weeks of either SSRIs and tandospirone or SSRIs alone treatment. The efficacy was measured by HAMA total scores, HAMD-17 total scores, and Clinical Global Impressions severity subscale (CGI-S) score.

Results: After a 6-week follow-up, two hundred and thirty patients completed this study. Tandospirone coupled with SSRIs significantly improved depressive and anxiety symptoms compared to monotherapy with SSRIs as assessed by HAMD-17 total score ($P = 0.003$), HAMA total score ($P = 0.010$), and CGI-S score at week 6 ($P = 0.003$). The incidence rate of treatment-emergent adverse events (TEAEs) was similar in both groups; the therapy was well-tolerated.

Conclusions: Short-term tandospirone augmentation was effective and well-tolerated in this study. Addition of tandospirone may improve outcomes in MDD patients with high anxiety.

1. Introduction

Accumulating evidences from epidemiological as well as cohort studies suggested that patients with depression commonly present anxiety disorder, and the rate of comorbidity of major depressive disorder (MDD) and anxiety disorder ranges from 45.7 to 75% (Fava et al., 2008; Kessler et al., 2015; Lamers et al., 2011). In China, approximately 68.9% MDD patients showed a comorbid anxiety disorder based on the study of China Anxiety Collaborating Group (Shi et al., 2009).

In contrast to MDD alone, comorbidity of MDD and anxiety disorder is defined by high rates of chronicity (Bruce et al., 2005), low adherence (Stein et al., 2006), increased risk of recurrence (Bruce et al., 2005), decreased likelihood of recovery (Bruce et al., 2005), great functional disability (Hirschfeld, 2001), and poor prognosis (Fava et al., 1997, 2008; Gaynes et al., 1999; Noyes, 2001; Sareen et al., 2005). The presence of depression and anxiety disorder also increased the risk of suicidal ideas and attempts (Bolton et al., 2008; Sareen et al., 2005) in a 3-year follow-up study. A systematic review also shown that coexisting

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anxiety was associated with increasing risk of suicide in patients with depression (Hawton et al., 2013).

Some evidences have shown that MDD patients who have comorbid anxiety symptoms potentially exhibit a poor response to pharmacotherapies (Fava et al., 2008; Ionescu et al., 2014). In a Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, patients with anxious depression have been associated with significantly lower rates of response and remission than non-anxious patients, and outcomes continued to be poor although augmented with bupropion or buspirone, or switching to sertraline, venlafaxine or bupropion (Fava et al., 2008).

Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) monotherapy is often used as a first-line pharmacotherapy in patients with comorbid depression and anxiety, which can improve both depressive and anxiety symptoms (Altamura et al., 2004; Boulenger et al., 2010; Maity et al., 2014; Rush et al., 2001; Saltiel and Silvershein, 2015). In clinical practice, major concerns of first-line therapy include partial response (Corey-Lisle et al., 2004), risk of agitation and anxiety at the initiation of treatment (Dunlop and Davis, 2008), delay in therapeutic effect, and high rate of sexual dysfunction (Clayton et al., 2002; Moll and Brown, 2011; Werneke et al., 2006).

Combination therapy with antidepressants and anxiolytics is widely used for treating patients with comorbid anxiety and depression for short-term usage to achieve rapid onset of effect and improve adherence (Dunlop and Davis, 2008; Rosenbaum, 2005). However, benzodiazepines (BZDs) have the risk of abuse (O'Brien, 2005), ataxia (Feighner et al., 1982) and cognitive impairment (Lucki et al., 1987), which may limit their use in clinical practice (Pradel et al., 2010).

The serotonin 1A (5-HT_{1A}) receptor partial agonists, including tandospirone and buspirone, has been recognized as novel anxiolytic drugs (Nishitsuji et al., 2004), with a low risk of psychomotor performance impairment, daytime wakefulness (Suzuki et al., 1993) and abuse or dependence potential than BZDs (Evans et al., 1994; Sasa, 1997; Suzuki et al., 1993). Some evidences have demonstrated that 5-HT_{1A} receptor agonists may improve depressive symptoms (Albert and Francois, 2010; Kishi et al., 2014; Lacivita et al., 2012; Murata et al., 2015) and cognition (Olsen et al., 2012; Sumiyoshi et al., 2007; Targum et al., 2015). And the findings from preclinical studies have shown that tandospirone can produce antidepressive effects by inhibiting the effect of stress-induced changes in hippocampal neurogenesis (Murata et al., 2015), and downregulating postsynaptic 5-HT_2 receptors (Wieland and Lucki, 1990).

Thus, it can be hypothesized that tandospirone may enhance the efficacy of antidepressants in patients with comorbid MDD and high level of anxiety symptoms. Although tandospirone is a commonly used anxiolytic in Asia (Hussain et al., 2016), especially Japan and China, yet, no randomized, controlled trials to date have investigated the efficacy and safety of tandospirone in treatment of this population.

2. Methods

2.1. Patients

This 6-week, 7 centers (Zhejiang province, Hubei province, Jiangsu province, Jiangxi province, Shandong province, 2 sites from Beijing), randomized, parallel-controlled, open-label study was conducted between March 2012 and January 2015, using SSRIs alone or coupled with a flexible dosage of tandospirone (30–60 mg/d).

The enrolled patients, 18–65 years of age (inclusive), were diagnosed with MDD based on DSM-IV-TR criteria and in the presence of anxiety symptoms. These patients were required to have a current major depressive episode, with a total score ≥17 on the Hamilton Depression Rating Scale 17-item (HAMD-17) (Hamilton, 1960) and ≥14 on the Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959) at both screening and baseline visits. Notably, not all the patients were naïve to any antidepressants at the first visit, but they were not treated adequate dose of antidepressants for more than two weeks in the current episode.

Patients who did not fulfill the criteria or had a history with respect to any of the following DSM-IV disorders were excluded: schizophrenia, bipolar disorder, substance abuse, delusional disorder, and schizoaffective disorder. Moreover, patients presenting the risk of suicide, severe or uncontrolled organic disorders, and any history of neurological disorders were also excluded. In addition, patients were excluded if they had received any of the following therapies recently: antipsychotics, mood stabilizers, anticonvulsant, electro-convulsive therapy (ECT).

The study protocol was approved by the Independent Ethics Committee of Beijing HuiLongGuan Hospital, Zhongda Hospital Southeast University, the First Affiliated Hospital of Nanchang University, Renmin Hospital of Wuhan University. For sites in Qingdao Mental Health Center, the First Affiliated Hospital of Zhejiang University and Peking University Sixth Hospital, all three sites were approved by the Ethics Committee of Peking University Sixth Hospital, the Central Ethics Committee. All the subjects provided written informed consent before participation in this study.

2.2. Study design

Simplified randomization sequence was assigned with EpiCalc 2000 (Brixton Health). All eligible patients were assigned at a 1:1 ratio to receive 6 weeks of SSRIs and tandospirone (30–60 mg/d) or SSRIs alone. The randomization grouping was settled with sealed envelope system. Patients were involved continually within each center and inclusion of subjects was competed among sites.

2.3. Concomitant medications

Treatment with zopiclone, alprazolam, and clonazepam for short-term use was permitted as needed (but not prophylactically) for sleep disorders.

2.4. Efficacy assessments

The efficacy measurements included HAMA total scores, HAMD-17 total scores, and Clinical Global Impressions severity subscale (CGI-S) score, which rates the overall severity of the illness on a 7-point scale. Additional efficacy measurements included HAMA somatic anxiety subscale, HAMA psychic anxiety subscale total score, and remission (which was defined as showing an HAMD-17 total score ≤ 7 at week 6).

2.5. Safety and tolerability evaluation

Safety and tolerability evaluation included the monitoring of spontaneously reported adverse events (AEs), physical examination, and vital signs (body weight, supine heart rate, and blood pressure). Laboratory tests included the hematological estimation and urinalysis.

2.6. Statistical analysis

Clinical characteristics and demographic data were analyzed using chi-square and *t*-test as applicable. All the efficacy analyses were performed based on the modified intent-to-treat (mITT) analysis. The mITT population consisted of randomly assigned patients who received at least