Published in final edited form as:

Bipolar Disord. 2012 March ; 14(2): 198–205. doi:10.1111/j.1399-5618.2012.00995.x.

Cognition in older adults with bipolar disorder versus major depressive disorder

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Abstract

Objectives—Bipolar disorder (BD) and major depressive disorder (MDD) are associated with cognitive dysfunction in older age during both acute mood episodes and remitted states. The purpose of this report is to investigate for the first time the similarities and differences in cognitive function of older adults with BD and MDD that may shed light on mechanisms of cognitive decline.

Methods—A total of 165 subjects with BD (n = 43) or MDD (n = 122) ages 65 years [mean (SD) 74.2 (6.2)] were assessed when euthymic using comprehensive measures of cognitive function and cognitive-instrumental activities of daily living (C-IADLs). Test results were standardized using a group of mentally healthy individuals (n = 92) of comparable age and education level.

Results—Both subjects with BD and MDD were impaired across all cognitive domains compared to controls, most prominently in Information Processing Speed/Executive Function. Despite the protective effects of having higher education and lower vascular burden, BD subjects were more impaired across all cognitive domains compared with MDD subjects. Subjects with BD and MDD did not differ significantly in C-IADLs.

Conclusion—In older age, patients with BD have worse overall cognitive function than patients with MDD. Our findings suggest that factors intrinsic to BD appear to be related to cognitive deterioration and support the understanding that BD is associated with cognitive decline.

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Disclosures

AGG has received research support from GlaxoSmithKline for an investigator-initiated study. MAB has received payment from Northstar Neuroscience and Medtronic for providing neuropsychological assessment services to clinical trials and from Fox Learning Systems (via a National Institute of Health (NIH)-funded SBIR) for computerized test development. CFR has received research support in the form of pharmaceutical supplies for his NIH-sponsored research from Bristol-Myers Squibb, Eli Lilly & Co., Forest, and Pfizer. BHM has received research support in the form of pharmaceutical supplies for his NIH-sponsored research from Bristol-Myers Squibb, Eli Lilly & Co., Pfizer, and Wyeth. DC, SJA, AB, MH, and JCR report no financial relationships with commercial interests.

Keywords

aged; bipolar disorder; cognition; IADLs; major depressive disorder

In late life, bipolar disorder (BD) and major depressive disorder (MDD) are associated with cognitive dysfunction even when patients are euthymic (1–6). Both disorders are also associated with increased rates of dementia (7, 8). In addition to impaired cognitive function, these disorders may interfere with everyday functional abilities (9). Whether BD and MDD have similar or different cognitive profiles and levels of impairment in older age is not clear. Identifying whether there are relevant differences may help in understanding the neurobiology of these illnesses and developing specific interventions for BD or MDD to prevent, halt, or remediate cognitive impairment and functional decline. For example, deficits in memory may require different treatments than deficits in executive function. Additionally, if both disorders are associated with comparable levels of cognitive function, but differing levels of everyday functional ability, interventions might need to consider targets other than cognition to enhance everyday function (10).

In this report, our primary aim was to examine the overall patterns of cognitive function in patients with BD and MDD. Our main hypothesis was that among older adults, BD and MDD would be associated with a similar pattern of deficits, primarily in information processing speed and executive function; however, the level of cognitive impairment would be more severe in individuals with BD. We also predicted that instrumental activities of daily living (IADLs) would be directly related to cognitive performance, most significantly with Information Processing Speed and Executive Function, and IADLs would be more impaired in subjects with BD. These hypotheses were based on our prior reports and the current literature concerning neurodegeneration in BD (11). Exploratory analyses were conducted to examine the relationship of cognition with lifetime history of psychosis and lifetime duration of illness since history of psychosis and longer duration of illness have been associated with worse cognitive function (12).

Methods

Study subjects

As previously described, patients with BD type I (BD-I) ($n = 33$) or BD type II (BD-II) ($n = 10$) were recruited from outpatient clinics or treatment studies carried out at the University of Pittsburgh (Pittsburgh, PA, USA) (13, 14). These 43 subjects with BD were compared with 122 subjects with MDD who participated in a maintenance intervention trial conducted at the University of Pittsburgh's Advanced Center for Intervention and Services Research for Late-Life Mood Disorders (15). In addition, a group of comparator subjects (controls) comprised 92 age- and education-comparable subjects with no psychiatric or neurologic history, who were used to standardize the measurement of cognitive function across various tests (see *Measures*). As described elsewhere, these controls were recruited through health fairs or advertisements and participated in ongoing projects studying the relationship between late-life mood disorders and cognitive function (1, 16). All subjects provided written informed consent approved by the Institutional Review Board at the University of Pittsburgh.

Diagnoses of BD-I, BD-II, or MDD (including lifetime history of psychosis) were established by a Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-IV) administered by trained clinicians. Other *inclusion criteria* were: (i) age 65 years or older; (ii) clinical euthymia for four weeks preceding neuropsychological (NP) assessment as demonstrated by scores of ≤ 10 on the Hamilton Rating Scale for Depression-17 item

(HRSD-17) (17) for subjects with BD or MDD and scores of ≥ 10 on the Young Mania Rating Scale (YMRS) (18) for subjects with BD; (iii) ability to comprehend and speak English fluently; (iv) corrected visual ability to read newspaper headlines; and (v) hearing capacity adequate to respond to a raised conversational voice. *Exclusion criteria* were: (i) pre-existing history of dementia or neurologic disorder affecting the central nervous system (e.g., Parkinson's disease, traumatic brain injury, or multiple sclerosis); (ii) electroconvulsive therapy (ECT) within the previous six months; (iii) substance abuse or dependence within the past twelve months; and (iv) unstable medical illness (e.g., active cancer or unstable heart disease). In addition, by design of the parent study, subjects with MDD had no lifetime history of psychosis and controls had no lifetime Axis I diagnoses except for simple phobia.

Treatment

Details on treatment for subjects in the intervention studies have been described elsewhere (13, 15, 19). In brief, the goals of the pharmacotherapy intervention for BD were to maximize the appropriate use of lithium (with typical doses of 300–900 mg/day titrated to a plasma level of 0.5–1.0 mEq/L) or divalproex (doses were in the range of 500–1500 mg/day, titrated to a plasma level of 40–100 mcg/ml), either alone or in combination, to achieve remission of acute mood episodes, maintain euthymia, and to limit adjunctive antipsychotic or antidepressant medication, except as judged clinically necessary by the study psychiatrist. Otherwise, except for trying to minimize polypharmacy, no restrictions were placed on the specific medications employed. The subjects with BD who did not participate in treatment studies received pharmacotherapy in our university-based clinic similar to what they would have received if they had participated in the intervention studies. Subjects with MDD initially received open-label escitalopram 10–20 mg/day (up to 20 mg/day). Those who did not respond fully were then switched to a serotonin-norepinephrine reuptake inhibitor (SNRI) (mostly duloxetine, up to 120 mg/day). Since subjects had cognitive assessment when they were stably euthymic for at least four weeks, medication changes at the time of testing were minimal.

Recruitment

Forty-eight patients with BD ages 65 years or older were invited to participate: eight declined participation in the study; six were excluded after initial screening (two due to Parkinson's disease, one due to dementia, one did not have BD, one had ECT within the previous six months, and one had a history of stroke); and four were deemed eligible, but did not complete the NP assessment for various reasons (did not return phone calls, moved out of state, etc). Thirteen subjects from a current and ongoing study of cognitive function in older adults with BD were added to this cohort. Thus, 43 subjects with BD who met all eligibility criteria and completed NP evaluation are included in this analysis.

There was a total of 151 subjects with MDD who were enrolled in a treatment study (15). Twenty-nine subjects were excluded from this analysis: 15 did not complete the NP assessment (refusal to complete the procedures, physical impairment, or administrative reasons unrelated to the subject) and 14 had HRSD-17 scores > 10 at the time of NP assessment. Thus, 122 subjects with MDD who met all eligibility criteria and completed NP evaluation were included in this analysis.

Measures of NP function

Evaluation encompassed 21 well-established and validated individual tests measuring multiple cognitive domains (see Table 1 for the individual tests) (20). As previously described (1, 3), we transformed raw scores for all individual tests into Z-scores using the distribution of the older adult controls (i.e., controls' performance on any test has mean of 0

and SD of 1). Based on our previous report (15), we developed four composite factor scores reflecting four distinct cognitive domains: Delayed Memory, Information Processing Speed/Executive Function, Language, and Visuomotor. Components of executive function were distributed throughout all domains, but predominantly loaded with Information Processing Speed. For each subject, *Z*-scores for the individual tests comprising each factor were averaged to produce four domain factor scores. Four tests that did not load uniformly on particular domains were excluded from the distinct cognitive domains, but were included in a global score produced by averaging all *Z*-scores (see Table 1). Internal consistency among the BD and MDD subjects was shown by Cronbach's alpha of 0.78 (Delayed Memory), 0.80 (Information Processing Speed/Executive Function), 0.80 (Language), 0.71 (Visuomotor), and 0.92 (Global). For reference, the raw scores of the individual tests of the mentally healthy comparators are available in an online addendum (see Supplementary Table 1).

C-IADLs

In a subset of BD subjects ($n = 29$) and MDD subjects ($n = 101$), we assessed C-IADLs using a criterion-referenced, performance-based instrument, the Performance Assessment of Self-care Skills (PASS) (21). An occupational therapist performed an in-home assessment of functional abilities, using 10 PASS items [three money management (shopping, bill paying by check, and checkbook balancing), one medication management, two current events (obtaining critical information from auditory and visual media), one home maintenance (small repairs), one environmental awareness (home safety), and two meal preparation (stovetop use and use of sharp utensils)]. The occupational therapist assigned a score from 0 (complete independence; requires no assistance for task initiation, continuation, or completion) to 9 (complete dependence; requires total assistance) such that higher scores indicate worse performance.

Other assessments

All subjects were assessed with the Cumulative Illness Ratings Scale – Geriatric (CIRS-G) (22). Total CIRS-G score was used as a measure of overall physical illness burden. Scores of items No. 1 (heart) and No. 2 (vascular) were added to produce a measure of vascular disease burden (4). Lifetime duration of illness was defined as age at onset of first mood episode subtracted from current age.

Statistical analysis

Prior to statistical testing, the data were examined for normality and transformations were used where necessary. Missing data due to cognitive impairment were imputed with the lowest score of the group for that test. Demographic and clinical characteristics of subjects with BD or MDD were compared using *t*-tests for continuous measures and Fisher's exact test for categorical variables. Analysis of covariance (ANCOVA) was used to examine group differences in the four NP domains, global NP score, and C-IADLs. Age, education, and vascular disease burden were included in the model because these are related to cognitive function (20). Pearson and Spearman correlations were used to examine the relationship between the NP domains, global NP score, and C-IADLs. Secondary analyses examined the impact of lifetime history of psychosis and lifetime duration of illness on cognitive function. Lifetime history of psychosis was examined by dividing BD subjects into those with, and those without, lifetime history of psychosis and comparing them with MDD subjects. ANCOVAs were repeated to test for group differences followed by Tukey post-hoc pairwise comparisons for significant group differences. Lifetime duration of illness was tested by including it as a covariate into the ANCOVA models.

Results

Subjects' baseline characteristics are presented in Table 2. Subjects with BD had a lower level of total medical, including cardiovascular, burden and higher education than subjects with MDD. While both groups of patients were assessed when mood symptoms were in remission and stably euthymic, subjects with BD had a lower level of residual mood symptoms than MDD subjects. Although not formally assessed in the study, most subjects were stably euthymic for several months prior to study entry. Mentally healthy comparators had a mean age (SD) of 74.0 (5.6) years with a mean (SD) education level between BD and MDD subjects of 14.3 (2.8) years, which was not statistically different from either group. Among the BD subjects with lifetime history of psychosis, subjects had a mean of 2.3 mood episodes with psychotic features (SD = 1.3; min = 1, max = 5).

NP function

Subjects with BD and MDD performed below the level of nonpsychiatric controls (see Table 1). Of the four cognitive domains, subjects with BD and MDD were most impaired in Information Processing Speed/Executive Function. Subjects with BD were more impaired across all cognitive domains than subjects with MDD. Overall, the differences among the means adjusted [least squares (LS)-mean] for age, education, and vascular burden of the four domains ranged from 0.47 (Delayed Memory) to 0.79 (Information Processing Speed/Executive Function). Age, education, vascular burden, and diagnostic group were significant covariates in the ANCOVA. Worse overall cognitive function was associated with higher age [$F(1,160) = 35.72, p < 0.0001$], lower education [$F(1,160) = 30.64, p < 0.0001$], greater vascular burden [$F(1,160) = 4.44, p = 0.037$], and BD diagnosis [$F(1,160) = 33.98, p < 0.0001$].

BD subjects without lifetime history of psychosis compared with MDD

subjects—Post-hoc (Tukey test), we compared cognitive function among BD subjects without lifetime history of psychosis ($n = 28$) to MDD subjects. BD subjects without lifetime history of psychosis continued to perform worse than those with MDD globally and across all cognitive domains, except for Delayed Memory.

Lifetime duration of illness—Among BD and MDD, lifetime duration of illness was not related to any cognitive domain or global cognitive score.

C-IADLs

Performance on the PASS did not differ significantly between subjects with BD ($n = 29$) or MDD ($n = 101$); mean (SD), [range]: BD 1.80 (1.65), [0.20–7.90] versus MDD 2.13 (1.46), [0–7.62]; [Group: $F(1,125) = 1.96, p = 0.16$].

Correlation between NP and C-IADLs

Cognitive domains were highly correlated with C-IADLs in BD and MDD subjects. As expected, worse cognitive performance was related to increased assistance required in task completion. C-IADLs were significantly correlated with all measures of cognition: Delayed Memory, $r = -0.57, p < 0.0001$; Information Processing Speed, $r = -0.64, p < 0.0001$; Language, $r = -0.39, p < 0.0001$; Visuomotor, $r = -0.46, p < 0.0001$; and Global score, $r = -0.64, p < 0.0001$. Among the individual PASS items, shopping, bill paying, checkbook balancing, and medication management, Global (cognitive) score was significantly correlated with assistance on those items: shopping ($r_s = -0.49, p < 0.0001$), bill paying ($r_s = -0.35, p < 0.0001$), checkbook balancing ($r_s = -0.45, p < 0.0001$), and medication management ($r_s = -0.43, p < 0.0001$).

Discussion

Comparing the cognitive function of older, nondemented adults with BD or MDD revealed that having a diagnosis of BD was related to worse overall cognitive performance. Among the four cognitive domains, Information Processing Speed/Executive Function was most impaired among BD and MDD subjects. We did not observe an overtly distinct pattern of cognitive impairment between the two groups. However, BD subjects had worse cognitive function despite protective factors, such as higher education and lower vascular burden. Not surprisingly, cognitive function was highly related to performance of C-IADLs. Although euthymic, the mean C-IADL scores indicated the need for assistance, ranging from visual encouragement to physical support. When restricting the comparison of cognitive function between BD and MDD subjects to BD subjects without lifetime history of psychosis, BD subjects without lifetime history of psychosis still had significantly more impaired cognitive function globally and across cognitive domains, except for Delayed Memory. The presence of significantly more impaired cognitive function without lifetime history of psychosis suggests that the more impaired cognitive function in the BD group was not due to a higher frequency of lifetime psychosis (12). Additionally, we did not find a relationship of cognitive function with lifetime duration of illness among our subjects, suggesting that the worse cognitive function in older adults with BD was likewise not a result of having longer lifetime duration of illness. To our knowledge, our report is the first comparison of cognitive and IADL function in euthymic older adults with BD versus MDD, and suggests that factors intrinsic to BD play a role in cognitive status.

Our findings are congruent with several reports that have compared and contrasted cognitive function in BD versus other disorders in middle age. A recent meta-analysis examined the magnitude of cognitive deficits in 27 studies comparing patients with *affective psychosis* ($n = 763$) with healthy controls ($n = 1,823$). Compared with controls, patients with *affective psychosis* performed 0.8 SD lower on 11 of 15 cognitive variables with the largest effect being observed for Executive Function and Information Processing Speed (symbol coding and Stroop interference), verbal learning, and category fluency tasks. The analysis also revealed some differences in the severity, but not in the overall profile of cognitive performance in patients with BD ($n = 550$) versus MDD with psychoses ($n = 213$) (23). Other reports have also found differences in severity, but not overall profile of cognitive function among patients with BD, generalized anxiety disorder, or schizophrenia (24–26).

Only a handful of reports have specifically examined cognitive function and associated disability in BD or compared BD with other disorders in older age where these impairments may be most significant (2–4, 27, 28). In these reports, older adults with BD, when compared with mentally healthy individuals of similar age and education, have worse cognitive function and exhibit faster decline over time (4, 28). Cross-sectionally, cognitive function has been associated with ability to perform IADLs (3, 27). Older patients with BD or schizophrenia present with a similar profile of cognitive function except that patients with schizophrenia are more severely impaired (2).

Our findings suggest that BD impacts cognition negatively and disproportionately compared to MDD. There has been a growing recognition that BD is a chronic, multi-system disorder, and that in the central nervous system, biochemical mechanisms appear related to neurodegeneration and cognitive deterioration (29, 30). Central nervous system abnormalities intrinsic to BD may result in greater brain vulnerability to comorbidities related to BD (e.g., vascular disease), the effects of aging, or pathological mechanisms unrelated to BD (e.g., Alzheimer's disease) (29, 31). In addition, medications used to treat BD may affect cognition specifically. While evidence suggests that lithium and divalproex are neuroprotective (32), lithium also has measurable serum anticholinergic activity that can

negatively affect cognitive function (33, 34). Similarly, many individuals with BD are treated with antipsychotic medications, some of which have significant serum anticholinergic activity (33) and have been shown to impair cognition in older patients with dementia (35). That BD negatively impacts cognition may predispose individuals with BD to increased risk of developing dementia in old age (36).

Study limitations include the relatively small number of older adults in various BD subgroups (e.g., BD-I versus BD-II, BD with specific medication exposure), limiting the power for subgroup analyses. A major challenge in conducting research in older adults with BD is the difficulty with recruiting a large sample. Also, all subjects were receiving psychotropic medications that may affect cognition. The need to treat subjects with BD or MDD to prevent symptomatic relapse or recurrence would make finding a large group of subjects off medications extremely difficult. Even if it was possible, it would make the findings less generalizable to the broader group of older adults with mood disorders who require long-term pharmacotherapy (37). Thus, even though maintenance pharmacotherapy may affect cognitive performance, these performances reflect patients' cognition in *real-world* and optimal conditions (i.e., euthymic and nonpsychotic).

In conclusion, our findings do not suggest a particular cognitive profile in BD that is distinct from MDD. However, BD is associated with worse overall performance across various cognitive domains. At this time, recommendations to preserve cognitive function target known risk factors associated indirectly with cognitive decline such as hypertension, hypercholesterolemia, diabetes mellitus, etc. The relative neglect of the management of severe medical comorbidity associated with BD is a significant problem (38, 39). Expert consensus guidelines have begun to emphasize the need to better coordinate (or integrate) general medical with psychiatric care (40). An important consequence of better integrated care may be better quality of life through decreased physical burden and better cognitive function as these individuals age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by Public Health Service grants K23 MH 073772 (AGG), U01 MH68846 (BHM, AGG), R01 MH 084921 (AGG), R01 MH072947 (MAB), P30 MH71944 (CFR), and K24 MH069430 (BHM); the UPMC Endowment in Geriatric Psychiatry (CFR) and the John A. Hartford Center of Excellence in Geriatric Psychiatry (CFR).

The authors thank the staff of the Clinical Trials Management Unit of the Intervention Research Center and the Advanced Center for Intervention and Services Research for Late-Life Mood Disorders for their care of the patients in this study. The authors also thank Ms. Michelle Zmuda for the recruitment of control subjects and coordination of all neuropsychological assessments.

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Table 1
Neuropsychological domain scores of subjects with bipolar disorder (BD) or major depressive disorder (MDD)

	BD (n = 43)	MDD (n = 122)	Test statistics ^a (ANCOVA)
Delayed Memory (Logical memory (WMS-III), Rey-Osterrieth Complex Figure Recall, California Verbal Learning Test, Wisconsin Card Sorting Test)	-0.51 (1.04) LSMEANS = -0.63	-0.20 (0.83) LSMEANS = -0.16	Age: $F(1,160) = 27.69, p < 0.0001$ Education: $F(1,160) = 13.72, p = 0.0003$ Vascular burden: $F(1,160) = 1.14, p = 0.29$ BD vs. MDD: $F(1,160) = 9.97, p = 0.002$
Information Processing Speed/Executive Function (Trails A, Stroop, Executive Interview, Animal Fluency, Digit Symbol Substitution Test)	-1.00 (1.52) LSMEANS = -1.14	-0.40 (0.91) LSMEANS = -0.35	Age: $F(1,160) = 48.63, p < 0.0001$ Education: $F(1,160) = 13.98, p = 0.0003$ Vascular burden: $F(1,160) = 2.20, p = 0.14$ BD vs. MDD: $F(1,160) = 21.93, p < 0.0001$
Language (Spot the Word, Letter Fluency, Silly Sentences)	-0.64 (0.99) LSMEANS = -0.82	-0.23 (0.80) LSMEANS = -0.16	Age: $F(1,160) = 0.87, p = 0.35$ Education: $F(1,160) = 42.67, p < 0.0001$ Vascular burden: $F(1,160) = 5.74, p = 0.018$ BD vs. MDD: $F(1,160) = 22.90, p < 0.0001$
Visuomotor (Rey-Osterrieth Complex Figure Copy, Simple Drawings, Finger Tapping, Block Design, Trails B)	-0.74 (1.36) LSMEANS = -0.90	-0.27 (0.83) LSMEANS = -0.21	Age: $F(1,160) = 15.20, p = 0.0001$ Education: $F(1,160) = 18.24, p < 0.0001$ Vascular burden: $F(1,160) = 3.40, p = 0.08$ BD vs. MDD: $F(1,160) = 17.30, p < 0.0001$
Global Score: (Grooved Pegboard, Digit span, Boston Naming Test, Clock (in addition to tests listed above))	-0.80 (1.08) LSMEANS = -0.95	-0.27 (0.70) LSMEANS = -0.22	Age: $F(1,160) = 35.72, p < 0.0001$ Education: $F(1,160) = 30.64, p < 0.0001$ Vascular burden: $F(1,160) = 4.44, p = 0.037$ BD vs. MDD: $F(1,160) = 33.98, p < 0.0001$

All results are presented as raw mean (SD) and least square (LS) meanadjusted for age, education, and vascular burden. WMS-III = Wechsler Memory Scale-III.

^aTest statistics without controlling for education or vascular burden are: Delayed Memory [group: $F(1,162) = 4.92, p = 0.0279$], Information Processing Speed/Executive Function [group: $F(1,162) = 13.33, p = 0.0004$], Language [group: $F(1,162) = 7.77, p = 0.006$], Visuomotor [group: $F(1,162) = 8.50, p = 0.004$], and Global Score [group: $F(1,162) = 16.87, p < 0.0001$].

Table 2

Demographics and clinical characteristics of subjects with bipolar disorder (BD) or major depressive disorder (MDD)

	BD (n = 43)	MDD (n = 122)	Test, statistics
Age, years	74.0 (6.3)	74.3 (6.1)	$t(163) = -0.25, p = 0.80$
Male, n (%)	17 (39.5)	28 (23.0)	$p = 0.046^b$
Caucasian, n (%)	36 (83.7)	113 (92.6)	$p = 0.13^b$
Education, years	15.1 (3.5)	13.8 (2.6)	$t(58.2) = 2.32, p = 0.024^c$
Age at onset, years	35.6 (17.0) ^d	55.4 (20.7)	$t(162) = -5.57, p < 0.0001$
Cumulative Illness Rating Scale–Geriatric			
Total score	8.7 (3.5)	10.6 (3.5)	$t(163) = -3.13, p = 0.002$
No. of organ systems affected	6.0 (1.9) ^e	6.3 (1.9)	$t(150) = -0.87, p = 0.39$
Vascular subscale ^a	2.1 (1.6)	2.7 (1.4)	$t(163) = -2.31, p = 0.022$
HRSD-17 score	3.9 (2.8)	6.0 (2.5)	$t(163) = -4.48, p < 0.0001$
YMRS score	2.2 (2.5)	-	-
Pharmacotherapy, n (%)			
Antidepressant	25 (58.1)	122 (100)	$p < 0.0001^b$
Lithium	12 (27.9)	0 (0)	$p < 0.0001^b$
Divalproex	10 (23.3)	0 (0)	$p < 0.0001^b$
Other anticonvulsant	12 (27.9)	9 (7.4)	$p = 0.001^b$
Antipsychotic	6 (14.0)	6 (4.9)	$p = 0.08^b$
Sedative-hypnotic	3 (7.0)	7 (5.7)	$p = 0.72^b$
Cholinesterase inhibitor	2 (4.7)	0 (0)	$p = 0.07$

All results are presented as mean (SD) unless indicated otherwise. HRSD-17 = Hamilton Rating Scale for Depression-17 item; YMRS = Young Mania Rating Scale.

^a Items No. 1 and No. 2.

^b Fisher's exact test.

^c Satterthwaite test reported due to unequal variances.

^d n = 42.

^e n = 30.