RESEARCH

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Galantamine-ER For Cognitive Dysfunction In Bipolar Disorder and Correlation with Hippocampal Neuronal Viability: A Proof-of-Concept Study

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Background: Many subjects with bipolar disorder experience significant cognitive dysfunction, even when euthymic, but few studies assess biological correlates of or treatment strategies for cognitive dysfunction.
Method: Nineteen subjects with bipolar disorder in remission, who reported subjective cognitive deficits, were treated with open-label galantamine-ER 8–24 mg/day for 4 months. Ten healthy volunteers matched for age and gender were also assessed. Mood and subjective cognitive questionnaires were administered monthly. At the beginning and the end of the trial all subjects were administered neuropsychological tests, including tests of attention (Conners CPT) and episodic memory (CVLT). Bipolar subjects underwent proton magnetic resonance spectroscopy (1H-MRS) measurements before and after treatment, healthy volunteers completed baseline 1H-MRS. We acquired 1H-MRS data at 4.0 T from voxels centered on the left and right hippocampus to measure hippocampal *N*-acetyl aspartate (NAA, a measure of neuronal viability) and choline containing compounds (Cho, a marker of lipid metabolism and membrane turn-over).
Results: Compared to healthy volunteers, bipolar subjects had higher baseline subjective cognitive deficits and lower scores on objective tests of attention (Conner's CPT) and verbal episodic memory (CVLT). After treatment, bipolar subjects experienced significant improvement of subjective cognitive scores and on objective tests of attention (Conner's CPT) and verbal episodic memory (CVLT). In the left hippocampus NAA increased and choline (Cho) decreased in bipolar subjects during treatment.
Conclusion: Bipolar subjects had cognitive dysfunction; treatment with Galantamine-ER was associated with improved cognition and with increases in neuronal viability and normalization of lipid membrane metabolism in the left hippocampus.
This study was registered on ClinicalTrials.gov (NCT00181636).

Introduction

Numerous studies have demonstrated the presence of neuropsychological deficits in subjects with bipolar disorder. Initially such impairments were considered to be related to acute or subsyndromal mood episodes. Deficits of verbal and visual memory as well as executive function have been described in acutely depressed patients [1–3]. Other researchers have reported attention and executive dysfunction in mania [4,5].

However, there is now substantial evidence that subjects with bipolar disorder exhibit cognitive impairments

even when they are euthymic [1,6–11]. Multiple studies reported euthymic bipolar subjects experience deficits in abstract reasoning and visuomotor skills [12], verbal memory [13–15], nonverbal memory [16], verbal fluency [17], visuospatial ability [18], and general cognitive function [19–21]. While impairment of executive function was reported by some [9] but not all studies [13,18], deficits of attention and verbal memory have been reported by a majority of researchers. The severity of neuropsychological deficits increases with both the number of affective episodes and the overall duration of illness [14,22–24].

Significant psychosocial functional impairment (e.g., limited ability to hold a job) is also present in patients with bipolar disorder, including during remission [25]. In a review of studies published until 2000, MacQueen et al. [26] reported that 30–60% of individuals with bipolar disorder fail to regain full functioning in occupational and social domains after remission of mood episodes. Zarate et al. [27] postulated that functional impairment in euthymic subjects with bipolar disorder may be related to persistent neuropsychological deficits. Indeed, the severity of cognitive deficits in asymptomatic patients with bipolar disorder has been associated with poor psychosocial functioning, such as inability to hold a job [28,29].

There is, however, very limited information on potential treatments for cognitive dysfunction in bipolar disorder. One set of potential candidates is represented by acetylcholinesterase inhibitors (AChEIs), a class of drugs approved for the treatment of cognitive dysfunction in subjects with dementia. Galantamine, an AChEI, is an allosteric potentiator of presynaptic nicotinic receptors and a cholinergic agonist, which was shown to improve significantly the declarative memory functions in patients with Alzheimer disorder [30]. Galantamine has a dual mechanism of action. It inhibits acetylcholinesterase, but it also appears to act directly on the brain nicotinic receptors. The modulation of nicotinic receptors results in the release of more acetylcholine, which may be the mechanism of enhanced positive effects on memory functions [31].

AChEIs and in particular galantamine have been used successfully for the treatment of cognitive dysfunction in psychiatric disorders. Treatment with galantamine was reported beneficial for neuropsychological deficits in schizophrenia [32], which may have both symptoms and mechanisms in common with cognitive deficits in bipolar disorder. Small open studies have also suggested AChEIs may be effective for cognitive deficits in affective disorders. In an open study donepezil (Aricept) for psychotropic induced memory loss in nondemented subjects with unipolar and bipolar affective illness, Jacobsen et al. [33] reported 19 of 21 (90%) subjects of those improved on subjective ratings of memory functions. Galantamine was also beneficial for cognitive deficits in two of four bipolar subjects reported by Schrauwen and Ghaemi [34].

In this study we tested whether open treatment with galantamine ER, an AChEIs, would be associated with improvements in specific measures of cognitive dysfunction, previously found to be altered in patients with bipolar disorder. We also measured subjective cognitive improvement. We hypothesized that bipolar subjects will experience deficits of attention and verbal memory, and that such deficits will improve after treatment. In parallel we tested the neuroprotective effects of galantamine using proton magnetic resonance spectroscopy (1H-MRS) acquired from the left and right hippocampus to measure *N*-acetylaspartate (NAA), a marker of neuronal viability and choline containing compounds (Cho), a key component of phospholipid membrane metabolism. We hypothesized that bipolar subjects will have low NAA and higher choline levels at baseline compared with healthy volunteers, and that NAA levels will increase while Cho levels will decrease after treatment.

Methods

Participants

We enrolled twenty subjects with bipolar disorder and ten matched healthy volunteers for a study conducted in the Bipolar Clinic and Research Program at MGH between 2003 and 2006. Written informed consent was obtained from all study participants. This study was registered on ClinicalTrials.gov (NCT00181636).

Bipolar Subjects

The inclusion criteria for this study were: men or women aged 18–65; meeting DSM-IV diagnostic criteria for bipolar disorder (diagnosed with the use of the Affective Disorder Evaluation, [35]); no acute episodes of depression or mania for the previous 12 weeks, a score of $\leq$10 on the 17-item Hamilton Rating Scale for Depression (Ham-D-17) and on the Young Mania Rating Scale (YMRS) at the screen visit, and reporting subjective cognitive deficits.

The exclusion criteria for this study were: subjects with suicidal ideation where outpatient treatment is determined unsafe by the study clinician; pregnant women or women of childbearing potential; serious or unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic or hematologic disease; history of seizure disorder, brain injury, any history of known neurological disease (multiple sclerosis,

degenerative disease, such as ALS, Parkinson disease and any movement disorders, etc.); history or current diagnosis of the following DSM-IV psychiatric illness: organic mental disorder, schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorders not otherwise specified, major depressive disorder, patients with mood congruent or mood incongruent psychotic features, patients with substance dependence disorders, including alcohol, active within the last 12 months; history of multiple adverse drug reactions; subjects who are active smokers or who stopped smoking less than 3 months prior to enrollment; clinical or laboratory evidence of hypothyroidism; patients who have had an episode of acute depression or mania during the 12 weeks prior to enrollment; patients who have had electroconvulsive therapy (ECT) within the 6 months preceding enrollment; no significant abnormalities on screening laboratory tests (which included complete blood count; urinalysis; comprehensive metabolic panel (CMP) (serum concentrations of electrolytes, BUN, creatinine, SGOT, SGPT, CPK, alkaline phosphatase, total bilirubin, albumin, total protein, and glucose); TSH and electrocardiogram (EKG); subjects with physical contraindications to magnetic resonance spectroscopy (ferrous surgical clips, cardiac pacemaker, ferrous prosthesis), which was determined by a clinical pre-MRI questionnaire; patients taking any of the following medications: other cholinesterase inhibitors, succinylcholine, neuromuscular blocking agents, cholinergic agonists (e.g., betanechol), cimetidine, ketokonazole, erythromycin, fluoxetine, and fluvoxamine.

We screened 23 bipolar subjects, 20 subjects met inclusion criteria. One subject discontinued the study before starting medications (moved for a new job). Nineteen subjects started study medication. One subject discontinued between weeks 0 and 4 (acute depression); three subjects discontinued between weeks 4 and 8 (2 = adverse reactions; 1 = relocation), two subjects discontinued between weeks 8 and 12 (1 = acute mania; 1 = depression), two subjects discontinued between weeks 12 and 16 (2 = lack of efficacy). Eleven bipolar subjects completed the 16-week study. The retention rate at endpoint (week 16) was 11/19 = 58%.

Concomitant medications: Out of 23 bipolar subjects screened for this study, 6 (26%) were treated with monotherapy: 4 (17%) on lithium and 2 (9%) on valproate. Of the 17 patients (74%) treated with combination therapies, 4 (17%) were on lithium and 5 (22%) were on valproate. Other medications used for the treatment of bipolar disorder in those subjects were lamotrigine [6], carbamazepine [2], oxcarbazepine [2], quetiapine [4], risperidone [2], ziprasidone [2], aripiprazole [1], buproprion [6], escitalopram [3], sertraline [2], and paroxetine [1].

Healthy Volunteers

We also recruited through advertisements 10 healthy volunteers, matched for age and gender with the first 10 bipolar subjects completing the study. Healthy volunteers underwent the physician administered Affective Disorder Evaluation [36] to rule out any Axis I psychopathology. All subjects were unmedicated. No healthy volunteer subject had a lifetime history of major neurological, medical, psychiatric disorder, or head injury.

Treatment

Bipolar subjects eligible for the study returned for their baseline visit after 2 weeks, during which they continued their existing psychotropic medication. Patients with a Ham-D-17 or YMRS score >10 at the baseline visit were excluded from the study. Those patients still eligible at the baseline visit started a 16-week open treatment with flexible doses of galantamine-ER 8–24 mg/day. After baseline patients had clinic visits every 4 weeks, during which we assessed Ham-D, YMRS and side-effects. Patients started galantamine-ER 8 mg/day for the first 4 weeks. During weeks 5–8 the dose was increased to 16 mg/day, if the previous dose was well tolerated. During weeks 9–16 the dose was increased to the maximum of 24 mg/day, if tolerated. The presence of adverse events (AEs) was documented by study psychiatrists at every visit by recording all spontaneously reported AEs, which were classified as mild, moderate, or severe. At every point during the study the patients experiencing significant AEs were given the option to reduce the galantamine-ER dose to 8 mg/day. Patients who could not tolerate galantamine-ER at 8 mg/day were discontinued from the study.

Assessments of Cognitive Functions

Before the onset of galantamine treatment and after 16 weeks of treatment we administered a battery of neuropsychological tests. The tests were chosen from three cognitive domains, based on their previously demonstrated sensitivity in subjects with bipolar disorder. This includes tests of attention (Conners Continuous Performance Test [36]); verbal episodic memory (California Verbal Learning Test [37]); executive functioning: Wisconsin Card Sorting Test (WCST [38]). On the basis of previous studies in bipolar subjects [15], for each of these neuropsychological tests we pre-selected the following scales as primary outcomes for this study: Conner's CPT commission errors, CVLT Trial 1, CVLT Trial 1–5, WCST Total errors, WCST Failure to maintain set. Healthy vol-

unteer subjects also had the same neuropsychological tests administered at baseline and at 16-week follow-up.

At every study visit we have also administered a self-report measure of cognitive function (The MGH Cognitive and Physical Function Questionnaire, CPFQ, 39)

Spectroscopy Measurements

We acquired proton magnetic resonance spectroscopy (1H-MRS) data from all bipolar subjects (before and after treatment) and healthy volunteer subjects (baseline only) on a 4.0 T Varian Unity/Inova whole body MR scanner (Varian NMR Instruments, Palo Alto, CA) equipped with a proton volumetric head coil (MR Instruments, Minneapolis, MN).

The proton spectrum were acquired from two separate voxels localized on the left and right hippocampus ($1.5 \times 1.5 \times 1.5$ cm) using the PRESS spectroscopy sequence. The hippocampus voxel was placed to maximize the hippocampus cross-section in the voxel in the superior/inferior and right/left directions, whilst staying clear of intercranial spaces (Fig. 2b). PRESS parameters include a repetition time (TR) = 2 s; echo time (TE) = 30 ms and averages = 256. The total PRESS acquisition time for each voxel is less than 10 min.

Following data acquisition the proton spectra were transferred to a Sun Ultra 60 (SUN, Mountain View, CA) Workstation and fit using LCModel [40] and a simulated basis-set. Following spectral fitting, LCModel produces a table and figure (Fig. 2a). The table includes absolute fits (in institutional units) and standard deviations (SD%). The standard deviation is a measure of the reliability of the fit. A standard deviation of 100% means the metabolite would need to double in order for a change to be seen. Spectra with metabolite (NAA, Cr, Cho) SD greater than 15% were excluded from analysis. This criterion was intended to prevent "noisy" spectra from reducing one's power to detect meaningful changes in metabolite levels.

Data Analysis

Group differences in demographic and clinical variables involving continuous data were computed using unpaired *t*-tests (age, HAM-D scores); we used chi-square for categorical data (gender). We have pre-specified the following six measures of cognitive function Conner's CPT commission errors, CVLT Trial 1, CVLT Trial 1–5, WCST Total errors, WCST Failure to maintain set and MGH CPFQ total score. We used unpaired *t*-tests to compare baseline cognitive scores and changes from baseline to endpoint in cognitive scores between bipolar subjects and healthy volunteers. We used the nonparametric Wilcoxon rank-sum (Mann-Whitney *U*) test to compare baseline levels of MRS metabolites (NAA, Cho) between bipolar subjects and healthy volunteers. Statistical significance was defined at the 0.05 level, two-tailed.

Results

Demographic characteristics of subjects with bipolar disorder (BD) and healthy volunteers are listed in Table 1. No statistically significant differences in age, gender, and YMRS scores were noted between BD and healthy subjects ($p > 0.05$ for all analyses). Baseline depression scores (Ham-D) were higher in bipolar subjects although still in the remission range (3.79 ± 2.92 vs. 1.60 ± 1.58, $p = 0.037$). Compared to healthy volunteers, bipolar subjects had more baseline subjective cognitive deficits (CPFQ, 21.05 ± 6.43 vs. 13.91 ± 2.47, $p < 0.01$) and lower scores on objective tests of attention (Conner's CPT, 11.82 ± 5.44 vs. 7.50 ± 4.93, $p < 0.05$) and verbal episodic memory (CVLT learning 1–5, 50.63 ± 10.58 vs. 60.18 ± 8.01, $p < 0.02$). There were no significant differences in executive function scores between bipolar subjects and healthy volunteers (Table 1).

Eighteen of the 19 bipolar subjects and N = 10 healthy volunteers had 1H-MRS scans of adequate quality for metabolite measurements. At baseline subjects with bipolar disorder had higher choline (Cho) levels in both left and right hippocampus, compared to healthy volunteers. Numerically NAA levels were increased in bipolar subjects; the difference was statistically significant in the right but not in the left hippocampus (Table 2).

After treatment, bipolar subjects experienced significant improvement of subjective cognitive scores ($p < 0.01$) and on objective tests of attention (CPT, $p < 0.04$) and verbal episodic memory (CVLT, $p < 0.03$) (Table 1). The subjective improvement in cognitive scores was gradual during the 16-week study; most of the benefit was achieved in the first 12 weeks of the treatment (Fig. 1).

Only bipolar subjects had repeat MRS testing. From the N = 11 bipolar subjects who completed the study, only eight had adequate pre- and posttreatment 1H-MRS scans to allow the comparison of metabolite levels. Cho levels decreased from baseline to week 16 in the left hippocampus; the end-of-study levels were close to the levels measured in healthy volunteers. The numerical decrease in Cho in the right hippocampus was not statistically significant. NAA levels increased in the left but not in the right hippocampus during the 16-week treatment with galantamine ER (Table 2).

Treatment with galantamine ER was relatively well tolerated. Two subjects (10%) discontinued the study due to side effects (nausea = 1, diarrhea and migraines = 1). Three subjects (16%) experienced new mood episodes (1 = mania, 2 = depression); this rate of new episodes in

Table 1 Demographic data and neuropsychological scores at baseline in bipolar subjects and healthy volunteers, and changes in the same neuropsychological tests during the 16-week study (mean ± SD)

		Baseline Data			Changes over 16 weeks		
		Bipolar Subjects (N = 20)	Healthy volunteers (N = 10)	Statistics	Bipolar Subjects Completers (N = 11)	Healthy volunteers (N = 10)	Statistics
Age		40.7 ± 11.9	38.9 ± 10.1	df = 28, $t = 0.43$, $P = 0.67$			
Gender (female)		6 (30%)	3 (30%)	$\chi^2 = 0.001$, df = 1, $P = 0.97$			
Diagnosis	Bipolar 1	15 (75%)			8 (73%)		
	Bipolar 2	5 (25%)			3 (27%)		
HAM-D-17		3.79 ± 2.92	1.60 ± 1.58	df = 28, $t = -2.2$, $P = 0.037$	2.92 ± 4.12	0.88 ± 1.73	df = 18, $t = 1.32$, $P = 0.20$
YMRS		1.85 ± 2.32	0.70 ± 1.25	df = 28, $t = -1.46$, $P = 0.16$	2.09 ± 4.44	1.63 ± 4.27	df = 18, $t = 0.23$, $P = 0.82$
WCST	Tot errors	16.82 ± 9.90	14.06 ± 9.48	df = 25, $t = -0.73$, $P = 0.47$	-3.00 ± 4.92	-0.72 ± 8.34	df = 18, $t = 0.72$, $P = 0.48$
	Fail maintain set	0.31 ± 0.23	0.73 ± 0.79	df = 25, $t = 1.71$, $P = 0.10$	-0.58 ± 0.67	0.22 ± 0.83	df = 19, $t = 2.46$, $P = 0.023^*$
Conner CPT	Commission errors	12.41 ± 4.82	7.50 ± 4.93	df = 25, $t = 2.54$, $P = 0.018^*$	-6.40 ± 3.78	-0.63 ± 4.34	df = 18, $t = 2.34$, $P = 0.031^*$
CVLT	Learning 1–5	50.80 ± 10.33	60.18 ± 8.01	df = 28, $t = -2.60$, $P = 0.014^*$	7.0 ± 7.4	0.78 ± 3.23	df = 18, $t = 2.34$, $P = 0.031^*$
CVLT	Recall trial 1	6.95 ± 2.35	8.73 ± 1.68	df = 28, $t = -2.21$, $P = 0.035^*$	1.27 ± 0.91	0.33 ± 0.87	df = 18, $t = 2.36$, $P = 0.030^*$
MGH CPFQ (subjective)		21.56 ± 6.46	13.30 ± 1.49	df = 26, $t = 3.95$, $P = 0.005^*$	6.8 ± 6.0	-2.1 ± 3.8	df = 23, $t = 3.85$, $P = 0.0008^*$

$^*P < 0.05$.

Table 2 Baseline levels of *N*-acetyl aspartate (NAA), choline compounds (Cho) and creatine in bipolar subjects and healthy volunteers, and changes in the same 1H-MRS metabolite levels in bipolar subjects who completed the 16-week treatment (Institutional Units, mean ± SD)

Metabolite	Hippocampus	Bipolar subjects (N = 18)	Healthy volunteers (N = 10)	Statistics	Bipolar completers–baseline (N = 8)	Bipolar completers–endpoint (N = 8)	Statistics
NAA	Left	5.26 ± 3.63	3.32 ± 3.68	df = 26, $t = 1.35$, $P = 0.19$	4.87 ± 1.78	8.15 ± 4.74	df = 7, $t = 2.63$, $P = 0.039^*$
	Right	6.41 ± 2.11	4.44 ± 2.01	df = 26, $t = 2.38$, $P = 0.025^*$	6.11 ± 1.49	5.38 ± 2.72	df = 7, $t = 1.37$, $P = 0.21$
Cho	Left	2.12 ± 1.08	0.90 ± 0.96	df = 26, $t = 2.99$, $P = 0.006^*$	2.41 ± 0.93	1.30 ± 0.84	df = 7, $t = 2.52$, $P = 0.040^*$
	Right	1.88 ± 0.66	1.24 ± 0.50	df = 25, $t = 2.66$, $P = 0.014^*$	1.88 ± 0.62	1.48 ± 0.67	df = 7, $t = 0.94$, $P = 0.38$
Creatine	Left	5.71 ± 2.90	2.97 ± 2.99	df = 26, $t = 2.36$, $P = 0.026^*$	6.17 ± 3.16	6.04 ± 3.45	df = 7, $t = 0.49$, $P = 0.64$
	Right	5.16 ± 1.86	3.58 ± 1.48	df = 26, $t = 2.29$, $P = 0.031^*$	5.90 ± 2.00	4.76 ± 2.03	df = 7, $t = 0.89$, $P = 0.40$

$^*P < 0.05$.

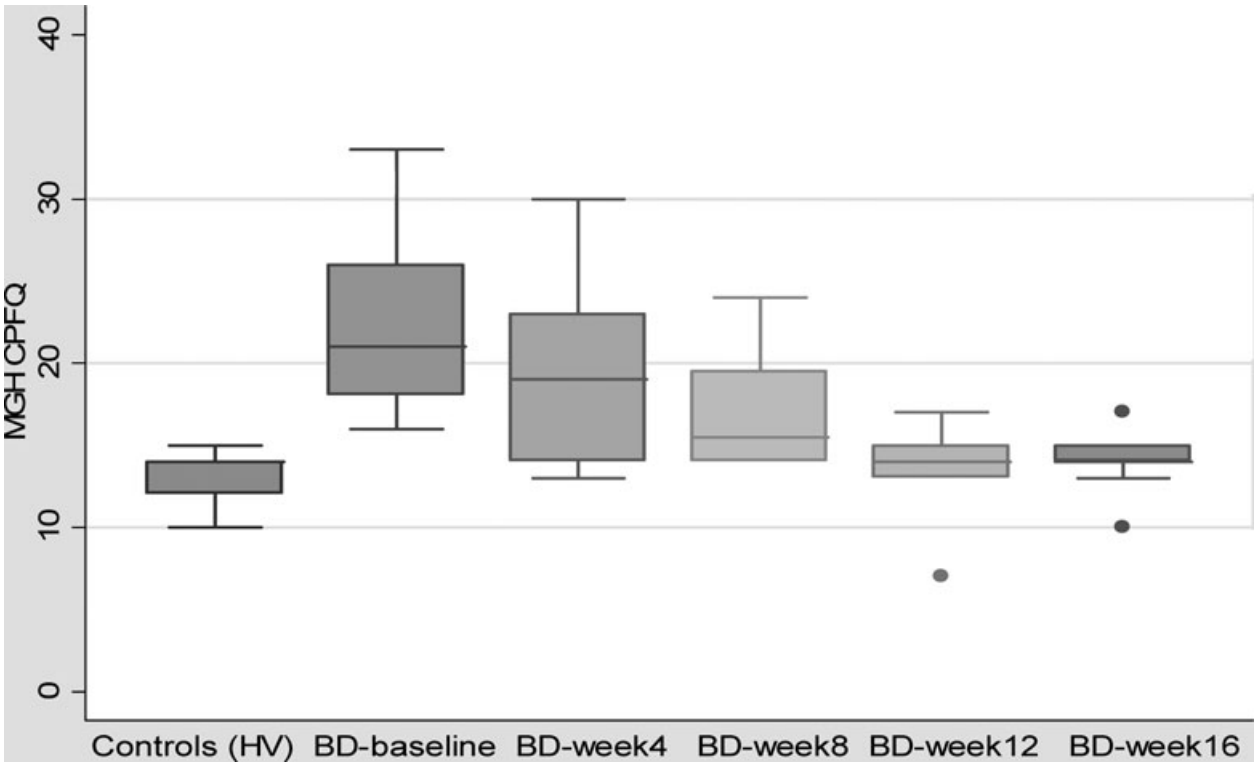

Figure 1 Changes in subjective cognitive scores (CPFQ) in bipolar subjects (BD) during treatment and comparison with healthy volunteers (HV).

bipolar subjects is consistent with larger samples where relapse of bipolar disorder is common [42,43].

Discussion

This is to our knowledge the largest study published to date on the treatment of cognitive dysfunction in bipolar disorder. In our study, bipolar subjects treated with galantamine ER for 16 weeks experienced significant improvement in their cognitive functions, especially in attention (Conner's CPT) and verbal memory (CVLT), as well as in their subjective cognitive scores (CPFQ). It is unlikely that the observed improvements in cognitive functions (attention, memory) could be explained by improvements in mood, since subjects in our study were euthymic at baseline.

At baseline bipolar subjects had more subjective and objective cognitive dysfunction, compared to healthy volunteers. This is consistent with multiple previous studies suggesting bipolar subjects experience cognitive dysfunction during periods of euthymia [1,6–11]. Savitz et al. [41] reviewed 40 studies examining neurocognitive function in euthymic individuals with bipolar disorder. Only three of those 40 studies failed to detect cognitive impairment in euthymic bipolar patients, suggesting that cognitive dysfunction may represent a permanent trait in this population and not only related to acute mood episodes. This could be an underlying genetic trait, as first-degree relatives of patients with bipolar disorder exhibit impaired attention set shifting [42], but can also be a progressive phenomenon as neuropsychological deficits are associated with both the number of affective episodes and the overall duration of illness [22–24].

In the current study, we are not able to assess the effect of concomitant bipolar medications on the cognitive dysfunction experienced by bipolar subjects at baseline. However, since other bipolar medications were continued unchanged during the study, it is likely that the cognitive improvement observed his related to treatment with galantamine. In general, the relation between cognitive deficits and the psychotropic medications used to treat the bipolar disorder cannot explain the majority of cognitive deficits in this population [43]. Lithium has been reported to have adverse effects on memory and psychomotor functioning [10,44,45], while valproate and carbemazepine may cause attentional difficulties [46]. Antipsychotics have been associated with deficits in sustained attention [47] and executive function [23]. However, longitudinal studies failed to detect evidence of cognitive decline in bipolar patients treated with lithium

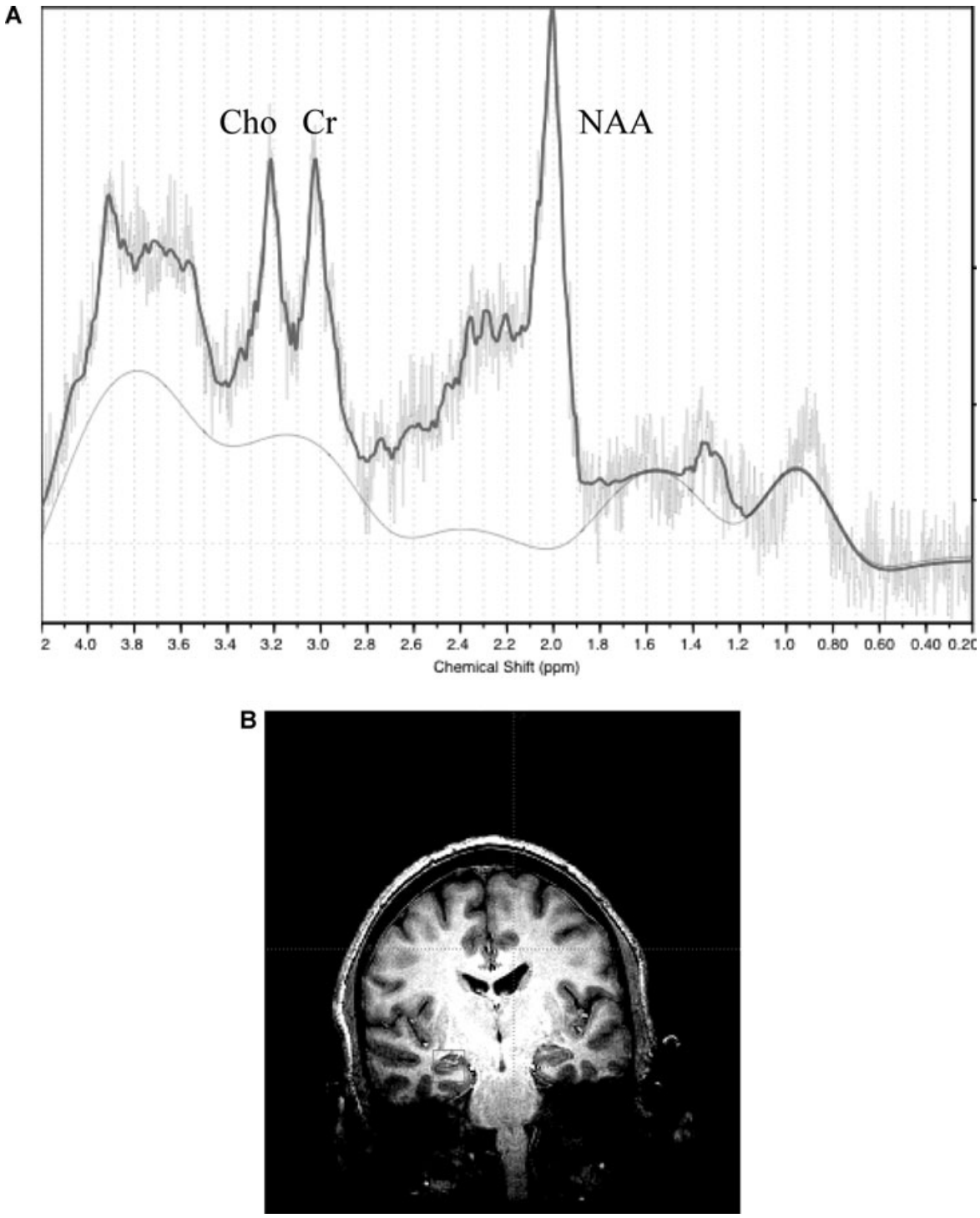

Figure 2 Typical proton spectroscopy (1H-MRS) spectrum from a subject with bipolar disorder (A) and positioning of the spectroscopy voxel in the left hippocampus (B).

[48]. In the same study, comparison of long- and short-term lithium treatment groups also failed to show significant differences in memory scores. Previous studies have also linked cognitive deficits in bipolar disorder with subsyndromal mood symptoms and to comorbid substance abuse. However, those factors do not play a significant role in our study since all bipolar subjects were euthymic and substance abuse was an exclusionary criterion.

We found that bipolar subjects at baseline had higher choline (Cho) levels compared to healthy volunteers. Our finding is consistent with multiple MRS studies in bipolar disorder [49–51]. The choline (Cho) signal consists primarily (approximately 80%) of phosphocholine (PC) and glycerophosphocholine (GPC) [52,53]. Choline is required for the synthesis of both the neurotransmitter acetylcholine and the phospholipid phosphatidylcholine. While acetylcholine is produced only by cholinergic neurons, phosphatidylcholine is produced in all cells as a major membrane constituent [52]. Consequently, changes in the Cho signal are primarily associated with alterations in membrane synthesis and composition [52]. Significant increases in the Cho signal have been observed in neurodegenerative disorders such as Alzheimer's disease and multiple sclerosis (MS), as well as cases of ischemia and head trauma, probably related to the release of Cho-containing compounds during membrane breakdown [53].

Contrary to our hypothesis, NAA levels were numerically higher at baseline in bipolar subjects compared to healthy volunteers (and the difference was statistically significant for the right hippocampus). NAA is located primarily within neurons and a reduction of NAA levels has been interpreted as reflecting neuronal loss or damage [54]. The increased NAA levels in our euthymic bipolar subjects may be the result of their existing treatments with potential role in increasing neuroprotection. Valproate and lithium have been previously associated with increased NAA levels in bipolar subjects [55,56].

During the 16-week treatment NAA levels increased and Cho levels decreased in the left hippocampus in bipolar subjects, which is consistent with a neuroprotective effect of galantamine. Our results are in agreement with previous studies in healthy volunteers and in neurological disorders where measures of cognitive function have been correlated with brain NAA and Cho levels as measured by 1H-MRS [57–61]. Moreover, in some studies NAA levels appear to increase (i.e., renormalize) in parallel with performance on neuropsychological testing [62] which is also consistent with the results reported here.

Our data is consistent with previous reports suggesting the mechanism by which AChEI would be effective for cognitive dysfunction may be mediated by neuroprotective effects. Preclinical studies suggest that AChEI protect neurons from death in cell culture models of neurodegenerative disease [63,64]. The activity of galantamine on nicotinic receptors may be associated with additional neuroprotective mechanisms [65]. Neurogenesis in the hippocampus is another important mechanism for enhancing the resilience of neuronal systems in stressful conditions, and galantamine (and other AChEIs) have also been reported to enhance neurogenesis *in vitro* and *in vivo* [66]. However, other mechanisms such as the role of galantamine in increasing prefrontal dopaminergic activity may also explain its cognitive benefits [67]

Our study has several limitations, including small sample size and open design with no placebo comparator, which makes it difficult to assess the true efficacy of galantamine-ER. Subjects in our study were taking multiple treatments for bipolar disorder it is difficult to assess the effect of concomitant treatments on the cognitive dysfunction and on the improvement of symptoms. Another limitation is that because we administered objective neuropsychological tests only twice during the study to minimize learning effects, therefore we can test the efficacy of galantamine only in study completers. Only subjective cognitive improvements can be estimated in subjects who dropped out during the study. Similarly, improvements in hippocampal NAA and Cho can only be assessed in subjects completing the 16-week study. Because this was an open study, we cannot differentiate between the cognitive and neuroprotective effects of galantamine ER and those related to placebo (i.e., the on-going healing which may occur in euthymic bipolar subjects). No correction for multiple comparisons was made in this small pilot study; larger studies will be needed to confirm our results.

Despite these methodological limitations our study suggests that Galantamine-ER can improve objective and subjective cognitive deficits in subjects with bipolar disorder (especially attention and verbal memory deficits). In our study treatment with Galantamine was also associated with increases in neuronal viability and lipid membrane metabolism in the left hippocampus. Larger studies, using a placebo controlled design will be needed to establish the efficacy of galantamine for cognitive dysfunction in bipolar disorder and to assess the eventual improvements in functional status triggered by the improvement in cognition.

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Conflict of Interest

Dr. Iosifescu has received research support from Aspect Medical Systems, Forest Laboratories and Ortho-McNeil Neurologics; he has been a consultant for Forest Laboratories, Gerson Lehrman Group and Pfizer, Inc., and he has been a speaker for Eli Lilly & Co., Forest Laboratories, Pfizer, Inc and Reed-Elsevier. Drs. Moore, Deckersbach and Ms. Tilley report no potential conflicts. Dr. Ostacher

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