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Brain-derived neurotrophic factor in generalized anxiety disorder: Results from a duloxetine clinical trial

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ABSTRACT

Background: Brain-derived neurotrophic factor (BDNF) has been implicated in the pathophysiology of depression and anxiety, but has not been examined systematically in generalized anxiety disorder (GAD). The objective of this study was to examine the relationship between baseline BDNF level and treatment response in patients with GAD.

Methods: Patients (N = 168) were from China, met criteria for DSM-IV GAD, had a Hospital Anxiety and Depression Rating Anxiety (HADS-A) subscale score ≥10, and a Sheehan Disability Scale (SDS) global functioning total score ≥12 at baseline. Study design was double-blind therapy for 15 weeks with duloxetine 60–120 mg or placebo. Efficacy measures included the HADS-A and Hamilton Anxiety Rating Scale (HAMA) total score. Change from baseline to endpoint for BDNF by treatment group was analyzed using ANCOVA models with baseline BDNF level as a covariate.

Results: No significant association was found between baseline plasma BDNF levels and anxiety illness severity. Patients who received duloxetine (n = 88) had a significantly greater mean increase in plasma BDNF level (957.80 picograms/ml) compared with patients who received placebo (n = 80; 469.93 pg/mL) ($P = .007$). Patients who met response and remission criteria (with either treatment) had greater mean increases in BDNF at endpoint from baseline ($P \leq .05$) but when compared with nonresponders and nonremitters, respectively, the differences in mean increase were not statistically significant between groups.

Conclusions: BDNF levels significantly increased with duloxetine treatment for GAD, but response and remission outcomes were not clearly related to an increase in plasma BDNF level.

1. Introduction

With a greater understanding of the pathophysiology underlying depression and anxiety, attention has shifted from effects of treatment not only on monoamine neurotransmitters, but also on other neurochemistries. In particular, growth factors, such as brain-derived neurotrophic factor (BDNF) have been observed to play an important role in neurogenesis, neuroplasticity, and resilience of neurons (as reviewed by Krystal et al., 2009; Lu et al., 2005). Preclinical animal models have suggested that under conditions of chronic stress, BDNF signaling may become dysregulated, resulting in neuronal atrophy and cellular loss as well as the behavioral manifestations of stress (Duman and Monteggia, 2006). Clinically, serum BDNF level has been studied in patients with major depressive disorder (MDD) to determine if there is any relationship between the growth factor and illness severity. A meta-analysis of 11 clinical studies concluded that patients with MDD have lower levels of serum BDNF at baseline compared with healthy controls, and that BDNF levels increase following antidepressant therapy (Sen et al., 2008). Furthermore, meta-analyses of 20 studies suggested that the increases in BDNF following antidepressant therapy are also significantly associated with improvement in depressive illness (Brunoni et al., 2008). Additionally, the clinical relevance of BDNF level has been supported by an association between lower BDNF levels and recurrent episodes of MDD as well as with suicidal behavior in patients with MDD (Lee et al., 2007).

Similar to depression, BDNF signaling has also been implicated in the expression of anxiety using preclinical models but the association of BDNF and clinical outcomes has been less well studied in anxiety disorders. In a recent study, the mean baseline serum BDNF level of 393 patients with social phobia, panic disorder, agoraphobia, and

Abbreviations: ANCOVA, Analysis of Covariance; BDNF, brain-derived neurotropic factor; CGI-S, Clinical Global Impression of Illness, Severity; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, 4th Edition; GAD, generalized anxiety disorder; HAMA, Hamilton Anxiety Rating Scale; HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Anxiety Subscale; MDD, Major Depressive Disorder; ml, mililiter; NS, nonsignficant; pg, picograms; SDS, Sheehan Disability Scale; SIGMA, Structured Interview Guide for the Hamilton Anxiety Rating Scale.

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generalized anxiety disorder (GAD) were compared with mean baseline serum BDNF values from 382 healthy comparison subjects. Patients with anxiety disorders did not differ in baseline BDNF by anxiety diagnosis or by anxiety severity. The mean serum BDNF value of patients did not differ significantly from controls. While this is the largest published study of BDNF levels in patients with anxiety disorders, the authors did not examine response to treatment (Molendijk et al., 2012). In an open-label study of panic disorder (N = 42), patients who achieved a treatment response (≥40% from baseline to endpoint) had a significantly higher serum BDNF level at baseline compared with patients who had a poor outcome, but change in serum BDNF levels from pre- to post-treatment was not examined (Kobayashi et al., 2005).

Given the shared diathesis between major depression and GAD (e.g., Kendler et al., 1992) understanding whether BDNF has a similar response to treatment could help to further elucidate the role of BDNF in depression and anxiety. Therefore, the present study was undertaken to examine whether plasma BDNF levels in patients with GAD change significantly in response to active treatment (duloxetine) compared with placebo treatment. An additional objective was to examine whether changes in plasma BDNF level were associated with response or remission status at endpoint of treatment. These biochemical objectives were secondary outcomes within a double-blind, placebo-controlled clinical trial of duloxetine, a selective serotonergic noradrenergic reuptake inhibitor, for the treatment of GAD that was conducted for regulatory purposes in the Republic of China. The primary outcome from this trial has been reported elsewhere (Wu et al., 2011).

2. Methods and materials

2.1. Clinical trial study design

Briefly, the study was a multicenter, parallel, double-blind, randomized, placebo-controlled study conducted at 9 sites in the People's Republic of China between December 2008 and January 2010.

After a screening period, patients were randomly assigned in a 1:1 ratio to duloxetine 60–120 mg once daily or placebo for 15 weeks of treatment. Patients assigned to duloxetine received 60 mg orally for 7 weeks; at this visit, patients who were nonresponders, defined as a Clinical Global Impressions Improvement (CGI-I) rating of ≥3 (i.e., minimal improvement, no change or worsening), were assigned an increased dose of duloxetine 120 mg daily for the remaining 8 weeks. After 15 weeks treatment, patients who were assigned duloxetine were tapered over a 2-week period.

2.2. Patient population

Male or female outpatients ≥18 years of age who met the disease diagnostic criteria for GAD as defined by the DSM-IV (American Psychiatric Association, 1994) were included in this trial. To ensure that patients warranted psychiatric intervention, they were required to have an illness of at least moderate severity (rating ≥4) as assessed by the Clinical Global Impressions of Severity (CGI-S; Guy, 1979). Patients were also required to have at least moderate functional impairment associated with their anxiety illness, which was defined by a Sheehan Disability Scale (SDS; Sheehan et al., 1996) global functioning score ≥12.

Exclusion criteria included any current DSM-IV Axis I diagnosis other than GAD; major depressive disorder (MDD) within the past 6 months; panic disorder, post-traumatic stress disorder, or an eating disorder within the past year; obsessive–compulsive disorder, bipolar affective disorder, psychosis, factitious disorder, or somatoform disorder during their lifetime; or the presence of an Axis II disorder or history of antisocial behavior which, in the judgment of the investigator, would interfere with compliance with the study protocol.

Each site's institutional review board approved the conduct of the study, which was developed in accordance with the ethical standards of Good Clinical Practice and the Declaration of Helsinki, as revised in 2000. Patients provided written informed consent before participation in any study related procedures.

2.3. Efficacy measures

Efficacy within the study was examined by both patient-reported and clinician-administered measures. The primary efficacy measure was the Hospital Anxiety and Depression Anxiety subscale (HADS-A; Zigmond and Snaith, 1983), which consists of 7 items that are scored from "0" to "3". Higher scores indicate greater severity of illness. The secondary efficacy measure was the Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1959) that was administered by clinicians using the Structured Interview Guide for the HAMA (SIGMA; Shear et al., 2001). The HAMA consists of a total score of 14 items that assess psychic and somatic symptoms of anxiety. Each item can be rated from "0" [not at all] to "4" [severely disability] with higher scores indicating greater illness severity. Role functioning was assessed using the SDS in which patients rate the impact of their anxiety illness on 3 domains: work/school, social life, and family/home management using a "0" [not at all] to "10" [extremely disabling] scale. A global functioning score is computed by adding the scores of the 3 items to obtain a total score. If the work/school item is not applicable to the patient, then the average of the other 2 items is imputed to allow for computation of the global functioning score.

2.4. Measurement BDNF level

Serum samples were collected in standard 4.5 mL sodium citrate vacutainers during study visits which were not standardized for time of day. Following collection, samples were centrifuged at 2500 g for 15 min to separate plasma. The supernatant plasma samples that were collected were further centrifuged under the same conditions. The platelet-poor supernatant plasma samples subsequently collected were frozen at −20 °C. Samples were shipped monthly, frozen on dry ice, from the sites to the central laboratory, where they were stored at −70 °C until assayed. Assays were performed on a weekly basis using the Quantikine Human BDNF Immunoassay (R&D Systems). The assay performance was a sensitive assay with a minimum detectable BDNF level of20 pg/mL and validated by Qlab at their Beijing, China facility. Interassay reliability was 8.8%CV (manufacturer precision 7.6–11.3%CV), under same conditions as conducted in study).

2.5. Statistical analysis

All analyses were conducted on an intent-to-treat basis. Pearson correlation coefficients were computed between baseline BDNF levels and baseline disease severity measures (HADS-A, HAMA). Analyses of mean change from baseline to endpoint in BDNF levels were conducted using analysis of covariance (ANCOVA) with treatment group, baseline BDNF level, and investigative site in the model. The statistical significance of within treatment group changes from baseline was examined using the Wilcoxon signed rank test. Response status was defined as ≥50% improvement in HAMA total score from baseline to endpoint. An analysis of mean change from baseline to endpoint in BDNF levels by response status was also conducted using an ANCOVA with treatment group, baseline BDNF level, investigative site, response status, and response status by treatment interaction in the model. Remission was defined using the definition of a HAMA total score as a score ≤7 at endpoint. An analysis of mean change from baseline to endpoint in BDNF levels by remission status (yes/no) was performed using an ANCOVA with treatment group, baseline BDNF measure, investigative site, remission status, and remission status by treatment interaction in the model. The ANCOVA analyses for response and remission status