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Original Article

Cognitive impairment in later life in patients with early-onset bipolar disorder

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Objectives: Cognitive impairment may interfere with psychosocial functioning in bipolar disorder (BD). There is limited information regarding the cognitive function of elderly bipolar patients with onset at a young age. The present study aimed to investigate the frequency and the determinants of cognitive impairment in elderly early-onset bipolar patients.

Methods: Using the Clock-drawing Test (CDT), the Mini Mental State Examination (MMSE), and the Cognitive Abilities Screening Instrument (CASI), we examined euthymic patients with bipolar I disorder in Taiwan, aged 60 years and older. Clinical data were obtained by reviewing medical records and personal interviews with patients and their family members. The onset of BD prior to the age of 40 years is defined as 'early-onset'.

Results: Of the 52 early-onset patients, 42.3% were determined to have cognitive impairment by exhibiting either abnormal CDT or education-adjusted MMSE scores. In a multiple regression model, years of education and the age at the last manic/hypomanic (but not depressive) episode accounted for the greatest variance in both MMSE and CASI scores. While educational level and the age at the last manic/hypomanic episode were not considered in the regression model, onset with depressive syndrome and current age explained 21.5% of the variance in MMSE scores. Age at the first depressive episode, the first manic episode before the age of 40 years, and comorbid diabetes accounted for 16.7% of the variance in CASI scores.

Conclusions: There appeared to be a sizable proportion of elderly early-onset bipolar patients having cognitive impairment. It is suggested that clinical manifestation of first-onset affective episode and impact of medical comorbidity affect the cognition of early-onset BD in later life.

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Neuropsychological deficits are evident in euthymic bipolar patients of mixed ages (1). These deficits often lead to impairment of psychosocial and occupational functioning (2). The number of affective episodes and chronicity of the illness are associated with the cognitive impairment (3). However, illness severity of bipolar disorder (BD) and aging are not independent, so it is not easy to assess their respective impacts on neuropsychological deficits, especially in the elderly patient.

More than half of euthymic bipolar patients over the age of 60 years might exhibit neuropsychological deficits (4). Within the literature on older BD patients, the reported mean age of the first affective episode varies significantly, from < 30 years, up to 57 years (5). The onset of manic episodes past the age of 40 years should lead to the consideration of the possibility that both the symptoms and cognitive impairment may be due to neurological

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disorders or other general medical conditions (6, 7). Thus, patient's age at the onset of the illness might be used to define homogenous disorder subtypes (8) and must be taken into account when studying BD in later life (7). However, studies examining age at onset of BD have used different definitions of 'early' and 'late' (9–12). It is therefore difficult to relate findings from such studies.

Most of the available information on BD in elderly adults tends to focus on those patients whose first onset of mania occurred in later life (7). Common methodological problems in the published studies regarding elderly patients with BD are small sample sizes, retrospective chart review, lack of standardized measures, overemphasis on inpatients, and lack of longitudinal data (5). Furthermore, as early-onset bipolar patients are at high risk for early mortality (13–15), little is known regarding the correlates of the cognitive function of early-onset BD in late life. The cut-off age for 'late onset' is generally accepted to be approximately 50 years (7). Bellivier et al. (8) classified age-at-onset of BD into three subgroups and found that approximately 20% of bipolar patients had late-onset, which they defined as a mean age of 40.4 years. Therefore, 40 years as a cut-off point for early-onset age could represent those patients with a more typical onset age.

Bipolar disorder itself, the effects of aging, and co-existing medical morbidity may increase the risk of cognitive impairment in later life of early-onset patients (2–5). With these considerations in mind, we conducted this pilot cross-sectional study to examine the frequency and determinants of cognitive impairment in elderly bipolar patients with onset occurring before 40 years of age. It is hypothesized that patients with early-onset BD tend to be at risk for cognitive impairment in later life, and that psychopathological outcome along with medical comorbidity may contribute to cognitive impairment.

Methods

Study sample and procedure

From 1 August 2000 to 31 December 2003, this study was carried out at Taipei Medical University Hospital (TMUH) and Taipei City Psychiatric Center (TCPC), the latter being a Taipei Medical University-affiliated psychiatric teaching hospital providing beds for a total of 300 acute patients and 350 chronic patients. Utilizing the computer data files of the two hospitals, all patients were recruited on the basis of meeting the following criteria at the time of their entry into the study: (i) age 60 years and over; (ii) having a final diagnosis of DSM-IV (16) bipolar I disorder; and (iii) having at least one psychiatric admission to TCPC or TMUH before the start of the study. Patients with comorbid dementia due to other general medical conditions, neurological diseases, and active substance abuse were excluded. Written informed consent as approved by the Institutional Review Board of TMUH and TCPC was required from all those participating in this study.

A case-note form has been in use at TMUH and TCPC since 1980. This form contains over 95 items structured to obtain information regarding patients admitted to TCPC or TMUH, including demographic data, clinical features, physical illness, and family history. All medical records were reviewed, with all extracted data subsequently rechecked in order to rule out any potential individual errors. Both the participants and their reliable companions (mostly family members) were directly interviewed by two of the experienced psychiatrists involved in this study, using the Chinese-version of Structured Clinical Interview for DSM–III–R, patient edition (17) to confirm the diagnosis of bipolar I disorder as well as any prior history of psychiatric disorders.

The onset of bipolar I disorder was defined as the first occurrence of affective symptoms causing severe impairment of the subject's psychosocial functioning or symptoms necessitating hospitalization. This study defines the onset of BD prior to the age of 40 years as 'early-onset'.

Measurements of the patient's electrocardiography, body weight, body height, and blood pressure were undertaken at the time of the interview, and any significant physical illnesses which, without regular medical care, that were potentially life threatening were also recorded. The most recent affective episode before the time of their entry into the study was considered as the last episode.

A cerebrovascular disease risk/burden score (range: 0–7) was determined from a review by the authors of all consensus Axis III diagnoses, with each of the following diagnoses being given a score of 1 point: hypertension, diabetes, peripheral vascular disease, coronary artery disease, history of transient ischemic attack or stroke, atrial fibrillation, and carotid bruit (11).

Affective symptoms were assessed using the Young Mania Rating Scale (YMRS) (18) and the Hamilton Depression Rating Scale (HDRS) (19). In terms of inter-episode adjustment, the highest level of relational functioning for at least six months during the last year was rated by the Global Assessment of Functioning scale (GAF) (16) and the Strauss–Carpenter Scales (20), including

psychiatric symptoms, rehospitalization, work, and social adjustment.

Cognitive assessment

The cognitive tests were administered only in fully remitted outpatients. Patients with affective syndrome were prospectively followed up by researchers until those patients had YMRS total scores < 5 and HDRS total scores < 7 continuously for two months (21). Cognitive function was rated by trained assistants or authors using the Clock-drawing Test (CDT), the standardized Chinese version of the Mini Mental State Examination (MMSE) (22), and the Cognitive Abilities Screening Instrument (CASI) (23). The CDT was scored using the method described by Shulman (24), in which all patients are given a blank sheet of paper and asked to draw a circle, fill in the hours of a clock and draw in the hands to represent the time 10 min past 11 o'clock. Within the 5-level scoring system, a score ≥ 4 was given for minor visuospatial errors, thereby indicating normality, whereas a score < 4 indicated cognitive impairment.

Since the Chinese version of CASI is well validated (25), it provides a quantitative assessment of attention, concentration, orientation, short-term memory, long-term memory, language ability, visual construction, category fluency, abstract thinking, and judgment. The scores range from 0–100, with a higher score indicating better performance.

Statistical analysis

The *t*-test was used to compare the MMSE and CASI scores with each categorical variable as the independent variable. Pearson's product-moment correlations were then used to examine the relationship between the continuous variables and the MMSE and CASI scores. Given the exploratory nature of this study, the univariate analyses are presented without Bonferroni corrections. Finally, in order to investigate the contribution of the clinical variables with regard to the MMSE and CASI scores, the relevant variables found to be significant in univariate analyses were selected to enter into a multivariate regression analysis with either MMSE or CASI scores as the dependent variable. Dummy coding was used to include the nominal variables in the multiple regressions.

Results

Based on the computer search and chart review of the data files, a total of 156 bipolar patients, representing various ages at onset, met the inclusive criteria. Of these potential subjects, 82 went on to participate in this study, 15 died before the study began, 35 could not be located as a result of moving to a new address or changing their telephone number, and 24 refused to be interviewed for research purposes.

Socio-demographic and clinical characteristics

Following our review of the charts, we found comparable clinical characteristics between those participants with a cumulative age (mean $\pm$ SD) of 67.9 $\pm$ 6.6 years ($n = 82$), and those non-participants with a cumulative age of 70.9 $\pm$ 7.3 years ($n = 74$), including their mean age at the last follow-up, their mean lifetime number of affective episodes, and the total number of psychiatric hospitalizations (data not shown).

The participant group ($n = 82$) contained significantly more female patients ($n = 57$, 69.5%) than the non-participant group ($n = 39$, 52.7%) ($\chi^2 = 5.07$, $p < 0.025$) and more often lived with a spouse or with children ($n = 72$, 87.8%) than the non-participant group ($n = 55$, 74.3%) ($\chi^2 = 5.47$, $p < 0.025$). Moreover, the remaining participant subjects included four patients receiving assistance with daily living in a nursing home, five living alone, and one living with friend.

Of the 82 participants enrolled in this study, there were 52 early-onset patients who became the final experimental subjects with 7.4 $\pm$ 5.0 hospitalizations in their lifetime, 16 with onset at the age of 50 years or later as the 'late-onset' group, and 14 with onset between 40 and 50 years. In the early-onset group, 20 patients (38.5%) experienced a depressive episode at the illness onset, 48 patients (92.3%) were married/widowed and 46 patients (88.5%) lived with a spouse and/or child/children. Nine patients (17.3%) had an alcohol use problem and 39 patients (75%) experienced at least one depressive episode during their lifetime. There were 14 early-onset patients (26.9%) with a GAF score below 60, which is rated as 'clearly dysfunctional, unsatisfying relationships tend to predominate', and considered to have impaired psychosocial function.

Medical comorbidity and medication

The two principal types of medical morbidity in the early-onset group were cardiovascular diseases (ICD-9 codes 390–429) ($n = 29$, 55.8%) and metabolic/endocrine diseases (ICD-9 codes 241–279) ($n = 24$, 46.2%). Furthermore, 22 of the early-onset patients (42.3%) had only one cerebrovascular

disease risk score, and nine patients (17.3%) had two or more cerebrovascular disease risk scores. In terms of medication status, one patient had been drug-free for at least six months, and two patients had been medicated with antipsychotic drugs alone. Each of the remaining 49 patients had taken at least one mood stabilizer at the time of entry into the study, including lithium (n = 15), valproate (n = 9), carbamazepine (n = 4), lithium plus valproate (n = 8), lithium plus carbamazepine (n = 8), valproate plus carbamazepine (n = 3), and a combination of lithium, valproate and carbamazepine (n = 2); 28 patients were treated with a combination of an antipsychotic and mood stabilizer; 4 patients used one mood stabilizer with an antidepressant.

There were also 35 patients (67.3%) who had been given benzodiazepine or non-benzodiazepine sedative-hypnotics for more than one year. There was no significant relationship between the results of laboratory examination in the recent admission (including electrolytes, hematology, liver function test, renal function test, and thyroid hormone) and MMSE along with CASI scores (data not shown). The total scores of MMSE and CASI were also not affected by symptomatic severity (scores of YMRS and HDRS) and cerebrovascular disease risk/burden score (data not shown).

Cognitive function assessment

The mean ± SD MMSE (21.7 ± 6.5), CASI (74.1 ± 19.1) and CDT (3.8 ± 1.6) scores of the early-onset patients were comparable to the MMSE (23.6 ± 5.1), CASI (80.3 ± 14.3) and CDT (3.6 ± 1.4) scores of the patients with onset age over 50 years. Conventional cut-off points have been used by Folstein et al. (22) for the MMSE (23–24/30) and by Teng (23) for CASI (80–81/100); however, these have been shown to be less appropriate for those with limited education. Therefore, significant cognitive impairment is defined as exhibiting either abnormal CDT or education-adjusted MMSE scores (26).

Among the early-onset group, there were a total of 25 patients (48.1%) with MMSE scores <24, 27 patients (51.9%) with CASI scores <81, and 19 patients (36.5%) with CDT scores <4. Among patients with onset between 40 and 50 years, there were 8 patients (57.1%) with MMSE scores <24, 9 patients (64.3%) with CASI scores <81, and 7 patients (50%) with CDT scores <5.

Years of education had a significantly positive relationship with MMSE and CASI scores (Table 1). Based on previous Chinese reports (27), MMSE cut-off scores of 17/18, 20/21, and 23/24 were subsequently used for 6 years or less, 9 years, and ≥ 10 years of schooling, respectively. There were 22 patients in the early-onset group (42.3%) having either abnormal CDT scores or education-adjusted MMSE scores and were therefore identified as having significant cognitive impairment.

Table 1 summarizes the results of the analyses of the relationship between the various factors and the overall test scores. The psychosocial function

Table 1. Correlation between clinically continuous variables, Mini Mental State Examination (MMSE) and Cognitive Abilities Screening Instrument (CASI) in early-onset bipolar patients over the age of 60 years (n = 52)

		MMSE		CASI	
Continuous variables	Mean (SD)	γ	p	γ	p
Age (years)	66.0 (65)	−0.40	0.003	−0.39	0.004
Years of education	7.0 (5.7)	0.58	< 0.001	0.59	< 0.001
Age (years)					
At onset	27.1 (6.1)	−0.13	NS	0.02	NS
First manic episode	30.9 (8.9)	0.17	NS	0.12	NS
First depressive episode	31.6 (11.5)	−0.38	0.01	−0.32	0.04
First psychiatric hospitalization	37.3 (14.0)	−0.12	NS	−0.7	NS
Recent psychiatric hospitalization	58.5 (8.2)	−0.26	0.08	−0.31	0.04
Last manic/hypomanic episode	60.6 (8.8)	−0.43	0.004	−0.50	0.001
Last depressive episode	56.3 (12.3)	−0.29	NS	−0.301	0.09
Length of last cycle (years)	2.7 (5.1)	0.21	NS	0.30	0.04
Years of use:					
Lithium (n = 46)	10.2 (8.3)	0.28	0.06	0.21	NS
Carbamazepine (n = 30)	4.6 (4.5)	0.11	NS	−0.01	NS
Antipsychotics (n = 47)	8.7 (7.3)	−0.01	NS	−0.30	0.04
Valproate (n = 26)	2.9 (2.4)	0.22	NS	0.25	NS
Lifetime number of affective episodes	19.4 (13.4)	−0.22	NS	−0.27	0.05
Global Assessment of Functioning scores	69.6 (12.2)	0.414	0.002	0.63	< 0.001
Strauss–Carpenter score	10.8 (3.4)	0.32	0.02	0.54	< 0.001

Table 2. Mini Mental State Examination (MMSE) and Cognitive Abilities Screening Instrument (CASI) by subgroup with dichotomous variables in early-onset bipolar patients over the age of 60 (n = 52)

	MMSE			CASI		
Dichotomous variables	Mean (SD)	*t*	p	Mean (SD)	*t*	p
Gender						
Female (n = 39)	20.8 (7.1)	−2.668	0.01	71.2 (20.4)	−2.615	0.01
Male (n = 13)	24.5 (2.8)			82.9 (11.0)		
Onset with depressive syndrome						
No (n = 32)	20.1 (6.0)	−2.341	0.02	69.9 (16.3)	−2.069	0.04
Yes (n = 20)	24.3 (6.4)			80.8 (21.5)		
First manic episode before the age of 40 years						
No (n = 6)	26.8 (2.6)	2.14	0.04	90.1 (5.2)	5.058	<0.001
Yes (n = 46)	21.0 (6.5)			72.0 (19.2)		
Comorbid diabetes mellitus						
No (n = 36)	22.6 (6.2)	1.578	NS	77.8 (16.3)	2.094	0.04
Yes (n = 16)	19.6 (6.8)			66.2 (22.5)		
Increased frequency of recurrence within the past 5 years						
No (n = 34)	22.2 (6.9)	0.936	NS	77.8 (18.2)	2.080	0.04
Yes (n = 18)	20.4 (5.8)			66.0 (19.4)		

Degrees of freedom = 49.

variables, both GAF and Strauss–Carpenter score, had a positive relationship with MMSE as well as CASI scores, respectively. We further examined whether there was any correlation between age and any of the continuous variables listed in Table 1 with Pearson's product-moment correlation. It revealed that chronological age had a significant correlation with age at the last manic/hypomanic episode ($\gamma = 0.715$, $p < 0.0001$) and with age at the initiation of lithium prophylaxis ($\gamma = 0.611$, $p < 0.0001$).

Factors associated with MMSE and CASI scores

The effects of the categorical variables on the mean MMSE and CASI scores are summarized in Table 2. The early-onset patients whose first manic episode occurred after the age of 40 years had significantly higher mean MMSE scores than the remaining patients. The mean MMSE and CASI scores of patients with smoking habits (28.8%), co-existing diabetes mellitus (30.8%), or hypertension (25.0%) were comparable to those of patients without such conditions (data not shown).

Of those independent variables with statistical significance in the univariate analysis, the age at the last manic/hypomanic episode and years of education collectively accounted for the greatest variance in the MMSE scores (adjusted $R^2 = 0.503$, $F = 16.70$, $p < 0.001$), with age at the last manic/hypomanic episode accounting for 37.3% of the variance, followed by years of education (an additional 13%). Similar to the MMSE model, the age at the last manic episode explained 46.5% of the variance in CASI scores, followed by years of education accounting for an additional 12.2% (adjusted $R^2 = 0.587$, $F = 21.58$, $p < 0.0001$).

While current age and only psychopathology-related variables were considered, the age at the last manic/hypomanic episode, onset with depressive syndrome, and current age accounted for the greatest variance in the MMSE scores (adjusted $R^2 = 0.595$, $F = 16.19$, $p < 0.001$). Furthermore, the age at the last manic/hypomanic episode and the first manic episode before the age of 40 years had the greatest validity for predicting CASI scores (adjusted $R^2 = 0.523$, $F = 16.87$, $p < 0.001$). However, age at the most recent mania may be confounded by the chronological age. While educational level and the age at the last manic/hypomanic episode were not considered in the regression model, onset with depressive syndrome and current age explained 21.5% variance in MMSE scores (adjusted $R^2 = 0.215$, $F = 7.98$, $p < 0.001$). Age at the first depressive episode, the first manic episode before the age of 40 years, and comorbid diabetes accounted for 16.7% of the variance in CASI scores (adjusted $R^2 = 0.167$, $F = 3.73$, $p < 0.025$).

Discussion

Our study of elderly people with early-onset BD suggested that cognitive impairment may be present in approximately 50% of these patients in their euthymic state, regardless of the various cut-off ages for early-onset. However, using an interview schedule and MMSE, a survey of

community-dwelling elders aged 65 years or older in Taipei showed that the prevalence rate of dementia was merely 1.7% (26). Therefore, in comparison to demographically and geographically similar elderly persons, our results confirmed that cognitive impairment does exist in a large proportion of euthymic elderly patients and does not appear to be due to the effects of active illness (28).

Though our subjects had an average of 7 years of education, our rate for the whole bipolar sample exhibiting cognitive deficits is similar to that (44%) of American elderly bipolar patients with comparable age and a mean 15 years of education, who were also tested with the MMSE (4). This finding indicates that BD may routinely result in older patients being persistently impaired in various neurocognitive functions. On the other hand, this discrepancy in educational level should be emphasized when estimating the prevalence of cognitive impairment and discerning its risk factors among various ethnic groups with mental illness in late life.

Without considering the effect of educational level and the recent manic/hypomanic episode, our analyses found that early-onset manic episode (before the age of 40 years), the first depressive episode at older age, and comorbid diabetes are associated with lower CASI scores in elderly bipolar patients. Furthermore, bipolar illness onset with depression and younger age at cognitive measurement are associated with higher MMSE scores. Taken together, our findings imply that clinical manifestation of affective episode at onset and medical comorbidity, particularly diabetes mellitus and its complications, could affect the cognitive function of bipolar patients in later life.

A later age for the last manic/hypomanic episode may also contribute to lower cognitive measures among elderly early-onset bipolar patients, unlike a reported study of bipolar patients with wide age range (18–70 years) (28). Our results, similar to the study reported by Beyer et al. (29), did not support any influence on cognitive function by number of previous affective episodes or age at onset. One possible explanation is that retrospective memory of age at onset and episode frequency is often inexact for elderly patients (29), particularly with early-onset. Furthermore, mild forms of manic episodes are common in elderly bipolar patients and are probably diagnosed as hypomania (30); therefore, the last hypomanic episode was taken into consideration in this study. Age is an important risk factor for developing cognitive impairment in elderly people, regardless of the presence of BD. Caution is recommended with respect to the fact that the confounding effect of chronological age on the age at the last manic/hypomanic episode could not be excluded entirely.

In terms of illness onset as a depressive episode in early-onset patients, our rate came very close to the 40% reported in a similar Western study (12). Within our early-onset sample, the age at the onset of BD appeared to be more in line with the results previously reported for younger bipolar samples (31). The rate of positive first-degree family history of BD is within the 23–57% range estimated in the literature (5). Moreover, 26.9% of our sample having GAF scores below 60 is very close to 26% reported for a group of European patients with a mean age of 68 years (32). In this predominantly female sample, the existence of gender differences in medical morbidity and outcome may limit the generalizability of our findings. However, it has been consistently found that older people with BD are more likely to be female, by a ratio of about 2:1 (5). Approximately one out of six of the early-onset bipolar patients had two or more cerebrovascular risk factors, which is close to 24% in a Western geriatric bipolar study (11) and indicates that a substantial proportion of older bipolar patients bear a high risk of cerebrovascular disease. These aforementioned clinical features suggest that the present sample is representative of early-onset bipolar groups in other reported studies.

There is a higher false-positive rate in the assessment of cognitive deficits among poorly-educated elderly people. With regard to the effect of level of education, the total scores of MMSE were affected, whereas some CASI domains, long-term memory and orientation, were not (33). Therefore, for a poorly-educated and non-English-speaking group, the CDT is able to identify probable dementia cases with better sensitivity and specificity than either the MMSE or CASI scores (34). The existing literature suggests that the cognitive profile of BD is characterized by persistent deficits in either mnemonic or executive abilities, or a combination of these two functions (35). Thus, we used the MMSE and CASI in conjunction with the CDT to measure such functions and increase the sensitivity and specificity of the cognitive screening process.

The present study had two major strengths. First, alcohol or substance use disorder comorbidity was low among our patients, although such a phenomenon may be attributable to the high ratio of female subjects in our study. Previous reports on patients with BD in a number of Western countries had estimated the comorbidity of alcohol or drug use disorders as being in excess of 30% (31). The factors contributing to cognitive function in BD that have emerged from the present sample could

be less contaminated by substance use and its consequent problems. Second, most of the patients in this study lived at their own residences, with more than 90% of the patients being married and living with their families. The Western studies on early-onset BD found that 36–50% of patients lived alone, and that 25–40% were either divorced or separated in later life (11, 36). Thus, it may be assumed that Taiwanese patients receive more favorable home care.

Several methodological shortcomings should also be mentioned. First, most patients had received several medications at varying dosages. Though the literature is inconsistent with regard to benzodiazepine use and its association with cognitive decline (37), the fact that benzodiazepines, or hypnotics are often given to our patients for a longer period of time may confound cognitive measurement. Furthermore, our analysis suggested that long-term treatment with lithium may be more likely to reduce any recurrences, and thereby may indirectly prevent cognitive impairment, rather than result in such impairment due to its neurotoxic effects. Therefore, it remains uncertain what the effects of medication on cognition might be, particularly over time. Second, recall bias is more common in patients who are interviewed at a later age, particularly for information regarding the first episode. Thus, we did not emphasize the impact of the subtype and age of the first affective episode on MMSE scores. Additionally, individual variations with relevance to the risk of cognitive impairment, such as combination treatment with other prescribed drugs, a family history of dementia, and eating habits, had not been specifically examined in this study. Third, without any comprehensive neurological test battery, some mild forms of cognitive decline might have been overlooked by this study. Fourth, the present study did not use the education-adjusted CASI score to assess the cognitive function. Finally, the absence of non-bipolar patients within our sample limited the generalizability of our finding.

Patients with early-onset BD are very likely to have cognitive impairment in later life. In addition to lower educational level, we suggest that bipolar illness onset with mania before the age of 40 years and the first depression in later age may place patients at higher risk for subsequent cognitive impairment in late life. On the other hand, awareness and management of risk factors for diabetes and its complications are important to protect patients against cognitive dysfunction and premature mortality. Cross-national comparisons of BD in late life, particularly among clearly distinct ethnic groups, are necessary to identify differences and similarities in the aging process of BD across populations and to clarify ethnically- and racially-independent correlates of cognitive impairment that are inherent to the illness.

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References

1. Murphy FC, Sahakian BJ. Neuropsychology of bipolar disorder. Br J Psychiatry 2001; 178: 120–127.
2. Harvey PD, Powchik P, Parrella M, White L, Davidson M. Symptom severity and cognitive impairment in chronically hospitalized geriatric patients with affective disorders. Br J Psychiatry 1997; 170: 369–374.
3. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry 2004; 75: 1662–1666.
4. Gildengers AG, Butters MA, Seligman K, McShea M, Miller D, Mulsant BH, Kupfer DJ et al. Cognitive functioning in late-life bipolar disorder. Am J Psychiatry 2004; 161: 736–738.
5. Depp CA, Jeste DV. Bipolar disorder in older adults: a critical review. Bipolar Disord 2004; 6: 343–367.
6. Cassidy F, Carroll BJ. Vascular risk factors in late onset mania. Psychol Med 2002; 32: 359–362.
7. Shulman KI. Mania and cerebrovascular disease. In: Chiu E, Ames D, Katona C eds. Vascular Disease and Affective Disorders. London: Martin Dunitz, 2002: 235–244.
8. Bellivier F, Golmard JL, Rietschel M, Schulze TG, Malafosse A, Preisig M et al. Age at onset in bipolar I affective disorders: further evidence for three subgroups. Am J Psychiatry 2003; 160: 999–1001.
9. Broadhead J, Jacoby R. Mania in old age: a first prospective study. Int J Geriatr Psychiatry 1990; 5: 215–222.
10. Sajatovic M. Aging-related issues in bipolar disorder. A health services perspective. J Geriatr Psychiatry Neurol 2002; 15: 128–133.
11. Wylie ME, Mulsant BH, Pollock BG, Sweet RA, Zubenko GS, Begley AE et al. Age at onset in geriatric bipolar disorder. Effects on clinical presentation and treatment outcomes in an inpatient sample. Am J Geriatr Psychiatry 1999; 7: 77–83.
12. Shulman KI, Tohen M, Satlin A, Mallya G, Kalunian D. Mania compared with unipolar depression in old age. Am J Psychiatry 1992; 149: 341–345.
13. Tsai SY, Lee CH, Kuo CJ, Chen CC. A retrospective analysis of risk and protective factors for natural death in bipolar disorder. J Clin Psychiatry 2005; 66: 1586–1591.
14. Tsai SY, Kuo CJ, Chen CC, Lee HC. Risk factors for completed suicide in bipolar disorder. J Clin Psychiatry 2002; 63: 469–476.
15. Ösby U, Brandt L, Correia N, Ekbom A, Sparén P. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001; 58: 844–850.
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edn (DSM-IV). Washington, DC: American Psychiatric Association, 1994.

17. Spitzer RL, Williams JBW, Gibbon M, First MB. Structured Clinical Interview for DSM-III-R. Patient edition (SCID-P). Washington, DC: American Psychiatric Press, 1990.
18. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978; 153: 429–435.
19. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23: 56–62.
20. Strauss JS, Carpenter WT. The prediction of outcome in schizophrenia: characteristics of outcome. Arch Gen Psychiatry 1972; 27: 739–746.
21. Strakowski SM, DelBello MP, Fleck DE, Adler CM, Anthenelli RM, Keck PE Jr et al. Effects of co-occurring alcohol abuse on the course of bipolar disorder following a first hospitalization for mania. Arch Gen Psychiatry 2005; 62: 851–858.
22. Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–198.
23. Teng EL. Cross-cultural testing and the Cognitive Abilities Screening Instrument (CASI). In: Yeo G, Gallagher–Thompson D eds. Ethnicity and the Dementias. Washington, DC: Taylor & Francis, 1996: 77–85.
24. Schulman KI. Clock-drawing: is it the ideal cognitive screening test? Int J Geriatr Psychiatry 2000; 15: 548–561.
25. Liu HC, Fuh JL, Wang SJ, Liu CY, Larson EB, Lin KN et al. Prevalence and subtypes of dementia in a rural Chinese population. Alzheimer Dis Assoc Disord 1998; 12: 127–134.
26. Zhang MY, Katzman R, Salmon D, Jin H, Cai GJ, Wang ZY et al. The prevalence of dementia and Alzheimer's disease in Shanghai, China: impact of age, gender, and education. Ann Neurol 1990; 27: 428–437.
27. Yeh EK, Hwu HG, Chang LY, Yeh YL. Life time prevalence of cognitive impairment by Chinese-Modified NIMH Diagnostic Interview Schedule among the elderly in Taiwan communities. J Neurolinguistics 1990; 5: 83–104.
28. Cavanagh JTO, Beck MV, Muir W, Blackwood DHR. Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. Br J Psychiatry 2002; 180: 320–326.
29. Beyer JL, Kuchibhatla M, Payne ME, Moo-Young M, Cassidy F, Macfall J et al. Hippocampal volume measurement in older adults with bipolar disorder. Am J Geriatr Psychiatry 2004; 12: 613–620.
30. Young RC, Klerman GL. Mania in late life: focus on age at onset. Am J Psychiatry 1992; 149: 867–876.
31. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press, 1990.
32. Angst J, Preisig M. Course of a clinical cohort of unipolar, bipolar, and schizoaffective patients. Results of a prospective study from 1959 to 1985. Schweiz Arch Neurol Psychiatr 1995; 146: 7–16.
33. Meguro K, Ishii H, Yamaguchi S, Sato M, Hashimoto R, Meguro M et al. Prevalence and cognitive performances of clinical dementia rating 0.5 and mild cognitive impairment in Japan. Alzheimer Dis Assoc Disord 2004; 18: 3–10.
34. Borson S, Brush M, Gil E, Scanlan J, Vitaliano P, Chen J et al. The clock drawing test: utility for dementia detection in multi-ethnic elders. J Gerontol A Biol Sci Med Sci 1999; 54: 534–540.
35. Ferrier IN, Thompson JM. Cognitive impairment in bipolar affective disorder: implications for the bipolar diathesis. Br J Psychiatry 2002; 180: 293–295.
36. Meeks S. Bipolar disorder in the latter half of life: symptom presentation, global functioning and age of onset. J Affect Disord 1999; 52: 161–167.
37. Prince M, Rabe-Hesketh S, Brennan P. Do antiarthritic drugs decrease the risk for cognitive decline? An analysis based on data from the MRC Treatment Trial of Hypertension in Older Adults. Neurology 1998; 50: 374–379.