Published in final edited form as:
Bipolar Disord. 2009 November ; 11(7): 744–752. doi:10.1111/j.1399-5618.2009.00739.x.

The longitudinal course of cognition in older adults with bipolar disorder

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Abstract

Objectives—Epidemiological studies suggest that elders with bipolar disorder (BD) may be at increased risk for dementia compared to the general population. We sought to investigate whether older adults with BD would present with more cognitive dysfunction than expected for their age and education, and whether they would experience a more rapid cognitive decline over three-year prospective follow-up.

Methods—Thirty-three subjects age ≥ 50, mean (SD) age 69.7 (7.9) years, with BD I (n = 28) and II (n = 5) had neuropsychological examination at baseline and longitudinally over three years. All subjects were administered the Dementia Rating Scale (DRS) when euthymic. Thirty-six mentally healthy comparators ('controls'), equated on age and education, were selected from ongoing studies in our research center examining the longitudinal relationship between late-life mood disorders and cognitive function.

Results—Compared to mentally healthy comparators, subjects with BD performed significantly worse on the DRS at baseline [mean (SD) 135.2 (4.7); n = 33 versus 139.5 (3.3); n = 36], and over follow-up [131.9 (7.7); n = 14 versus 139.1 (3.4); n = 22]. There was a group-by-time interaction between the subjects with BD and the controls [group × time: $F(1,64) = 5.07$, p = 0.028].

Conclusions—In our study, older adults with BD had more cognitive dysfunction and more rapid cognitive decline than expected given their age and education. Cognitive dysfunction and accelerated cognitive decline may lead to decreased independence, with increased reliance on family and community supports, and potential placement in assisted-living facilities.

Keywords

aged; bipolar disorder; cognition

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AGG, AB, SM, AVH, DJK and MAB have no conflicts of interest to report.

More than 30 cross-sectional studies have revealed cognitive impairments in mixed-aged adults with bipolar disorder (BD) that are present even with symptomatic recovery (1–4). Deficits have been identified in multiple cognitive domains, including information processing speed (5,6), executive function (5–10), memory (7,11–14), attention/concentration (15,16), and visual-spatial abilities (17,18). In turn, cognitive impairment has been associated with impairment in functional abilities (5,6,13). Epidemiologic studies have suggested that BD is associated with increased risk of developing dementia (19–21).

Despite the large number of cross-sectional studies, to our knowledge, there have been just six published studies on the longitudinal course of cognitive function in BD patients of any age (22–27), with only one study focused on older adults (23). This study by Dhingra and Rabins (23) used the Mini-Mental State Exam (MMSE) (28) to follow older patients for 5–7 years after they were hospitalized for mania. The investigators found that 8 (32%) of the 25 BD subjects followed-up experienced a decline in their MMSE to a score below 24 (indicating significant cognitive impairment), including 5 subjects (20%) who became so cognitively impaired that they required nursing home placement. Although no control group was included, this is ten-fold higher than the 1–2% expected incidence rate of dementia, given the age of these patients. Furthermore, the MMSE may have underestimated the level of cognitive dysfunction present in their subjects, since the instrument has low sensitivity to detect cognitive impairment in older adults with mood disorders (29).

More recently, Depp and colleagues (26) examined the ‘short-term’ course of neuropsychological abilities in middle-aged and older adults with BD. They examined 35 community-dwelling outpatients with BD (mean age 58 years) with a battery of neurocognitive tests, repeated once (1–3 years after baseline), comparing the performance with that of demographically matched samples of normal comparison subjects (n = 35) and patients with schizophrenia (n = 35). They found that patients with BD did not differ from normal comparators or patients with schizophrenia in the mean trajectory of change between time-points, but that the patients with BD showed more intra-individual variability over time than either comparison group. In their study, although subjects with BD or schizophrenia had mild/minimal levels of psychopathology, they were not specifically tested when stable or symptom-free.

The reports from middle-aged adults with BD present a mixed picture of stability or decline of cognition over longitudinal follow-up (22,24,25,27). The reports from Engelsmann et al. (24) and Balanza-Martinez et al. (22) in midlife subjects showed that impairments in cognitive function were present in memory (24) or overall cognitive function (22); however, no significant decline was evident over the three to six years of follow-up. When assessed in euthymic states, Mur and colleagues (27) observed stable cognitive deficits in executive function and information processing speed over two-year follow-up in patients treated with lithium as their primary mood stabilizer. In contrast, in Moorhead et al.’s study (25), 20 patients with bipolar I disorder (BD I) (mean age: 42 ± 9) and 21 controls (group-matched for age, gender, and premorbid IQ) underwent cognitive assessment and had MRI brain scans at baseline and four years later. Patients with BD showed a larger decline in hippocampal, fusiform, and cerebellar gray matter density over four years than control subjects. Reductions in temporal lobe gray matter correlated with decline in cognitive function (verbal IQ) and number of mood episodes during the follow-up period. Taken together, the reports from middle or older age suggest that cognitive impairments may manifest in early life, but significant decline may not be apparent until late middle or older age.

Not surprisingly, cognitive function is strongly associated with performance of ‘cognitive’ instrumental activities of daily living (IADLs) (e.g., medication management, managing finances, or home safety) and the ability to live independently (6). Determining whether elders

with BD genuinely exhibit accelerated cognitive decline is critical for investigators to design or optimize treatments targeting specific factors or subgroups of patients with BD. For instance, patients with BD who exhibit a specific pattern of cognitive impairment or a cluster of risk factors indicating a very high risk of further cognitive decline may be candidates for cognitive remediation or interventions designed to enhance cognitive function or halt decline. To clarify whether cognitive decline is 'accelerated' in older adults with BD, we have assessed a group of patients with BD over several years with the Dementia Rating Scale (DRS) (30), along with a group of age-equated, mentally healthy comparators. We decided to include both BD I and bipolar II disorder (BD II) in our investigation to describe the cognitive course of BD in older adults that may generalize to individuals in the community. Based on our prior research in bipolar and major depressive disorders (6,31,32), we hypothesized that subjects with BD would exhibit cognitive deficits in relation to age-matched, mentally healthy comparators and that they would exhibit faster decline over longitudinal follow-up. We secondarily examined whether the profile of cognitive function across the DRS subscales revealed greater levels of impairment or decline in attention, executive function, or memory in patients with BD.

Methods

Study subjects

As previously described, patients with BD I or II were recruited from outpatient clinics (n = 3) or treatment studies (n = 30) carried out at the University of Pittsburgh, Pittsburgh, PA, USA (33,34). All subjects provided written informed-consent, approved by the Institutional Review Board at the University of Pittsburgh, in accordance with the Helsinki Declaration of 1975. *Inclusion criteria* were: age 50 years or older; current BD I or II diagnosis; clinical euthymia for four weeks preceding neuropsychological (NP) assessment with scores of 10 or less on both the Hamilton Rating Scale for Depression-17 item (HRSD-17) (35) and Young Mania Rating Scale (YMRS) (36) at the time of assessment; ability to comprehend and speak English fluently; and corrected visual ability to read newspaper headlines and hearing capacity adequate to respond to a raised conversational voice. *Exclusion criteria* were: pre-existing history of dementia or neurologic disorder affecting the central nervous system (for example, Parkinson's disease, traumatic brain injury, or multiple sclerosis); electroconvulsive therapy within the past six months; and substance abuse or dependence within the past 12 months.

Diagnosis and treatment

Diagnosis was established by a Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-IV) administered by trained clinicians. Details on medication for subjects (n = 30) in the treatment studies have been described elsewhere (33,37). In brief, the goals of the pharmacotherapy intervention were to maximize the appropriate use of lithium or divalproex, either singly or in combination, to achieve remission of acute mood episodes, maintain euthymia, and limit adjunctive antipsychotic or antidepressant medication, except as judged clinically necessary by the study psychiatrist. Daily doses of lithium carbonate were typically in the range of 300–900 mg/day titrated to a plasma level of 0.5–1.0 mEq/L; divalproex doses were in the range of 500–1500 mg/day, titrated to a plasma level of 40–100 μg/mL. Except for trying to minimize polypharmacy, no specific restrictions were placed on the medications employed. The three subjects treated outside of the treatment studies received treatment consistent with what would have been received had they participated in the treatment studies.

Recruitment

Between March 1, 2003 and October 1, 2008, approximately 100 subjects with BD were screened. Seventy-five subjects met inclusion/exclusion criteria and consented to study participation. Of the 75 subjects who consented, 48 completed the baseline DRS and 27 withdrew consent or were withdrawn from the study for various reasons: unable to contact

(12), subsequent decision against study participation (6), unstable mood (3), unstable medical illness (3), English not first language (2), and incarceration (1). Of the 48 subjects with BD who had DRS assessment, 15 subjects did not yet have follow-up assessment data available, yielding a study group of 33 subjects with BD who were included in this analysis. Baseline DRS data from 15 of these subjects were included in a previously published report (32).

Comparators

Thirty-six age- and education-equated subjects with no psychiatric or neurologic history served as comparators ('controls') for the NP testing battery. We selected comparison subjects to make the groups similar in average age and education. We did not equate for overall medical burden because our research has not shown overall medical burden to be correlated with cognitive function in subjects with major depressive disorder (31,38). As described elsewhere, these subjects have been recruited through health fairs, advertisements in local papers, and ongoing projects studying the relationship between late-life mood disorders and cognitive function (31).

Assessment schedule

Subjects were assessed yearly with the DRS when stably euthymic. All subjects were outpatients at the time of assessment. The first testing with the DRS was set as the baseline testing. Follow-up testing was anchored to the nearest yearly interval. Subjects who were not euthymic at the time of their scheduled assessment had testing delayed for up to three months to reestablish euthymia. Subjects who did not reestablish euthymia within three months were not tested that year. Hence, testing results were not available annually on every subject. Data from all available assessments were included in this analysis.

Measures

Cognition was assessed using the DRS. This well-known and widely-accepted screening measure has demonstrated sensitivity and specificity in elderly individuals, including those with mood disorders (29). It assesses cognitive function in several domains, including attention, executive function (Initiation/Perseveration), visuospatial ability (Construction), abstraction (Conceptualization), and memory. We also examined the relationship between two illness course variables (age at onset and duration of illness) and baseline cognitive function or longitudinal change in the BD group. Age at onset was defined as age of first mood episode (depressive, manic, hypomanic, or mixed). Duration of illness was defined as age at onset subtracted from current age.

Procedures and statistical methods

We used SAS Software Version 9.2 (2008; SAS Institute, Cary, NC, USA) for statistical analyses. We compared BD and comparison subjects on each of the demographic and clinical variables using group *t*-tests for continuous measures and χ^2 or Fisher's exact test for categorical ones. The distributions of the continuous measures were examined prior to analyses; transformations were used, if necessary, to normalize the distributions.

To analyze the longitudinal DRS total scores, we employed a repeated-measures mixed-effects linear model with subject as a random effect and time as random and linear, rendering random slope. In our models, we assumed that missing data were 'missing at random.' Effect of group or time, and group × time interactions were examined. A significant group-by-time interaction would indicate that the change in DRS over time differed between the two groups.

To analyze the subscale scores, we used the age and education adjusted scaled scores due to ceiling effects when analyzing the raw subscale scores. For two subjects below age 56 (ages

52 and 54), we used the scaled scores for age 56, which is the minimum age available for adjustment. For eight subjects with BD who had more than 18 years of education, we used the scaled scores for 18 years of education, which is the highest education available for adjustment.

In this analysis, we examined the DRS scores over three years of follow-up because of the small numbers of subjects who have been followed for more than three years at this point. Of the 33 BD subjects, 11 (33.3%) had NP assessment at two time-points and 22 (66.6%) at three or more timepoints. Of the 36 comparators, 9 (25%) comparators had NP assessment at two time-points and 27 (75%) comparators at three or more time-points.

Results

Baseline characteristics of subjects with BD and comparators are displayed in Table 1. There were no significant differences in age, gender, race, or education. Subjects with BD had greater overall medical illness burden and showed a trend towards higher cardiovascular disease burden. Eleven subjects with BD had history of psychotic symptoms. Ten subjects with BD had history of alcohol use disorder (abuse or dependence). One subject had history of opioid abuse. Two subjects with history of alcohol use disorder also had history of psychotic symptoms. Table 2 displays the psychotropic medications taken by the subjects with BD at each assessment timepoint. Subjects with BD had significantly lower mean (SD) DRS scores than subjects with age- and education-equated comparators: 135.2 (4.7) (n = 33) versus 139.5 (3.3) (n = 36) (see Fig. 1), as indicated by a group effect [$F(1,64) = 21.28$, $p < 0.001$]. The mean DRS scores of both subjects with BD and comparators declined over the three-year follow-up to 131.9 (7.7) (n = 14) versus 139.1 (3.4) (n = 22), as indicated by a time effect [$F(1,67) = 4.44$, $p = 0.039$]. Subjects with BD experienced a faster decline than comparators, as indicated by a group × time interaction effect [$F(1,64) = 5.07$, $p = 0.028$]. Similar effects and interaction were observed when the analysis was repeated and limited to subjects with BD I (n = 28): group [$F(1,61) = 28.53$, $p < 0.001$], time [$F(1,62) = 8.52$, $p = 0.005$], and group × time interactions [$F(1,61) = 9.16$, $p = 0.004$]. There was no difference in cognitive performance among subjects with BD with or without history of psychosis: group [$F(1,17) = 0.09$, $p = 0.76$], time [$F(1,31) = 3.81$, $p = 0.06$], and group × time interactions [$F(1,17) = 0.01$, $p = 0.92$]. There were too few subjects in later years of follow-up to test differences in the subjects with BD based on history of alcohol use. However, from inspection we observed no difference in cognitive performance among subjects with BD with or without history of alcohol use disorder.

Including age, gender, education, general medical and cardiovascular burden in the repeated-measures mixed-model revealed age as a significant covariate [$F(1,64) = 8.24$, $p = 0.006$] and a trend for education [$F(1,64) = 3.91$, $p = 0.052$]. The following were not significant covariates: gender [$F(1,64) = 0.00$, $p = 0.960$], general medical [excluding cardiovascular burden; $F(1,64) = 0.38$, $p = 0.541$] and cardiovascular burden [$F(1,64)$]= 0.05, $p = 0.825$]. When controlling for age, education, general medical and cardiovascular burden, the effects for group [$F(1,64) = 22.72$, $p < 0.001$) and time [$F(1,67) = 4.13$, $p = 0.046$], and the group × time interactions [$F(1,64) = 5.18$, $p = 0.026$] remained significant.

To characterize the number of subjects with BD who declined, we employed the estimated slope of the comparison subjects from the mixed model, controlling for age, education, gender, cardiovascular and general medical burden. Using this method, there were 5 subjects (15%) with BD who exhibited stable cognitive function over follow-up (i.e., their scores remained within 0.5 standard deviations of the estimated slope of the comparison subjects) and 28 (85%) who declined (i.e., their scores deviated by more than 0.5 standard deviations from the estimate slope of the comparison subjects). Using a standard cutoff for dementia (DRS of 129) (39), three subjects started at or below the cutoff: one showed improvement with scores above 130 over follow-up assessments; one showed no change; and one showed deterioration, then some

improvement. Eight subjects had a score above the 129 cutoff at baseline and experienced a decline below this threshold over follow-up. There were no mentally healthy comparators scoring at or below the threshold of 129 at baseline or follow-up. Last, we examined the intra-individual variability among the trajectories between subjects with BD and comparators. Examining the change in DRS per year between the groups revealed a mean [SD; 95% confidence interval (CI)] change in the BD group of −1.1 (4.0; −2.5 to 0.3) versus 0.2 (2.4; −0.6 to 1.0) in the comparators [equality of variances $F(32,35) = 2.86$, $p = 0.003$]. There was greater variability among the BD versus comparator subjects.

We examined the DRS subscales of Attention, Conceptualization, Construction, Initiation/Perseveration, and Memory controlling for gender, general medical (non-cardiovascular) and cardiovascular burden. Although there was adequate distribution of the DRS total score (3 subjects at the top score in the comparator group and 1 in the BD group), as indicated in the Methods, ceiling effects necessitated the use of the subscale scores adjusted for age and education for these analyses (that did not control for age and education otherwise). Using the age/education adjusted subscale scores, our analysis revealed significant group, but not time, effects for Attention [$F(1,130) = 9.27$, $p = 0.003$) and Memory [$F(1,63) = 30.10$, $p < 0.001$) (subjects with BD performed worse on both subscales), and significant time, but not group, effects for Conceptualization [$F(1,130) = 6.68$, $p = 0.011$] (both groups showed improvement over time) and Initiation/Perseveration [$F(1,67) = 7.07$, $p = 0.010$] (both groups showed deterioration over time). Ceiling effects prevented examination of the Construction subscale. There were no group-by-time interaction effects detected for any of the subscales examined.

Illness course variables exhibited no relationship with baseline cognitive function or longitudinal decline in total DRS scores. Baseline DRS was not significantly correlated with either age at onset ($r_s = -0.12$, $p = 0.51$) or duration of illness ($r_s = -0.03$, $p = 0.83$). Similarly, longitudinal decline was not significantly correlated with either age at onset ($r_s = -0.31$, $p = 0.08$) or duration of illness ($r_s = 0.23$, $p = 0.22$).

To examine the potential neuroprotective or neurotrophic effects of lithium and divalproex, we divided the subjects with BD into those exposed to lithium or divalproex (n = 18) versus those not exposed (n = 15). With the exception of three subjects with less than six months exposure to lithium or divalproex, subjects in the lithium/divalproex group remained on lithium or divalproex for the duration of their follow-up. There was no significant difference between subjects exposed to lithium or divalproex versus those not exposed: group [$F(1,17) = 0.02$, $p = 0.877$), time [$F(1,31) = 4.28$, $p = 0.047$], group × time [$F(1,17) = 0.72$, $p = 0.409$]. Too few subjects were treated with either lithium (n = 9) or divalproex (n = 9) to examine each separately.

We examined the differences of the baseline demographic and clinical characteristics between completers and non-completers. We identified only current age as significantly different between completers [BD group: n = 14; mean (SD) age 72.7 (8.0) years; comparators: n = 22; 71.5 (7.2) years] and non-completers [BD group: n = 19; 67.5 (7.3)years; comparators: n = 14; 69.0 (7.5)] (ANOVA: completer $F = 4.38$, $p = 0.04$; patient type $F = 0.68$, $p = 0.94$; completer × patient type $F = 0.54$, $p = 0.47$). Older subjects were followed longerthanmore newly recruited younger subjects. No cognitive domain, including DRS total score, was different between completers and non-completers.

Discussion

Older adults with BD exhibit worse cognitive function and greater decline over time than mentally healthy comparators, equated on age and education. Further, when controlling for age, education, and cardiovascular burden, having a BD diagnosis was a significant predictor

of cognitive dysfunction and cognitive decline over time. Our findings extend the work conducted in midlife and older adults with BD, highlighting cognitive dysfunction as an important comorbidity to mood disturbance.

Our findings are in accord with Dhingra and Rabins (23), but differ from those of Depp and colleagues (26). Many subjects studied by Dhingra and Rabins (23) exhibited significant cognitive decline. By contrast, subjects with BD studied by Depp and colleagues (26) exhibited great variability in cognitive function, as our subjects exhibited, but essentially no change between baseline and follow-up, similar to their subjects with schizophrenia and normal comparators. Our subjects were on average 10 years older than those of Depp and colleagues —69.7 (7.9) years versus 57.7 (10.0). This suggests that the detrimental effects of BD on brain reserve capacity (40) do not become evident until older age. In addition, there may be a pattern of cognitive deficits that changes over the lifespan, characterized by subtle, fairly stable executive dysfunction and verbal memory impairment early on in the disorder and more prominent deficits in information processing speed later on in older age (4,41).

Many possible mechanisms may underlie cognitive deficits in older adults with BD. They include genetic (or possibly neurodevelopmental) abnormalities that are present early during the illness but cause cognitive deficits only later in life when combined with the effects of repeated mood episodes, medical comorbidity, substance use/iatrogenic effects, or aging (41). Given glial cell reductions shown in postmortem studies throughout the brain tissue of patients with BD, their brain tissue may be more vulnerable to toxic, metabolic, and ischemic insults throughout adult life (42–45). In turn, a decreased brain reserve associated with BD would show up as impaired cognitive function in older age and put patients with BD at greater risk for cognitive deterioration associated with age-related pathology (e.g., Alzheimer's disease, cerebrovascular disease, etc.).

Limitations of this study need to be acknowledged. First, subjects were followed naturalistically, and assessments were not completed annually in subjects who were not euthymic. Thus, not all subjects completed the three-year follow-up. However, comparing completers versus non-completers revealed no evidence suggesting retention of more cognitively impaired subjects in the BD group. Second, we cannot factor out practice effects. Nonetheless, comparing BD subjects and mentally healthy comparators should control for practice effects: BD subjects deteriorated faster than comparators regardless of practice. Third, the DRS does not provide the fine-grained assessment of performance across cognitive domains that would be available through more comprehensive NP assessment. Fourth, our subjects with BD had greater overall medical comorbidity than comparators. BD is now well recognized to be associated with high medical burden (46). In particular, BD is associated with circulatory disorders, obesity, and diabetes mellitus (47). Hence, it is difficult to disentangle medical burden from BD. However, our results were unchanged when we controlled for general medical burden or cardiovascular burden. Fifth, our two measures of illness course variables in the BD group were coarse and may have missed the effect of other important variables related to decline, such as number of mood episodes, history of psychosis, or number of hospitalizations. Additionally, the cognition of subjects with BD exposed to lithium and divalproex did not differ significantly from the cognition of those not exposed. Nonetheless, we cannot conclude that lithium and divalproex are not neuroprotective or neurotrophic given the small numbers of subjects at years 2–3 and their heterogeneity. Last, the marginally higher education and prevalence of cognitive enhancer use in the BD subjects compared to the healthy comparators may have attenuated the decline in the BD group. The use of cognitive enhancers in the treatment of BD reflects the interest of this research group in attempting to treat cognitive dysfunction in this patient population rather than an attempt to treat Alzheimer's type dementia (48).

Despite the limitations described, our findings build upon the studies of cognitive function of midlife patients with BD and extend them to older adults. Future investigations need to focus on the predictors of cognitive dysfunction to help personalize treatment, so that individuals with BD predisposed to cognitive dysfunction receive interventions to prevent, halt, or remediate their cognitive decline. During the past two decades, initiatives from the National Institute of Mental Health (NIMH) and Food and Drug Administration (FDA), such as Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) have advanced understanding the cognitive impairment associated with schizophrenia, paving the way for study of its remediation through pharmacologic or psychosocial approaches (49). We and other investigators (49) argue that similar efforts can and should be carried out to address cognitive dysfunction and disability associated with BD. Important areas of focus might include determining the longitudinal pattern of cognitive dysfunction to understand which cognitive domains are affected first, and what can be done to intervene and halt the progression at particular time points in the illness. Additionally, given the difficulties of completing long term follow-up studies, investigators studying BD, along with the assistance of the NIMH and FDA, may wish to develop a standardized NP assessment battery to deploy across research sites and studies.

Acknowledgments

Supported in part by Public Health Service grants K23 MH 073772 (AGG), T32 MH19986 (CFR, AGG), P30 MH52247 (CFR), P30 MH71944 (CFR), K23 MH67710 (MAB), K24 MH069430 (BHM), R01 MH072947 (MAB); the UPMC Endowment in Geriatric Psychiatry (CFR), John A. Hartford Foundation Center of Excellence in Geriatric Psychiatry (CFR), and the Commonwealth Center of Excellence for Bipolar Disorder from the Pennsylvania Department of Health, grant ME-02385 (DJK).

The authors thank the staff of the Clinical Trials Management Unit and the Geriatric Neuropsychology Research Program 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.

BHM has received research support or honoraria from AstraZeneca, Corcept, Eisai, Eli Lilly & Co., Lundbeck, Forest, GlaxoSmithKline, Janssen and Pfizer; and owns stock of less than $10,000 in value in Akzo-Nobel, Alkermes, AstraZeneca, Biogen Idec, Ceslsion, Elan, Eli Lilly & Co., Forest, General Electric, Orchestra Therapeutics and Pfizer. CFR has received research support in the form of pharmaceutical supplies for his NIH-sponsored research from GlaxoSmithKline, Forest, Pfizer, Eli Lilly & Co., Bristol-Myers Squibb and Wyeth.

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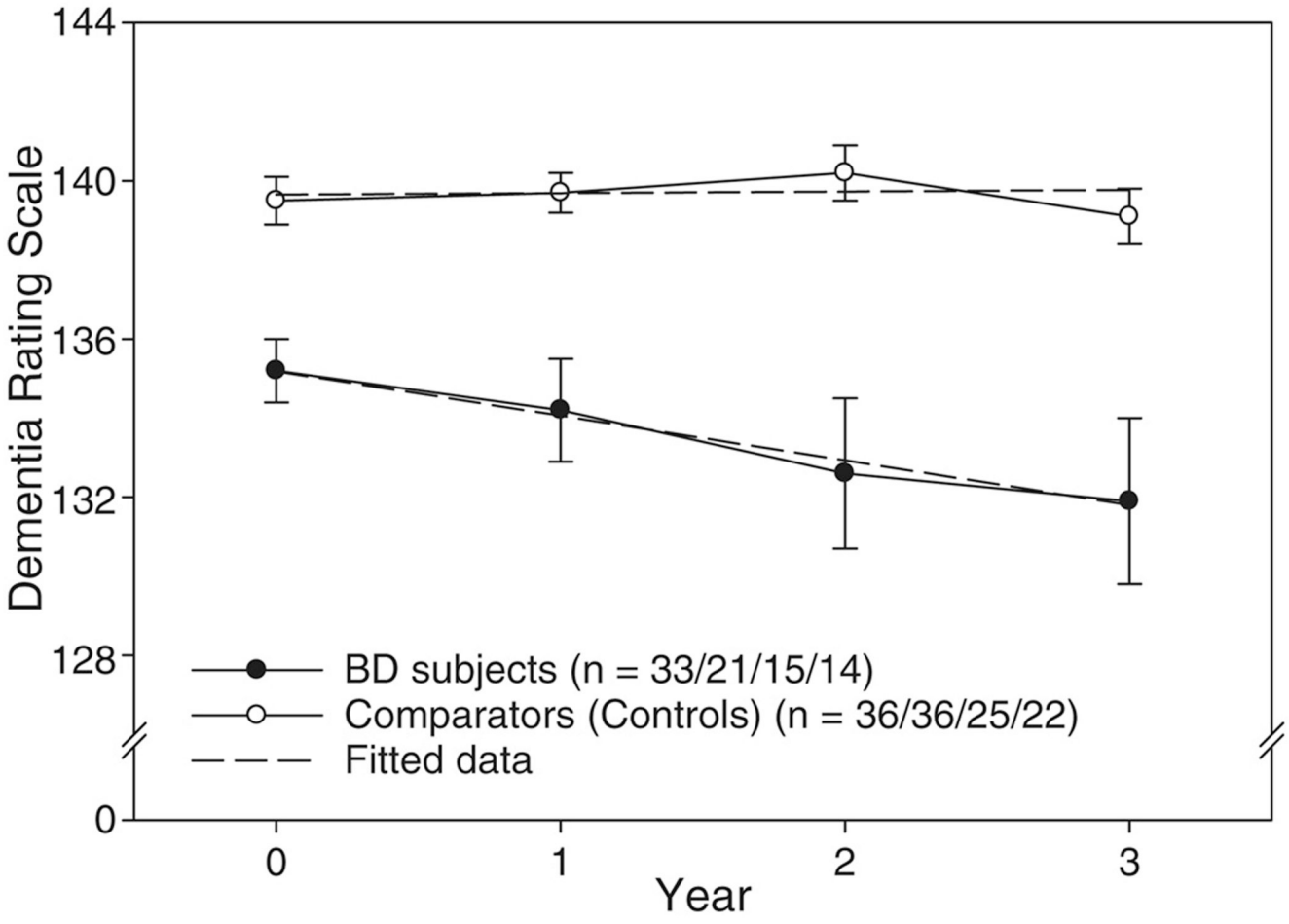

Fig. 1.
Observed and fitted Dementia Rating Scale (DRS) total scores in subjects with bipolar disorder (BD) and age- and education-equated comparators over up to three years of follow-up. Values reported as mean and standard error of the raw data.

Table 1

Demographic and clinical characteristics of bipolar disorder (BD) and comparator subjects

	BD subjects (n = 33)	Comparators ('controls') (n = 36)	*t*-test or χ^2
Age, years[a]	69.7 (7.9) Median = 66.8 Range [54.9–84.6]	70.5 (7.3) Median = 68.9 Range [52.6–84.0]	$t = -0.44$, df = 67, p = 0.66
Female, n (%)	24 (72.7)	20 (55.6)	$\chi^2 = 2.20$, df = 1, p = 0.14
Caucasian, n (%)	32 (97.0)	31 (86.1)	Fisher's exact test = 0.20
Education, years	15.2 (2.8) Median = 16 Range [9–20]	14.4 (2.9) Median = 14.5 Range [10–20]	$t = 1.11$, df = 67, p = 0.27
Cumulative Illness Rating Scale–Geriatric (CIRS-G) Total score[a]	9.5 (3.5) Median = 9 Range [3–20]	5.3 (3.5) Median = 4.5 Range [0–13]	$t = 5.09$, df = 67, p < 0.01
Count[a]	6.4 (2.1) Median = 6 Range [2–12]	3.6 (2.1) Median = 3 Range [0–8]	$t = 5.42$, df = 67, p < 0.01
Cardiovascular items scores (#1 + #2)	2.2 (1.5) Median = 2 Range [0–6]	1.5 (1.4) Median = 1.5 Range [0–5]	$t = 1.84$, df = 67, p = 0.07
Age at onset, years[b]	31.5 (16) Median = 25.0 Range [11–71]	–	–
Duration of BD, years[b]	38.8 (14.9) Median = 40.0 Range [0.6–63]	–	–

Values expressed as mean (SD) except where indicated otherwise.

[a] Means (SD) reported in their original units. Transformation used in the analyses.

[b] n = 31.

Table 2

Psychotropic medications employed in subjects with bipolar disorder (n) by assessment time-point

Psychotropic class	T0 (n = 33)	T1 (n = 21)	T2 (n = 15)	T3 (n = 14)
Mood stabilizer				
Lithium	9 (27)	6 (29)	2 (13)	3 (21)
Divalproex	9 (27)	6 (29)	4 (27)	4 (29)
Carbamazepine	2 (6)	0 (0)	1 (7)	1 (7)
Lamotrigine	4 (12)	2(10)	3 (20)	2(14)
Other[a]	1 (3)	2 (10)	1 (7)	0 (0)
Antidepressant	24 (73)	15(71)	12 (80)	10(71)
Antipsychotic	11 (33)	10 (48)	5 (33)	4 (29)
Anxiolytic/sedative	24 (73)	5 (24)	10 (67)	8 (57)
Sedative other[b]	5 (15)	1 (5)	3 (20)	2 (14)
Cholinesterase inhibitor	3 (9)	4 (19)	5 (33)	4 (29)
Cognitive enhancer other[c]	1 (3)	2(10)	2 (13)	2 (14)

Values expressed as n (%).

T0 = baseline; T1 = one-year follow-up; T2 = two-year follow-up; T3 = three-year follow-up.

[a] Mood stabilizer other: gabapentin, topirimate.

[b] Sedative other: trazodone or tricyclic antidepressant (used at subtherapeutic antidepressant dose).

[c] Cognitive enhancer other: memantine, methylphenidate, modafinil.