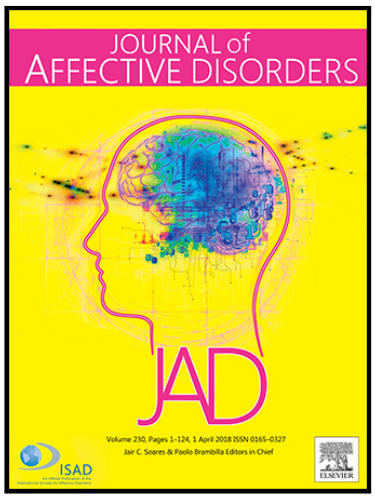

Cognitive impairment in late life bipolar disorder: risk factors and clinical outcomes

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Highlights

- Older patients with bipolar disorder display high risk of MCI or dementia
- We examined risk factors and correlates of MCI and dementia in older bipolar pts
- Impairments were associated with education, type I disorder, physical comorbidity
- Impairments predicted disability and aggressive behavior but not suicidality
- Cognitive impairments should be assessed among patient at high risk

Cognitive impairment in late life bipolar disorder: risk factors and clinical outcomes

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Abstract

Background. Late Life Bipolar Disorder (LLBD) is associated with a high prevalence of cognitive impairments, but few studies have examined their risk factors and clinical correlates

Methods. Participants with bipolar disorder older than 60 (n=86) were recruited from psychiatric outpatient and inpatients units. Patients were assessed with various instruments, including the Clinical Dementia Rating scale, the Montreal Cognitive Assessment and the Cumulative Illness

Rating Scale. The distribution of disorder-specific and general risk factors was compared between patients with LLBD plus cognitive impairments (mild cognitive impairment or dementia) and those with LLBD but no cognitive impairment. Analyses were first conducted at the bivariate level, then using multiple regression. The association with disability, aggressive behavior and suicidal ideation, was also explored.

Results. Cognitive impairments in LLBD were associated with a diagnosis of type 1 bipolar disorder (OR=6.40, 95%CI: 1.84 – 22.31, p=0.004), years of education (OR=0.79, 95%CI: 0.69 – 0.91, p=0.001) and a higher severity index relative to physical diseases (OR 26.54, 95%CI: 2.07 – 340.37, p=0.01). Moreover, cognitive impairments were associated with an increased likelihood of disability and recent aggressive behavior, but not suicidal ideation.

Limitations. retrospective design, conflation of MCI and dementia, not all subjects were in euthymia

Conclusions. In LLBD, the presence of cognitive impairments was associated with a diagnosis of type I bipolar disorder, lower education and more severe physical comorbidities. In turn, MCI or dementia were associated with increased disability and aggressive behavior. These findings may aid the identification of patients at risk for cognitive deterioration in everyday clinical practice.

Keywords. Bipolar disorder; old age; cognitive impairment; dementia; cardiovascular; disability

Word count: 3193

Contributors. MBM designed the study, performed statistical analyses and wrote the manuscript; MR, AB and NG contributed to design the study, clinical assessments and writing of the manuscript; LP, MB, BP, EDA, FS, VV, VT conducted clinical assessments and wrote the manuscript; FN and MA contributed to design the study and writing of the manuscript. All authors have approved the final article.

1. Introduction

Late life bipolar disorder (LLBD) is associated with significant cognitive impairments but little is known about its associated risk factors and clinical correlates.

Recent studies have made it clear that patients with LLBD display worse cognitive function compared with their peers (Sajatovic et al., 2015; Samamé et al., 2013; Young et al., 2006). When older patients with bipolar disorder are contrasted with healthy controls, in fact, they display multi-

domain neurocognitive deficits with medium-large effect sizes, slightly larger than those observed in younger cohorts (Aprahamian et al., 2014, 2013; Bourne et al., 2013; Gildengers et al., 2013, 2004; Sajatovic et al., 2015; Samamé et al., 2013). The dearth of longitudinal research on cognition in LLBD prevents from establishing whether such impairments are progressive or stable in time: available studies, in fact, are considered inconclusive either because of short follow up duration (not more than 3 years) or other methodological limitations (Sajatovic et al., 2015; Samamé et al., 2014). Nonetheless, population studies suggest that bipolar disorder is associated with a two-fold increased risk of developing dementia, even accounting for the role of multiple health-related risk factors (Diniz et al., 2017; Wu et al., 2013).

Understanding this phenomenon is complicated by the difficulty to disentangle pre-existing neurocognitive impairments from further decline: it is widely known that patients with bipolar disorder display varying degrees of impairments compared with age-matched non-bipolar subjects. Impairments involve working memory, executive functions, verbal memory, response inhibition and other domains, and are evident since adulthood (Bora, 2018; Bourne et al., 2013) or even earlier (Elias et al., 2017). Such deficits, however, may be stable, at least in the short-term. A recent meta-analysis of longitudinal studies examined the rate of cognitive decline in adults with bipolar disorder with a mean follow up of three years (range 1 – 9 years) and failed to detect significant differences from that of healthy controls (Bora and Özerdem, 2017). Of note, this is only apparently in contrast with the hypothesis of neuroprogression or “accelerated aging”, positing that multiple illness episodes predispose to neural and cognitive deterioration (Cardoso et al., 2015; Kessing and Andersen, 2004; Rizzo et al., 2014). Progressive deficits may in fact go undetected over the short term, and could also be confounded by differences in age at onset. LLBD, in fact, includes both older patients who were diagnosed in younger age and those who developed this condition in later adulthood. Late-onset bipolar disorder (LOBD) and early-onset bipolar disorder (EOBD) seem to be underlined by distinct pathogenesis, the former burdened by a greater load of medical comorbidities (Dols and Beekman, 2018; Sajatovic et al., 2015) and cognitive impairments than the latter (Samamé et al., 2013).

Cognitive impairment has been indicated as one of the most important predictors of real-world functioning in adult bipolar disorder (Orhan et al., 2018; Paans et al., 2018; Sajatovic et al., 2015). Nonetheless, it remains dramatically understudied and was recently identified as a priority for further research (Sajatovic et al., 2015). In the light of these premises, we sought to explore disorder-specific and other risk factors for cognitive impairment among patients with LLBD. We used a case-control design, that is, contrasted subjects with bipolar disorder and cognitive impairment with subjects with bipolar disorder but no cognitive impairment. The selection of candidate risk factors for cognitive impairments was based on recent studies conducted on the general population (Bellou et al., 2017; Knopman et al., 2018). Several putative mechanisms have been suggested to underlie cognitive deterioration in LLBD, including illness-specific factors

(Cardoso et al., 2015; Rizzo et al., 2014), or health-related factors, (Bellou et al., 2017). Thus we included factors acting at the general population level, i.e. socio-demographic factors, depression, benzodiazepine use, type 2 diabetes mellitus (T2DM), cardiovascular and cerebrovascular disease severity and treatments (Bellou et al., 2017). Also, we examined specific features of bipolar disorder, such as indicators of illness course, use of lithium and other psychotropic medications (Sajatovic et al., 2015).

As a secondary aim, we sought to explore the association of cognitive impairment with disability, suicidal ideation and aggressive behavior, three clinically relevant outcomes that predict hospitalization rates, poorer quality of life and increased healthcare costs (Ballester et al., 2014; Costa et al., 2015; A. Gildengers et al., 2013; Látalová, 2009; Lehmann and Rabins, 2006; Plans et al., 2019). In line with previous literature (Cardoso et al., 2015; Sajatovic et al., 2015) we hypothesized that among patients with LLBD, indicators of worse physical health and more severe illness course would be associated with a greater risk of displaying clinically significant cognitive impairments.

2. Methods

The study includes a case-control approach (outcome: presence of cognitive impairment or dementia, exposure: risk factors), and a cross-sectional approach, examining the association between cognitive impairment, other known predictors and three secondary clinical outcomes (disability, suicidal ideation and aggressive behavior).

2.1 Participants

Participants were recruited from consecutive admissions in the wards, or visits to the outpatient services of the Psychiatric Clinic of Policlinico S. Martino, Genoa, Italy in the years 2014-2017. The psychiatric clinic of Genoa has a specific experience with bipolar disorder and includes a Cognitive Disorders evaluation unit. Inclusion criteria were as broad as possible: diagnosis of type 1 or 2 bipolar disorder, age at recruitment of 60 or older, fluency in the Italian language and willingness to participate. Consistent with literature, we defined LOBD those who had the onset of bipolar disorder at age 50 or later, and the remainder as EOBD (Sajatovic et al., 2015). For patients with evidence of cognitive impairment (MOCA <24), completion of an in-depth interview of one or more informants (spouse, relative or cohabitants) was also required. The study was conducted in accordance with the Helsinki Declaration and approved by the local ethics committee; each patient gave written informed consent.

2.2 Psychiatric and General Medical Assessments

Participant assessment comprised a thorough psychiatric, medical and neurocognitive assessment aided by various sources of information, namely patients' informant, the treating psychiatrist from the local Community Mental Health Center, Primary Care Physician, available clinical charts and hospital records. Psychiatric diagnoses and comorbidities were obtained from the DSM 5 screener followed by the MINI interview. Features of bipolar disorder were evaluated with an ad-hoc structured interview focused on the illness course, adapted on the Structured Interview for Mood Disorder – Revised (SIMD-R) (Perugi et al., 2001). To increase reliability and minimize recall bias, we only focused on treatment and illness phases during to the five years preceding the interview. Among other information, the following was recorded: type and duration of illness episodes, treatments (including psychological treatment or psychotherapy, ECT treatment), hospitalizations and current level of functioning. Symptom severity was rated using the Montgomery-Asberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS). Predominant polarity in the past five years was calculated based on the most common definition in literature, that is a 2/3rds or higher prevalence of episodes (depression vs. manic/hypomanic) (Carvalho et al., 2014).

Participants underwent a medical interview and a physical examination where the following information was collected: medical history, treatments, lifestyle, anthropometric measurements, blood pressure. The Cumulative Illness Rating Scale (CIRS) was used to assess physical comorbidities: the Severity and Comorbidity indices were computed excluding item 14, which rates psychiatric conditions, and factoring out the role of cognitive impairment when rating item 12 (neurological) (Miller et al., 1992). Results of routine laboratory tests were also collected, including but not limited to blood count, metabolic parameters, electrolytes, thyroid, liver and renal functions.

All subjects were rated with the Clinical Dementia Rating scale (CDR) (Morris, 1993) and Montreal Cognitive Assessment (MOCA) (O'Bryant et al., 2010; Santangelo et al., 2014). Patients scoring 18 or higher in the MOCA underwent an in-depth neurocognitive assessment for further study. The cognitive assessments were conducted by psychiatrists under the supervision of expert clinical neuropsychologists (N.G., A.B.), as soon as the subject reached a phase of euthymia (defined as MADRS ≤8 and YMRS score <6) or, in any case, within a month of the start of the interview. This approach was chosen to minimize the impact of mood on cognitive performance. Researchers shared multiple evaluations at the beginning of the study to reach optimal inter-rater reliability.

2.3 Outcome definition

In the case-control part of the study, Mild Cognitive Impairment (MCI) was defined following the recommendations of the International Working Group on Mild Cognitive Impairment (Winblad et al., 2004). MCI requires the presence of cognitive deterioration with preservation of general and

instrumental activities of daily living. This criterion needed to be endorsed by both patients and informants, given the widespread presence of trait-like cognitive impairment in bipolar disorder (Bourne et al., 2013). Dementia was diagnosed using the DSM 5 criteria for Major Neurocognitive Disorder as operationalized in a recent study, that is, requiring the presence of impaired ADL or IADL (Salvadori et al., 2018).

In the cross-sectional part of the study, to explore the clinical impact of cognitive impairments in LLBD, three outcomes were considered: disability in activities of daily living was estimated from the sum of ADL and IADL scores (LaPlante, 2010), while suicidal ideation from the score of item 10 of the MADRS. Aggressive behavior was defined as any act of aggression in the month preceding the interview (including verbal, physical or towards objects). Information on aggressive behavior was obtained from direct ad-hoc questions to patients, caregivers and PCPs.

2.4 Statistical analysis

For the purpose of the cross-sectional part of the study, subjects with LLBD plus MCI were grouped with those suffering from LLBD plus dementia (LLBD+CI) and contrasted with cognitively intact LLBD subjects (LLBD-CI). To identify risk factors for cognitive impairment we first conducted univariate analyses by comparing continuous and categorical variables using chi-square and T-test. Variables associated at the stronger statistical significance level ($p<0.01$) were then entered in a multiple regression analysis to identify the most robust risk factors.

In the cross-sectional part of the study, we tested whether cognitive impairment was associated with selected clinical correlates (disability, suicidal ideation and aggressive behavior) first, by testing the association with known factors at the bivariate level, then entering significant ones in multiple regression analyses with stepwise backward selection. Values of R squared are reported: Nagelkerke for logistic regression, adjusted R squared for linear regression. Analyses were conducted with SPSS version 15.0.

3. Results

3.1 Sample characteristics

Eighty-six subjects with LLBD were recruited. Of these, 24 were diagnosed with MCI (27.9%) and fourteen with major neurocognitive disorder-dementia (16.3%). Together they comprised the LLBD+CI subgroup (n=38, 44.2%). The majority were cognitively intact (LLBD-CI, n=48, 55.8%). Only ten patients, four in the group with cognitive impairments, had not reached the formal criteria for euthymia when they underwent their cognitive assessment and displayed mostly residual depressive symptoms. Overall, subjects with LOBD did not display significant differences with EOBD in terms of gender, marital status, living accommodation, symptoms' severity or CIRS

scores, however subjects with LOBD were older and had lower education levels (p<0.01). Also, patients with LOBD were less frequently diagnosed with type 1 BD than those with EOBD (40% vs 65.2%, p=0.045).

3.2 Risk Factors associated with cognitive impairment

Patients with LLBD and cognitive impairment were compared to those with LLBD but no cognitive impairment (Table 1). The presence of cognitive impairment was associated with older age, lower levels of education, more frequent diagnosis of type 1 BD, older age at onset and, at statistical trend level, more severe manic symptoms (p=0.07). Considering physical health, those with LLBD+CI displayed higher CIRS severity and comorbidity index scores than LLBD-CI subjects. CIRS greater scores were driven by the severity scores of cardiologic (p=0.002), hypertension (p=0.003), vascular (p=0.04), respiratory (p=0.02) diseases. The most significant risk factors (associated at p<0.01 level) were entered into a multiple logistic regression analysis, while age of onset and CIRS comorbidity scores were not. In the resulting model (χ^2=79.9, df=4, p<0.001, R^2=48%) the presence of cognitive impairment was negatively associated with years of education (OR=0.79, 95%CI: 0.69 – 0.91, p=0.001) and positively with a diagnosis of type 1 LLBD (OR=6.40, 95%CI: 1.84 – 22.31, p=0.004) and with higher CIRS severity scores (OR 26.54, 95%CI: 2.07 – 340.37, p=0.01). Whereas, age did not show a significant association with the outcome (OR=1.08, 95%CI: 0.98 – 1.20, p=0.14).

3.3 Associations between cognitive impairment and secondary outcomes

Patients with LLBD+CI had greater levels of disability, and had displayed aggressive behavior more frequently than their counterparts. However, they did not display more severe suicidal ideation than LLBD-CI (Table 1).

At the bivariate level, the sum of ADL and IADL scores was associated with older age (r= -0.38, p<0.001), years of education (r= 0.40, p<0.001), type 1 diagnosis (type 1: 11.6 ±2.4; type 2: 12.7 ±2.3, p=0.04), CIRS severity scores (r= -0.25, p=0.02) and cognitive impairment but not with age of onset, the type of mood episode, MADRS or YMRS scores or other socio-demographic and clinical variables. Suicidal ideation was associated with living alone (57.1% vs. 27.8%, p=0.03) widowhood (35.7% vs. 11.1%, p=0.02), recent depressive episode (85.7% vs. 38.9%, p=0.001) and higher MADRS scores (15.5 ±11.6 vs. 32.2 ±5.2, p<0.001) but not with gender, age, education, diagnosis of type 1 BD, age of onset, cognitive impairment or CIRS scores. Recent aggressive behavior displayed significant associations with type 1 BD diagnosis (80.8% vs. 50.0%, p=0.008), most recent manic/mixed episode (69.2% vs. 31.7%, p=0.001), YMRS scores (15.9

±11.3 vs. 6.3 ±8.1, p=0.001) and cognitive impairment, but was not associated with gender, age, education, other sociodemographic factors, age of onset, MADRS and CIRS scores.

In stepwise regression, the sum of ADL and IADL scores was significantly associated with old age, education, diagnosis of type 1 BD and cognitive impairment (Table 2). In addition cognitive impairment was associated with a four-fold increased likelihood of displaying aggressive behavior in the past month, together with current manic episode. However, cognitive impairment did not contribute to explain the severity of suicidal ideation ($p>0.05$ at the bivariate level) that was instead associated with depression severity and widowhood.

4. Discussion

In older subjects with bipolar disorder, the presence of physical comorbidities, a diagnosis of type 1 bipolar disorder and lower education levels were associated with an increased likelihood of having MCI or dementia. Cognitive impairment, in turn, contributed to explain not only the burden of disability, but also that of aggressive behavior. To our knowledge, this study is the first to investigate the risk factors and correlates of cognitive impairment with a specific focus on LLBD.

In our sample, nearly half of the patients with LLBD displayed additional cognitive impairment, according to widely used operational criteria. This striking figure is in line with other studies showing that bipolar disorder is associated with a increased risk of developing dementia (Kessing and Nilsson, 2003; Wu et al., 2013) and varying degrees of cognitive dysfunction compared with the general population (Sajatovic et al., 2015; Samamé et al., 2013; Young et al., 2006). However, by comparing patients with LLBD with and without CI, we were able to identify one risk factor that is specific for this condition, namely the diagnosis of type I bipolar disorder. Compared with type II bipolar disorder, type I is not only characterized by more severe mood symptoms, but also by a slightly greater degree of cognitive impairment, that is already evident since adulthood (Bora, 2018; Dickinson et al., 2017). Worse performance involve, among others, the domains of executive functions, verbal memory and processing speed (Bora, 2018; Dickinson et al., 2017), and could explain the greater incidence of MCI and dementia in old age, even admitting that the two subtypes had similar rates of cognitive decline (Cipriani et al., 2017; Sajatovic et al., 2015; Samamé et al., 2014, 2013). In addition, recent studies suggest that the two subtypes of bipolar disorder may be also characterized by distinct neurobiological profiles (Atagün et al., 2018; Phillips and Swartz, 2014) and different underlying CNS activity during the same cognitive task (Abé et al., 2018). Lastly, even if we did not detect significant differences in these regards, a greater risk of cognitive impairment in type I BD may also depend on worse lifestyles or different medication regimens (Hunt et al., 2016; Schuch et al., 2016). For instance, type I BD may present with differences in benzodiazepine use (Karanti et al., 2015), time spent in depression

and/or social contacts, all of which have been recently appraised as robust risk factors for dementia in the general population (Bellou et al., 2017).

Cognitive impairment in LLBD was also associated with more severe physical diseases, specifically cardiovascular, and with lower levels of education. Both are recognized as significant risk factors for MCI and dementia in the general population (Bellou et al., 2017; Gorelick et al., 2011; Harrison et al., 2017) and, increasingly, among bipolar patients (Cipriani et al., 2017; Goldstein, 2017; Sajatovic et al., 2015). Education levels, together with premorbid IQ and intellectual activities in later life might help delay or prevent dementia in older adults, according to the cognitive reserve model (Grande et al., 2017; Hinrichs et al., 2017; Lee et al., 2018). Whereas, cardiovascular comorbidities may favor the onset of severe cognitive impairments through heterogeneous mechanisms that include cerebrovascular disease (Gunde et al., 2011; Lin et al., 2007), metabolic abnormalities (SayuriYamagata et al., 2017), inflammation (Lotrich et al., 2014; Rosenblat et al., 2015) and neurotoxicity due to HPA axis hyperactivity (Belvederi Murri et al., 2016). Lastly, some (Jakobsson et al., 2013; Rolstad et al., 2015), but not all studies (Forlenza et al., 2016) found evidence suggestive of neurodegenerative processes, such as increased levels of amyloid-related peptides.

The strengths of this study include a thorough medical and psychiatric assessments and the inclusion of a population that is largely representative of individuals with LLBD. However, findings must be interpreted in light of the study limitations: first, a small sample size, which may have precluded the detection of meaningful risk factors, such as older age or, notably, age of onset (Martino et al., 2018). Second, we did not adopt a prospective design, increasing the risk of recall bias in the collection of retrospective data; however, an attempt to control it was made by employing multiple sources of information and by focusing on a restricted time window. Third, the absence of subjects without a diagnosis of bipolar disorder, or the lack of separate analysis of EOBD and LOBD, which would have allowed to examine more in depth the differential role of risk factors in these populations. Fourth, despite a large number of comparisons, we did not correct analyses for multiple comparisons but used a conservative alpha level threshold to select risk factors to examine in further analyses. Fifth, although MCI and dementia were defined as changes from a previous level in cognitive functions, we cannot entirely exclude that pre-existing cognitive deficits may have partly confounded the results; similarly their conflation in a single group may have hindered the detection of specific risk factors.

In conclusion, a diagnosis of type I BD, lower levels of education and severe physical comorbidities were associated with an increased likelihood of cognitive impairment among patients with late life bipolar disorder. These preliminary findings may aid the early identification of patients with bipolar disorder at higher risk for cognitive impairment, and may favor the implementation of targeted assessment and monitoring procedures (Miskowiak et al., 2018) that may ultimately improve the outcomes of patients (Gitlin and Miklowitz, 2017).

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Conflicts of interest: none

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Table 1. Comparison between subjects with and without cognitive impairment

	LLBD (n=48)	LLBD with MCI/dementia (n=38)	Statistics
Sociodemographic			
Age	67.1 ±5.9	70.6 ±6.6	F=2.82, df=1, p=0.006 *
Gender, F	68.8	63.2	χ^2=0.30, df=1, p=0.59
Marital status, married	54.2	44.7	χ^2=0.81, df=2, p=0.67
Living alone	31.3	34.2	χ^2=0.09, df=1, p=0.77
Years of education	12.8 ±4.1	9.1 ±4.0	F=4.19, df=1, p<0.001 *
Currently employed	18.8	7.9	χ^2=2.08, df=1, p=0.15
Mental health			
Type 1 Bipolar disorder	37.5	76.3	χ^2=12.9, df=1, p<0.001 *
Age of onset first manic/hypomanic	33.5 ±13.5	41.3 ±16.2	F=3.01, df=1, p=0.02 *
Late onset (≥50 years)	14.6	34.2	χ^2=4.58, df=1, p=0.03 *
Current episode, depressive	39.6	55.3	χ^2=2.10, df=1, p=0.15
Current episode, manic/hypomanic	43.8	42.1	χ^2=0.02, df=1, p=0.88
Predominant polarity, depressive [a]	31.3	21.1	χ^2=1.13, df=1, p=0.29
Predominant polarity, manic/hypomanic [a]	31.3	39.5	χ^2=0.63, df=1, p=0.43
MADRS score during episode	17.2 ±12.1	19.6 ±12.8	F=0.89, df=1, p=0.37
YMRS score during episode	7.9 ±10.1	12.1 ±10.5	F=1.87, df=1, p=0.07
Lifetime lithium	60.4	55.3	χ^2=0.23, df=1, p=0.63
Lifetime antipsychotics	78.3	83.8	χ^2=0.40, df=1, p=0.53
MOCA total score	24.9 ±2.6	17.9 ±3.4	F=10.7, df=1, p<0.001 *
CDR total, median (range)	0 (0)	0.5 (2)	Z= -6.86, df=1, p<0.001 *
Physical health			
CIRS severity index	1.26 ±0.19	1.48 ±0.37	F=2.66, df=1, p=0.01 *
CIRS comorbidity index	1.04 ±1.09	2.08 ±2.06	F=2.43, df=1, p=0.02 *
Cigarette smoke	52.1	52.6	χ^2=0.003, df=1, p=0.96
Alcohol abuse	18.2	22.9	χ^2=0.26, df=1, p=0.61
Systolic pressure (mmHg)	120 ±19	126 ±20	F=1.36, df=1, p=0.18
Diastolic pressure (mmHg)	75.3 ±11.2	75.9 ±10.4	F=0.25, df=1, p=0.81
HDL, mg/100 ml	50.0 ±19.6	49.5 ±17.4	F=0.09, df=1, p=0.93
LDL, mg/100 ml	101 ±34	105 ±45	F=0.35, df=1, p=0.73
Cholesterol	168 ±55	174 ±57	F=0.43, df=1, p=0.67
Triglycerides	117 ±53	103 ±49	F=0.91, df=1, p=0.37
BMI	26.6 ±5.1	26.5 ±5.8	F=0.06, df=1, p=0.95
Diuretics	18.8	16.2	χ^2=0.09, df=1, p=0.76
ACE inhibitors	12.5	24.3	χ^2=2.01, df=1, p=0.16
Statins	23.4	11.1	χ^2=2.08, df=1, p=0.15
Cardioaspirin	22.9	21.6	χ^2=0.02, df=1, p=0.89
Beta-blockers	14.6	18.9	χ^2=0.28, df=1, p=0.59
NSAIDS	16.7	13.5	χ^2=0.16, df=1, p=0.69
Number of non-psychotropic drugs	2.63 ±2.10	3.08 ±2.36	F=0.91, df=1, p=0.37
Clinical correlates			
Disability [b]	13.2 ±1.5	10.6 ±2.7	F=5.3, df=1, p<0.001 *
Suicidal ideation [c]	1.19 ±1.74	1.14 ±1.58	F=0.15, df=1, p=0.88
Aggressive behaviour last month [d]	18.8	44.7	χ^2=6.8, df=1, p=0.009 *

a. Number of index episodes ≥ 2/3 of total mood episodes in the past five years; b. Sum of ADL and IADL score; c. MADRS item 10 score; d. Any act of aggression in the month preceding the interview (including verbal, physical or towards objects)

Table 2. Cognitive impairment as predictor of clinical outcomes

Correlate	***Predictor***	***Beta***	***95%CI***	***p***	***Model, p, R^2***
Disability (ADL+IADL)	Age	-0.11	-0.19; -0.04	0.004	F=13.1, p<0.001, 36%
	Years of education	0.12	0.005; 0.23	0.04	
	Type 1 LLBD	-1.08	-2.04; -0.12	0.03	
	Cognitive impairment	*-1.52*	*-2.55; -0.49*	*0.004*	
Suicidal ideation	MADRS total score	0.09	0.07; 0.11	<0.001	F=44.1, p<0.001, 51%
	widowhood	0.75	0.06; 1.45	0.04	
		aOR	***95%CI***	***p***	***Model, R^2***
Aggressive behavior	Manic episode	6.02	2.03; 17.83	0.001	χ^2=18.8, p<0.001, 28%
	Cognitive impairment	*4.51*	*1.53; 13.30*	*0.006*	