Decreased Brain-Derived Neurotrophic Factor in Older Adults with Bipolar Disorder

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Objectives: *Decreased levels of brain derived neurotrophic factor (BDNF) have been found in adult patients with bipolar disorder (BD) compared with a comparison group, yet there are no data specifically examining this in geriatric patients. The objective of this study was to examine whether euthymic late-life BD patients have lower BDNF levels than healthy comparators.* **Design:** *Cross-sectional study.* **Setting:** *Clinics at the University of Pittsburgh and the Centre for Addiction and Mental Health (Toronto).* **Participants:** *Older patients with BD (age ≥50 years, N = 118) and similarly aged healthy comparators (N = 76). There were both BD type I (N = 91) and type II (N = 27) patients.* **Measurements:** *Serum BDNF levels were assessed in BD patients and healthy comparators.* **Results:** *We found lower levels of BDNF in patients with BD than in healthy comparators (9.0 ± 6.2 versus 12.3 ± 8.9 pg/μg, $t_{(192)} = -3.01$, $p = 0.002$), which remained even after controlling for age, sex, lithium use, and site ($F_{(1,176)} = 4.32$, $p = 0.039$). This decrease was found specifically in patients with BD type I (8.0 ± 5.5 versus 12.3 ± 8.9 pg/μg, $t_{(165)} = 3.7$, Bonferroni $p < 0.001$), but not type II (12.0 ± 7.5 versus 12.3 ± 8.9 pg/μg, $t_{(101)} = 0.14$, Bonferroni $p = 1.0$).* **Conclusions:** *Older patients with BD have lower serum levels of BDNF compared with similarly aged comparators. These effects appear to be specific to patients with BD type I. Future studies are needed to investigate the impact of reduced BDNF levels on cognition, mood, and other aspects of BD throughout the life course.* (Am J Geriatr Psychiatry 2016; ■■:■■–■■)

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INTRODUCTION

Bipolar disorder (BD) is a complex illness involving multiple biological pathways. Several studies have implicated brain-derived neurotrophic factor (BDNF) as having a pivotal role in this illness.[1,2]

BDNF is a neuronal growth factor extensively distributed and expressed in the central nervous system.[3] It promotes neuronal survival, neurogenesis, synaptic plasticity, and memory processing.[4,5] Decreased circulating (serum) levels of BDNF have been linked with gray matter loss, reduced volume of hippocampus, and memory deficits in older adults.[6] Conversely, higher serum BDNF levels have been associated with a lower risk of development of dementia, especially in women.[5] Preclinical studies have demonstrated that circulating levels of BDNF (i.e., serum or plasma BDNF) are positively correlated with cortical and hippocampal BDNF levels,[7,8] suggesting that peripheral levels of BDNF reflect brain function.

Decreased levels of circulating BDNF have been consistently reported in adult patients with BD.[9] In Fernandes et al.'s recent meta-analysis,[9] adult patients with BD had decreased circulating levels of BDNF during both manic (effect size = –0.81) and depressive episodes (effect size = –0.97) when compared with healthy comparators. There was no significant difference in BDNF levels between euthymic adult patients with BD and healthy comparators, however.[9] To date, most of the studies of BDNF and BD include patients receiving treatment with psychotropic medications. Machado-Vieira et al.[10] reported decreased BDNF levels in untreated patients with BD during a manic episode when compared with healthy comparators. de Oliveira et al. found decreased serum BDNF levels in both medicated and drug-free patients with BD,[11] although lithium and other BD medications may increase BDNF levels.[12]

Some studies suggest that the association between BDNF and BD may change during the life span. In one small study of adolescents with BD, BDNF was not associated with manic symptoms.[13] Yatham et al.,[14] in a cross-sectional study of first-episode mania patients, non-geriatric adult BD patients, and comparators, reported an accelerated age-related decrease of BDNF levels among patients with BD (mean age: 31.9 years) in comparison with healthy comparators.[15] In a small study of older adults, Lotrich and colleagues focused on the relationship between inflammation and cognitive function in older adults with BD.[16] Among the biomarkers they examined, they did not identify statistically significant differences in BDNF levels in older adults with BD (N = 21) versus similarly aged mentally healthy comparators (N = 25).

In this study, we proposed to further evaluate serum BDNF levels in a larger sample size of older euthymic patients with BD (N = 118) and similarly aged healthy comparators (N = 76), including those previously analyzed by Lotrich et al.,[16] to achieve greater power to detect statistically significant differences. We hypothesized that older patients would have lower BDNF levels than healthy comparators. We also explored whether BDNF levels differed 1) in patients with BD type I versus BD type II (disorders which appear to have important clinical, phenomenological, and neuropsychological differences)[17,18] and 2) in those being treated with lithium versus those not on lithium.

METHODS

Samples

Serum levels of BDNF were measured in 118 euthymic older patients with BD type I or II (mean ± SD age: 64.0 ± 9.7 years) and 76 healthy comparators aged 50 years or older (mean: 65.9 ± 9.5 years). Groups were similar with regards to age and sex. Young Mania Rating Scale (YMRS) and 17-Item Hamilton Depression Rating Scale (HDRS) scores were lower in comparators compared with bipolar disorder (BD) type I and type II groups, which we would expect since subsyndromal mood symptoms are common in BD. BD subtypes did not differ from one another with regard to YMRS and HDRS.[19] Their demographic and clinical characteristics are shown in Table 1. Patients and healthy comparators were recruited and evaluated at the University of Pittsburgh and the Centre for Addiction and Mental Health in Toronto. Similar evaluations were performed at both sites, as reported elsewhere.[16,20–22] BD I (N = 91) and BD II (N = 27) diagnoses were determined using the Structured Clinical Interview for Axis I DSM-IV Disorders. All subjects were clinically euthymic for 4 weeks or more at the time of evaluation and blood draw, with a score of 10 or less on both the YMRS[23] and 17-item HDRS.[24] All patients and comparators provided written informed