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Research report

Risk factors for cognitive impairment in elderly bipolar patients

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ABSTRACT

Objective: Cognitive impairment in elderly bipolar patients persists during euthymic state, yet the aetiology of such impairment is not well understood. The objective of this study is to identify factors contributing to cognitive impairment in elderly patients with bipolar disorder.
Method: 119 older patients (age >60) with bipolar I or II disorder in a euthymic state were extensively tested on cognitive functioning including attention, memory, visuoconstruction, executive function and verbal fluency with regard to potential risk factors.
Results: Regression analysis shows that health related factors, medication and illness characteristics are associated with cognitive impairment in several cognitive domains: attention, memory, visuoconstruction, executive function and verbal fluency. More vascular burden factors are related to poorer outcome of cognitive functioning. Patients with lithium pharmacotherapy performed worse compared to those with other mood stabilizers, but this was no longer significant in multivariate analysis.
Conclusions: In elderly bipolar patients, more vascular risk factors and more hospital admissions are associated with more cognitive impairment.

1. Introduction

Many studies have demonstrated that aged patients with bipolar disorder have impaired functioning across a range of cognitive domains (Young et al., 2006), even after resolution of mood symptoms. Cognitive dysfunction in elderly patients with bipolar disorder is consistent with results obtained in younger patients with bipolar disorder, which include deficits in attention, memory and executive functioning (Robinson and Ferrier, 2008).

However, cognitive decline is not an inevitable consequence of bipolar disorder. There is a great variability in the level of cognitive functioning among elderly bipolar patients. It appears that, while some patients may be more prone to long term cognitive decline, other patients retain normal functioning. Cognitive impairment may have many adverse effects, including hampering compliance to treatment strategies, so effort should be made to prevent such a decline. However, the aetiology of cognitive impairment in bipolar disorder is not well understood. A number of factors may, directly or indirectly, influence cognitive functioning, firstly, the potential neurotoxic effects of the disorder itself (Vieta et al., 2008). For instance cognitive impairment is found to be associated with a worse prior course of illness, particularly the number of manic episodes, hospitalizations and the length of illness (Kessing and Andersen, 2004). Also the presence of subsyndromal symptoms appears to influence the general level of cognitive functioning of bipolar patients. Even few residual depressive symptoms are known to have impact on cognitive performance (Ferrier et al., 1999; Clark et al., 2002). Secondly, neurodegenerative changes that can accompany the normal aging process may explain cognitive decline in bipolar patients. Vascular risk factors may cause cognitive impairment, as there is a higher cerebrovascular risk in elderly bipolar patients and the late-onset group has a higher vascular risk compared to the patients with an early onset (Subramaniam et al., 2007). With respect to neurodegenerative disorders some studies suggest that the risk of

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developing dementia seems to increase with the number of episodes in bipolar disorder. Thirdly, potential toxic agents, like medication and the consumption of alcohol may play a role. Pharmacotherapy, especially lithium, has been associated with poorer performance on tests of memory and motor speed (Pachet and Wisniewski, 2003). It has also been shown that alcohol abuse which is highly prevalent in individuals with bipolar disorder, worsens the course of illness and may also cause cognitive deficits (van Gorp et al., 1998).

The purpose of this study was to investigate whether demographic characteristics, bipolar illness characteristics, vascular burden and potential toxic effects of medication and alcohol were associated with functioning in important neuropsychological domains such as attention, verbal memory, visuoconstruction, executive functioning and verbal fluency. We hypothesized that bipolar patients with a longer and more severe course of illness and more cerebrovascular risk factors have greater cognitive impairment and that these different factors independently influence cognitive functioning.

2. Method

2.1. Sample

Included were 119 older patients (>60 years) with bipolar-I and bipolar-II disorder, who were currently euthymic (Schouws et al., 2009). Since most of the bipolar patients reside in the community, we focused on outpatients. Patients were recruited from outpatient clinics in four regions in the Netherlands. With help from the Dutch bipolar patient association (VMDB, Association for Manic Depressives and their Relatives) extra patients were recruited. Extensive care was taken to exclude patients with current mood symptoms, which could influence cognition. Eligible subjects were reported to be euthymic for at least three weeks by their psychiatrist. Excluded were patients with a primary diagnosis of alcohol dependence or substance abuse and patients with dementia according to DSM-IV criteria. Lithium (66% of the patients), valproid acid and carbamazepine were the typical medications for the remitted patients in this study. Among the 119 patients only 7 subjects (6%) did not use any medication. Of the 119 patients 94 (79%) had a Bipolar-I diagnosis, 19 (16%) a Bipolar-II diagnosis and 6 (5%) a rapid cycling disorder. The study was approved by the institutional review board and written informed consent was obtained from all subjects.

2.2. Measurements

Clinical diagnosis of bipolar disorder was reached using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996). Current depressive symptoms were assessed using the Centre for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) and current mania symptoms with the Young Mania Rating Scale (YMRS) (Young et al., 1978). Illness characteristics such as age of onset and medication were derived from patient interviews and hospital medical records. In our analysis age of onset was defined as age at which the first mood episode occurred. The presence of somatic *chronic diseases* was assessed by asking respondents whether they currently or previously had any of the following chronic diseases or disease events: cardiac disease (including myocardial infarction), peripheral artherosclerosis, stroke, diabetes mellitus, COPD (asthma, chronic bronchitis or pulmonary emphysema), arthritis (rheumatoid arthritis or osteoarthritis) or cancer. Answers were coded as either 'yes' or 'no' for each of these diseases. Compared to general practitioner information, the accuracy of self-reports of these diseases was shown to be adequate and independent of cognitive impairment (Kriegsman et al., 1996). For this study a cerebrovascular risk score (range 0–2; 0 = 0 risk factors, 1 = 1 risk factor and 2 = more than 1 risk factor) was determined as follows: respondents were asked whether they currently or previously had any of the following chronic diseases or disease events: disease of circulatory system (myocardial infarction, angina pectoris, heart failure, and cardiac dysrhytmia), hypertension, history of ischemic attack or stroke and diabetes. Answers were coded as either 'yes' or 'no' for each of these diseases. Premorbid intelligence was estimated using the Dutch Reading Test for Adults (NLV), the Dutch version of the New Adult Reading Test (NART) (Nelson and O'Connell, 1978). The Mini Mental State Examination (MMSE) (Folstein et al., 1975) was used to provide an overall assessment of cognitive functioning.

All subjects completed a comprehensive battery of neuropsychological tests grouped into five cognitive domains.

(a) *Attention*: Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1981), Trail Making Test part A (Reitan, 1958) The Amsterdam Short Term Memory Test (ASTM) (Schmand and Lindeboom, 2005).
(b) *Learning and memory:* The 10 Words Test, a modified version of the Auditory Verbal Learning Test (Rey, 1964).
(c) *Visuo constructional ability*: Figure Copying subtest of the Amsterdam Dementia Screening Test (ADS6) (Lindeboom and Jonker, 1989), and Clock Drawing (Shulman et al., 1993).
(d) *Executive functioning*: Trail Making Test part B (Reitan, 1958), Modified version of the Stroop Color Word Test (Golden, 1978), Mazes (1 to 4) subtest of the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 1976), and the Rule Shift Cards subtest of the Behavorial Assessment of the Dysexecutive Syndrome (Wilson et al., 1996).
(e) *Verbal fluency*: Control Oral Word Association Test (COWAT) (Benton and Hamsher, 1976), Animal and Occupation Naming subtest of the Groningen Intelligence Test (GIT) (Luteijn and van der Ploeg, 1983).

2.3. Statistical analyses

Composite scores for each neurocognitive domain were calculated by converting the subject's raw scores to standardized z scores. The *z* scores were then summed in each domain to provide a single score. Higher scores indicated better neurocognitive performances.

To test the impact of illness characteristics on cognitive functioning in bipolar patients, Pearson's correlations and hierarchical regression analysis were carried out. Clinical variables that were hypothesized to influence cognitive