The Maudsley Bipolar Disorder Project: The Effect of Medication, Family History, and Duration of Illness on IQ and Memory in Bipolar I Disorder

Stuart Donaldson, R.M.N., B.A., B.Sc. Psychology; Laura H. Goldstein, Ph.D.; Sabine Landau, Ph.D.; Vanessa Raymont, M.D.; and Sophia Frangou, M.D., Ph.D.

Background: Despite the growing recognition of the importance of cognitive impairment in psychiatric disorders, the effect of clinical factors, such as medication use and family history of affective disorders, on cognition in bipolar I disorder patients still remains unclear. This study examines the contribution of known and potential predictors to both general intellectual function and memory in a representative population of bipolar I disorder patients.

Method: Of the 425 patients receiving treatment within a defined catchment area, 63 were identified as having bipolar I disorder. Of these patients, 43 were enrolled in the study and participated in a personal interview by a psychiatrist. All patients were invited to participate in a personal interview by a psychiatrist, and information on family history, past psychiatric history, past and current treatments, duration of illness, and age at onset was collected, in addition to demographic data. Cognitive performance was assessed using the Wechsler Adult Intelligence Scale-Revised, the National Adult Reading Test, and the Wechsler Memory Test III.

Results: Forty-three patients with DSM-IV bipolar I disorder were enrolled into the Maudsley Bipolar Disorder Project. Patients on treatment with antipsychotic drugs had a lower current full scale IQ, lower general memory scores, and lower working memory scores. A family history of affective disorders was associated with a higher full scale IQ, but not with either general or working memory measures. Duration of illness was negatively associated with general memory scores, but had no effect on either IQ or working memory measures.

Conclusion: Current antipsychotic medication, duration of illness, and family history of affective disorder were the most significant predictors of IQ and memory function in bipolar I disorder patients.

(J Clin Psychiatry 2003;64:86–93)

Received March 21, 2002; accepted June 7, 2002. *From the Section of Neurobiology of Psychosis (Mr. Donaldson and Drs. Raymont and Frangou), the Department of Psychology (Dr. Goldstein), and the Department of Biostatistics and Computing (Dr. Landau), Institute of Psychiatry, De Crespigny Park, London, England.*

The authors report no financial affiliation or other relationship relevant to the subject matter of this article.

Corresponding author and reprints: Sophia Frangou, M.D., P066-Section of Neurobiology of Psychosis, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK (e-mail: s.frangou@iop.kcl.ac.uk).

Many psychiatric disorders have been associated with impairment in cognitive function, and, since this is known to influence functional outcome, there is a growing interest in the factors that affect cognition.[1,2]

In bipolar disorder, cognitive impairment has been reliably shown in symptomatic patients,[3] and evidence for trait deficits is mounting.[4–6] It has been suggested that between 30% and 50% of patients with bipolar disorder experience significant social disability that may be linked to persistent cognitive impairment.[2,7] The number of studies that have tried to identify potential determinants of cognitive deficits in bipolar disorder is limited. However, there is some empirical and theoretical evidence for the relationship of a number of factors to disease-induced impairment. Cognitive deficits may be more persistent the longer the duration of illness or the higher the number of episodes,[8] although these relationships have not always been confirmed.[4] In addition, an effect of a history of psychosis has been noted, although findings are ambiguous, with some studies reporting a negative effect[9,10] or none at all.[11,12]

There are several explanations for these often conflicting results. First, patients with bipolar disorder are commonly prescribed antipsychotic medication, as well as a host of other agents including lithium, anticonvulsants, and antidepressants. The effect of these drugs (and their combination) on cognition is still unclear, despite a surge of research examining this issue in other disorders, particularly in schizophrenia.[13] There are, however, long-standing concerns about the possible negative impact of treatment with lithium,[14] and it is, therefore, possible that medication plays an important role in the cognitive deficits observed in bipolar disorder. Second, the pattern of the observed cognitive impairment is related to the level

of psychopathology experienced by patients at the time of testing. Acutely symptomatic bipolar disorder patients show performance decrements in most cognitive tests, and there is some suggestion that memory and executive function may be affected even in the presence of residual symptoms.[3,4] Third, family history of affective disorders (or its absence) may be another source of heterogeneity in the cognitive profile of patients with bipolar disorder. This hypothesis has not been tested directly; however, the observed differences in the clinical presentation of patients with and without a family history of bipolar disorder suggest the possibility of differences in cognitive profile. For example, bipolar disorder patients with a family history of affective disorders usually have an earlier age at onset,[15,16] more psychotic symptoms,[17] possibly more episodes,[18] and higher levels of comorbidity.[17] Fourth, sample selection may also increase the variance in the nature and degree of the cognitive impairments noted in bipolar disorder.

In view of the above, the aim of the present study was to examine the contribution of recognized (age at onset, duration of illness, psychopathology, and history of psychosis) and likely predictors (medication and familiality) to general intellectual function and memory in a representative treatment sample of bipolar I disorder patients.

METHOD

Patient Identification

We performed a 1-month prevalence survey of all patients (N = 425) receiving treatment within a defined catchment area of the South London and Maudsley National Health Service (NHS) Trust. The surveyed service provides secondary psychiatric care for a population of 67,650 patients aged between 15 and 64 years. All case notes were screened; however, only those patients whose case notes showed unambiguously that they fulfilled *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[19] operational criteria for bipolar I disorder were included in the study. Patients without at least 1 clearly documented manic episode or who may have had psychosis in the absence of significant affective symptoms were not included. For those patients identified as fulfilling criteria for bipolar I disorder (N = 63), diagnostic status was also confirmed with their treating physicians. This study was part of the Maudsley Bipolar Disorder Project, an ongoing case-control examination of cognition, brain structure, and brain function of a catchment area treatment sample of bipolar I disorder patients. The study was approved by our local ethics committee, and informed consent was obtained from all subjects prior to participation.

Clinical Assessment

Following enrollment into the study, all patients who agreed to enroll in the study (N = 43) were invited to participate in a personal interview by a qualified psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorders,[20] the 31-item Hamilton Rating Scale for Depression (HAM-D),[21] and the Mania Rating Scale (MRS) from the Schedule for Affective Disorders and Schizophrenia-Change Version.[22]

Demographic data were systematically obtained and included gender, age, years of education, paternal and personal (best-ever) socioeconomic status (determined using the Standard Occupational Classification[23]), current employment, marital status, and ethnicity. Family history was obtained using the Family Interview for Genetic Studies,[24] and information about past psychiatric history, past and current treatment, duration of illness, and age at onset (defined as the age when subjects first experienced an episode of either polarity) was collected. Cognition was assessed when patients were either euthymic or in remission. Patients were described as being in remission if they were clinically stable according to their treating physician for at least 3 months prior to assessment and had been on the same treatment regimen over the same period of time. In addition, patients were characterized as euthymic if they had a total HAM-D score and a total MRS score below 10 when assessed.

Neuropsychological Assessment

Cognitive function was assessed using a number of tests. In this article, we report only those tests for which there are standardized normative data, namely, the Wechsler Adult Intelligence Scale-Revised (WAIS-R; 7-subtest version incorporating the digit span, vocabulary, arithmetic, similarities, picture completion, picture arrangement, and block design subtests),[25] the National Adult Reading Test (NART),[26] and the Wechsler Memory Test III (WMS-III).[27] The WAIS-R was chosen in preference to the Wechsler Adult Intelligence Scale-III in view of the standardization of the NART against the WAIS-R, which permits a comparison of estimated premorbid and current IQ scores. As yet, no such comparison is possible between the NART and WAIS-III. The WMS-III was chosen in preference to an earlier version of the Wechsler Memory Scale in view of its greater fractionation of memory functions and, in particular, its incorporation of a measure of working memory abilities.

Statistical Analysis

The aim of the statistical analysis was to explore the relationship between the hypothesized potential predictors and cognitive variables. The following variables were considered as potential predictors: age at onset, duration of illness, total scores on the HAM-D and MRS, lifetime presence of psychotic symptoms, positive family history for affective disorders, and type of medication at the time of testing. Age at onset, duration of illness, HAM-D scores, and MRS scores were used in regression models

Table 1. Demographic and Clinical Characteristics of 43 Bipolar I Patients

Characteristic	Value
Age, mean (SD), y	42.9 (11.1)
Gender, N (%), male:female	20 (47):23 (53)
Education, mean (SD), y	13.12 (2.89)
Duration of illness, median (IQR), y	16.0 (19.0)
Age at onset, mean (SD), y	25.5 (9.2)
Mania Rating Scale total score, median (IQR)	0.0 (1.0)
HAM-D total score, median (IQR)	7.0 (13.0)
Global Assessment of Functioning score, mean (SD)	70.79 (15.07)
Patients with past psychotic episode, N (%)	34 (79.1)
Patients negative for substance abuse, N (%)	38 (88.4)
Patients with positive family history for affective disorders, N (%)	32 (74.4)

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, IQR = interquartile range.

Table 2. Current Medication of 43 Bipolar I Patients

Type of Medication	N (%)
Any antipsychotic	22 (51.2)
Atypical antipsychotic	12 (27.9)
Typical antipsychotics	10 (23.3)
Any mood stabilizer	30 (69.8)
Lithium	15 (34.9)
Sodium valproate	7 (16.3)
Carbamazepine	6 (14.0)
Other anticonvulsant	2 (4.7)
More than 1 mood stabilizer	5 (11.6)
Any antidepressant	8 (18.6)
Tricyclic antidepressant	3 (7.0)
SSRI antidepressant	5 (11.6)
Two or more psychotropics of different classes	20 (46.5)

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

as continuous variables; antipsychotic use, mood stabilizer use, antidepressant use, psychotic symptoms, and family history were used as binary variables. The correlation structure of the cognitive variables of our sample was explored to identify outcome variables that represented different areas of neuropsychological ability, and the number of cognitive variables was reduced accordingly. Pearson correlation coefficients were then used to estimate and test the association between each potential predictor and each selected outcome. In the final step, explanatory variables that were found to predict cognitive variables singly at the 5% significance level were considered empirical predictor variables and combined in a multiple regression model. These multiple regression analyses were then used to estimate and test the correlation between empirical predictor variables and cognitive measures after adjusting for other empirical predictors.

RESULTS

Subjects

We identified 63 patients with bipolar I disorder (26 patients [41%] were male). Their mean age was 42 years (range, 20–70 years). For the majority of patients, best-ever occupation was consistent with social class II (20.6%) or III (47.6%). Of the 63 patients identified, 43 agreed to participate in the Maudsley Bipolar Disorder Project. Those patients that agreed to participate in the study did not differ in age ($t = 0.09$, $df = 61$, $p = .9$), gender distribution ($\chi^2 = 0.68$, $df = 1$, $p = .4$), years of education ($t = -1.40$, $df = 61$, $p = .1$), age at onset ($t = 0.49$, $df = 61$, $p = .6$), duration of illness ($t = 0.9$, $df = 61$, $p = .3$), or history of psychosis ($\chi^2 = 0.8$, $df = 1$, $p = .3$) from those that refused.

Table 3. Mean IQ and Memory Scores in Bipolar I Patients (N = 43)

IQ/Memory Test	Mean (SD)
WAIS-R	
Full scale IQ	101.16 (16.19)
Verbal IQ	99.85 (14.55)
Performance IQ	102.40 (18.62)
Premorbid full scale IQ (NART)	105.76 (11.92)
WMS-III memory index	
Auditory immediate	90.93 (15.77)
Visual immediate	89.18 (17.10)
Auditory delayed	94.04 (16.97)
Visual delayed	90.07 (18.24)
Auditory recognition delayed	89.88 (15.01)
Immediate	88.23 (16.43)
General	89.86 (17.23)
Working	94.93 (19.33)

Abbreviations: NART = National Adult Reading Test, WAIS-R = Wechsler Adult Intelligence Scale-Revised, WMS-III = Wechsler Memory Test III.

Clinical Characteristics

The demographic and clinical characteristics of the participants are shown in Table 1. Only 2 patients had an MRS score above 10 and were therefore just above the cutoff point for a manic episode. Seventeen patients had a HAM-D score above 10, and the median score was 7. The patients' medication at the time of their neuropsychological assessment is summarized in Table 2. Almost all patients on current antipsychotic treatment (21/22) had a history of psychotic symptoms when in episode. The mean ± SD dose of antipsychotic medication at the time of testing was 384.5 ± 457.4 chlorpromazine equivalents. The mean doses of mood stabilizers were 936.3 ± 222.3 mg for lithium, 833.3 ± 321.4 mg for sodium valproate, and 800.0 ± 400.0 mg for carbamazepine. Only 5 patients were taking a combination of mood stabilizers (lithium and an anticonvulsant).

Cognitive Profile

The mean scores and standard deviations on the 3 neuropsychological tests are shown in Table 3. The mean scores for current full scale, verbal, and performance IQ were all within the average range, as was the mean level of predicted premorbid IQ derived from the NART. Although data from different standardization samples were

Table 4. Pearson Correlation Coefficients (r) and p Values Showing the Relationship Between Each Potential Predictor and Cognitive Variable in Bipolar I Patients

Measure	Antipsychotics	Mood Stabilizers	Antidepressants	History of Psychosis	Duration of Illness	Age at Onset	HAM-D Score	Mania Rating Scale Score	Family History
Full scale IQ (N = 42)									
r	–0.57[a]	–0.08	0.13	–0.28	0.05	0.04	–0.2	–0.13	0.36[a]
p	< .001[a]	.63	.42	.07	.77	.8	.2	.41	.02[a]
General memory (N = 43)									
r	–0.3[a]	–0.13	–0.04	–0.11	–0.32[a]	0.16	–0.2	0.07	0.11
p	.048[a]	.42	.81	.47	.04[a]	.3	.19	.68	.48
Working memory (N = 43)									
r	–0.32[a]	0.09	0.23	–0.26	0.03	0.03	–0.19	–0.09	0.23
p	.035[a]	.55	.14	.09	.85	.87	.23	.56	.15

[a]Value was found to be statistically significant at the 5% level.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Table 5. Multiple Regression Analyses of the Effect of 3 Potential Predictors on Cognitive Variables in Bipolar I Patients[a]

	Antipsychotic Medication			Family History of Affective Disorders			Duration of Illness		
Measure	Estimated Difference	95% CI	p	Estimated Difference	95% CI	p	Estimated Difference per 10 Years	95% CI	p
Full scale IQ score	↓17.7	9.8 to 25.7	< .001	↑11.7	2.4 to 21.0	.02	↑1.1	–2.4 to 4.6	.53
General memory score	↓11.4	1.8 to 21.0	.02	↑3.0	–8.2 to 14.2	.59	↓4.5	0.3 to 8.7	.04
Working memory score	↓14.0	3.1 to 24.9	.01	↑8.4	–4.4 to 21.2	.19	↑0.9	–3.8 to 5.7	.7

[a]The effects for each variable are adjusted for the effects of the other 2 variables.

used, the WMS-III index scores for measures of auditory immediate and delayed memory and visual delayed and working memory were also within the average range, whereas the visual immediate memory, auditory recognition delayed memory, and immediate and general memory index scores were in the low average range.

As would be expected, full scale, verbal, and performance IQ, as assessed by the WAIS-R, were highly intercorrelated (all pairwise Pearson correlation coefficients were > 0.6), as were the WMS-III subscales, with the exception of the working memory index (all pairwise correlation coefficients between index scores excluding working memory were > 0.38). As a result of this correlation structure, the cognitive outcomes of full scale IQ, based on WAIS-R; WMS-III working memory index; and the WMS-III general memory index were used in further analyses. However, high correlations remained between the full scale WAIS-R IQ scores and the working memory index (correlation coefficient = 0.73).

Table 4 shows the relationships between each of the potential predictor variables and the 3 selected cognitive variables. Three of the potential predictors were associated with cognition at the 5% significance level: antipsychotic medication at the time of testing, duration of illness, and family history of affective disorders. These 3 predictors were not associated with each other within our sample. The percentage of patients on current antipsychotic medication was 60% for those with a positive family history of affective disorder and 50% for those with negative family history. The median duration of illness was 15.5 years for those with and 14.5 years for those without a family history of affective disorders. The median duration of illness was 15 years for those not on antipsychotic treatment at the time of testing and 16.5 years for those prescribed antipsychotics. Hence, effect estimates from a simple linear regression and a multiple linear regression model including all 3 empirical predictors gave similar results.

The multiple regression analysis quantified the effect of the 3 identified potential predictors on full scale IQ, general memory, and working memory scores (Table 5). First, taken together, the 3 variables predicted 44% of the variability observed in the full scale IQ scores, as estimated by the WAIS-R. Patients on treatment with antipsychotic drugs had lower current full scale IQ, whereas patients with a family history of affective disorders had higher full scale IQ. Current full scale IQ was not found to be affected by duration of illness. Second, taken together, the 3 variables predicted 49% of the variability observed in the general memory index scores, as assessed by the WMS-III. Patients on treatment with antipsychotic drugs had lower general memory scores, and, similarly, these scores were found to decrease with duration of illness. In contrast, family history was not predictive of general memory scores. Third, taken together, the 3 variables predicted 44% of the variability observed in the working memory index scores. Patients on treatment with antipsychotic drugs had lower working memory index scores. Neither family history nor duration of illness was predictive of working memory index scores.

As antipsychotic treatment was found to be predictive of lower full scale IQ, general, and working memory index scores, we were interested in the possibility that this effect may be different for typical and atypical antipsychotics. As the number of patients in each group was small, this comparison is purely exploratory. We performed a 1-way analysis of variance with the 3 cognitive outcome measures as dependent variables and antipsychotic treatment (none vs. typical vs. atypical) as an independent factor. The model was significant for full scale IQ ($F = 12.25$, $p = .0001$), marginally significant for the working memory index ($F = 2.98$, $p = .062$), and nonsignificant for the general memory index ($F = 2.04$, $p = .14$). Post hoc pairwise comparisons between medication groups showed that there was no statistically significant difference in full scale IQ between patients taking typical antipsychotics and those taking atypical antipsychotics ($p = .22$). Patients who were not prescribed antipsychotics had higher full scale IQ compared with both those taking typical ($p = .0001$) and atypical ($p = .01$) compounds. Similarly, patients not prescribed antipsychotics had marginally higher working memory index scores ($p = .06$) than patients in either of the 2 other groups, while there was no difference between patients taking atypical or typical antipsychotics.

DISCUSSION

Medication and Cognition

Current antipsychotic use was the only medication-related variable that had a significant effect on cognitive function. Treatment with an antipsychotic medication at the time of testing was associated with both lower current IQ scores and lower general and working memory index scores. This relationship persisted after adjustment for family history of affective disorder and duration of illness. Little is known about the effect of antipsychotic medication on cognition in bipolar disorder patients. In healthy volunteers, acute administration of typical antipsychotics such as haloperidol has a negative impact on cognition[28–31]; however, the effects of new atypical antipsychotics are largely unknown, although they may possibly be subtle.[32] An exploratory comparison of patients receiving atypical versus typical antipsychotics in this study revealed no significant group differences in any of the 3 main cognitive outcome measures. However, this issue should be addressed further in future studies.

Most of the literature on the relationship between cognitive impairment and treatment with antipsychotics has focused on schizophrenia. Generalization of these findings to other patient populations may be misleading, particularly since the cognitive profile of bipolar I disorder patients shows both quantitative and qualitative differences from that of schizophrenia patients.[33,34] However, a negative impact of antipsychotics on IQ in bipolar I disorder patients was observed in an early study by Abrams et al.[35] of 52 patients with affective disorder, 17 patients with schizophrenia, and 8 patients with organic brain syndromes. Treatment with either antipsychotics or lithium was a significant predictor of current IQ, as assessed by the WAIS. The effects of antipsychotics and lithium were equal, although in opposite directions; the former being associated with lower IQ scores, and the latter, with higher scores.

Patients on lithium treatment often report subjective cognitive impairment; however, attempts to quantify these cognitive changes have yielded conflicting results.[14] Some studies have reported impairments in memory, vigilance, and attention, whereas others have reported no changes, or even improvement.[36,37] A similar lack of consistency is seen in the assessment of the cognitive impact of anticonvulsants in psychiatric patients,[38] although any effects are considered to be modest at worst.[39] As it is often difficult to disentangle medication-related versus psychopathology-related effects, studies on healthy subjects can be very informative. In a recent double-blind, placebo-controlled study on the effect of medium-term lithium administration to healthy subjects, there was no evidence of impairment in measures of memory or attention.[40] Studies of anticonvulsants in healthy subjects have also found minor cognitive effects for sodium valproate, carbamazepine, and lamotrigine.[39,41,42] The lack of an association between cognition and use of mood stabilizer in this study is in line with these observations. The number of patients who were not being prescribed a mood stabilizer was small, however, and this may have prevented the detection of an effect.

Psychosis and Cognition

Patients with previous history of psychotic symptoms were more likely to have been on treatment with antipsychotic medication at the time of assessment; however, the effect of this variable did not reach statistical significance at the 5% level and was therefore not selected as an empirical predictor for inclusion in the final model (Table 4). However, a history of psychotic symptoms was associated with lower scores on all 3 cognitive outcomes, and, in the case of full scale IQ and working memory, these associations approached statistical significance ($p < .1$). It is, therefore, possible that the negative effects of a previous history of psychotic symptoms contributed to the detected effects of antipsychotic medication on cognitive outcomes. To explore this possibility, we repeated our analysis and set the initial inclusion threshold at 10%, thus including history of psychosis in the predictor variables. The effect of current antipsychotic medication on full scale IQ and general memory index remained significant ($p = .001$ and $p = .02$, respectively), while the effect of antipsychotic medication on working memory index became marginally significant ($p = .07$).

Previous literature on general intellectual function in bipolar disorder is not particularly informative on the relationship between psychosis and IQ. Most studies have found that the IQ scores of bipolar disorder patients,[5,43–47] even those with a prior history of psychosis, are within the normal range.[10] Similarly, all bipolar disorder patients, regardless of whether they have a history of psychosis, perform better on composite measures of intellect than patients with schizophrenia.[48–50] These observations suggest that the impact of psychosis on IQ in bipolar disorder should be considered modest. They do not, however, address the question directly.

Very few studies have examined possible differences in memory function between bipolar disorder patients with and without a history of psychosis, and the results produced are conflicting. Both Coffman et al.[10] and Albus et al.[9] found that patients with bipolar disorder and a history of psychosis performed worse than healthy controls on the visual subscales of the WMS, whereas Jones et al.,[12] who used the Rey-Osterrieth Complex Figure test, found no difference.

Clinical Characteristics and Cognition

Duration of illness was a statistically significant predictor of greater cognitive impairment in general memory, but not working memory. There are conflicting findings regarding the association between memory and duration of illness. Van Gorp et al.[6] used the California Verbal Learning Test (CVLT) to compare verbal memory between euthymic bipolar disorder patients and controls closely matched to the patients on years of education and general intellectual function. All patients performed poorly on the CVLT, and the degree of impairment correlated with the duration and number of previous episodes. Similarly, Denicoff et al.[51] found that longer duration of illness and higher number of episodes predicted more severe impairment in memory function in bipolar disorder patients. In contrast, Ferrier et al.,[4] who also used a verbal learning task in remitted bipolar disorder patients and controls, found that memory impairment was more pronounced in their "good outcome" subgroup of patients, who had fewer episodes and good interepisode recovery.

Several studies have found an association between symptoms and cognitive impairment in bipolar disorder. In acutely manic or recovering patients, general intellectual function, particularly the performance IQ subscales, may be moderately affected.[43,44,52] Impairments in verbal and nonverbal memory have also been reported during both manic and depressive episodes.[9,43,53] It has been suggested that, in bipolar disorder, cognitive function may be particularly sensitive to the presence of symptoms. Goldberg et al.[49] found that 15% to 30% of the variance in cognitive impairment in bipolar disorder was accounted for by symptoms. More recently, Ferrier et al.[4] found that, even in essentially recovered bipolar disorder patients, residual depressive symptoms accounted for the observed impairment in verbal learning and recall, but not in working memory. Given that nearly 40% of our sample had a HAM-D total score over 10, it is surprising that this variable was not found to be a significant predictor of cognitive impairment. As seen in Table 4, symptoms did have a negative effect on cognition, but the association did not reach statistical significance.

Family History and Cognition

Family history of affective disorders was predictive of higher current IQ but did not show a significant association with general or working memory function.

We know of no studies that have examined the effect of familiality for affective disorders on IQ in bipolar disorder patients. Several studies have, however, suggested that memory impairment may be associated with familial risk for bipolar disorder. Gourovitch et al.[54] used the WMS to compare monozygotic twins discordant for bipolar disorder with each other and with normal twins. The affected twins were either acutely unwell or in partial remission. Both affected and unaffected twins performed worse than controls in the WMS general memory quotient. In a study by Keri et al.,[55] healthy siblings of patients with bipolar disorder were impaired in verbal memory compared with controls. Although memory dysfunction may be a familial risk factor for bipolar disorder, our data suggest that familiality for affective disorders does not have a measurable effect in individuals who are already suffering from bipolar disorder.

In summary, we found that current antipsychotic use, duration of illness, and family history of affective disorders were the most significant predictors of IQ and memory function in bipolar I disorder. Our observations raise several issues that need to be addressed in further studies. One is the potentially detrimental effect of antipsychotics on cognition in bipolar patients. Our results suggest that, although a history of psychosis also has a negative impact on cognition, the use of antipsychotics may contribute further to these cognitive difficulties. We know of no other study to have made such an explicit link between cognitive impairment and antipsychotics in bipolar disorder, and we feel that further research into this field is necessary to explore the possibility that some of the cognitive difficulties in these patients may be iatrogenic. Our findings suggest that chronicity in bipolar disorder may be associated with decrements in some, but not all aspects of memory function. It is possible that there is deterioration over time in memory and other aspects of cognition in bipolar disorder. Alternatively, poor memory function may be a predictor of chronicity. The relationship between chronicity and cognition will need to be explored further with longitudinal follow-up studies of bipolar disorder patients. Finally, patients with a family history of affective disorders had an average advantage of

11.7 points in the full scale IQ score over patients without such a family history after the effects of chronicity and medication were controlled for. Given that the IQ scores of all patients were in the average range, this difference may not be clinically important, but it suggests that general intellectual impairment may not be a feature of familial risk to bipolar disorder. Further work is needed to ascertain whether familial risk to bipolar disorder is mediated through deficits in other, perhaps more specific aspects of cognition, such as verbal memory.

Drug names: carbamazepine (Tegretol, Epitol, and others), chlorpromazine (Thorazine and others), haloperidol (Haldol and others), lamotrigine (Lamictal).

REFERENCES

1. Green MF, Kern RS, Braff DL, et al. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull 2000;26:119–136
2. Zarate CA Jr, Tohen M, Land M, et al. Functional impairment and cognition in bipolar disorder. Psychiatr Q 2000;71:309–329
3. Frangou S, Bettany D. The neuropsychology of bipolar affective disorder [abstract]. Bipolar Disord 1999;1(suppl 1):130
4. Ferrier IN, Stanton BR, Kelly TP, et al. Neuropsychological function in euthymic patients with bipolar disorder. Br J Psychiatry 1999;175: 246–251
5. Sapin LR, Berrettini WH, Nurnberger JR, et al. Mediational factors underlying cognitive changes and laterality in affective illness. Biol Psychiatry 1987;22:979–986
6. Van Gorp W, Altshuler L, Theberge D, et al. Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. Arch Gen Psychiatry 1998;55:41–46
7. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
8. Tham A, Engelbrektson K, Mathe AA, et al. Impaired neuropsychological performance in euthymic patients with recurring mood disorders. J Clin Psychiatry 1997;58:26–29
9. Albus M, Hubmann W, Wahlheim C, et al. Contrasts in neuropsychological test profile between patients with first-episode schizophrenia and first-episode affective disorders. Acta Psychiatr Scand 1996;94:87–93
10. Coffman JA, Bornstein RA, Olson SC, et al. Cognitive impairment and cerebral structure by MRI in bipolar disorder. Biol Psychiatry 1990;27: 1188–1196
11. Atre-Vaidya N, Taylor M, Seidenberg M, et al. Cognitive deficits, psychopathology and psychosocial functioning in bipolar mood disorder. Neuropsychiatry Neuropsychol Behav Neurol 1998;11:120–126
12. Jones BP, Duncan CC, Mirsky AF, et al. Neuropsychological profiles in bipolar affective disorder and complex partial seizure disorder. Neuropsychology 1994;8:55–64
13. Sharma T. Cognitive effects of conventional and atypical antipsychotics in schizophrenia. Br J Psychiatry Suppl 1999;38:44–51
14. Dufresne J, Stip E. Les effets cognitifs du lithium. Synapse 1998;151: 38–45
15. Hays JC, Krishnan KR, George LK, et al. Age of first onset of bipolar disorder: demographic, family history, and psychosocial correlates. Depress Anxiety 1998;7:76–82
16. Strober M. Relevance of early age-of-onset in genetic studies of bipolar affective disorder. J Am Acad Child Adolesc Psychiatry 1992;31:606–610
17. Schürhoff F, Bellivier F, Jouvent R, et al. Early and late onset bipolar disorders: two different forms of manic-depressive illness? J Affect Disord 2000;58:215–221
18. Winokur G, Coryell W, Akiskal HS, et al. Manic-depressive (bipolar) disorder: the course in light of a prospective ten-year follow-up of 131 patients. Acta Psychiatr Scand 1994;89:102–110
19. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association; Washington, DC: 1994
20. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-I/P, Research Version). New York, NY: Biometric Research, New York State Psychiatric Institute; 2001
21. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
22. Spitzer RL, Endicott J. Schedule for Affective Disorders and Schizophrenia-Change Version, Third Edition. New York, NY: Biometric Research, New York State Psychiatric Institute; 1978
23. Office of Population Censuses and Surveys. Standard Occupational Classification. London, England: HMSO; 1991
24. Maxwell ME. Manual for the FIGS. Bethesda, Md: National Institute of Mental Health; 1992
25. Wechsler D. Wechsler Adult Intelligence Scale-Revised Manual. Anglicized ed. London, England: Psychological Corp; 1986
26. Nelson HE, Willison JR. The National Adult Reading Test (NART). 2nd ed. Test Manual. Windsor, England: NFER-Nelson; 1991
27. Wechsler D. Wechsler Memory Scale. 3rd ed. Administration and Scoring Manual. London, England: Psychological Corp; 1998
28. Danion JM, Peretti S, Grange D, et al. Effects of chlorpromazine and lorazepam on explicit memory, repetition priming and cognitive skill learning in healthy volunteers. Psychopharmacology (Berl) 1992;108:345–351
29. Jeste DV, Lohr JB, Eastham JH, et al. Adverse neurobiological effects of long-term use of neuroleptics: human and animal studies. J Psychiatr Res 1998;32:201–214
30. King DJ. The effect of neuroleptics on cognitive and psychomotor function. Br J Psychiatry 1990;157:799–811
31. Ramaekers JG, Louwerens JW, Muntjewerff ND, et al. Psychomotor, cognitive, extrapyramidal, and affective functions of healthy volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. J Clin Psychopharmacol 1999;19:209–221
32. Beuzen JN, Taylor N, Wesnes K, et al. A comparison of the effects of olanzapine, haloperidol and placebo on cognitive and psychomotor functions in healthy elderly volunteers. J Psychopharmacol 1999;13:152–158
33. Goldberg TE. Some fairly obvious distinctions between schizophrenia and bipolar disorder. Schizophr Res 1999;39:127–132
34. Rossi A, Arduini L, Daneluzzo E, et al. Cognitive function in euthymic bipolar patients, stabilized schizophrenic patients, and healthy controls. J Psychiatr Res 2000;34:333–339
35. Abrams R, Redfield J, Taylor MA. Cognitive dysfunction in schizophrenia, affective disorder and organic brain disease. Br J Psychiatry 1981;139:190–194
36. Engelsmann F, Katz J, Ghadirian AM, et al. Lithium and memory: a long-term follow-up study. J Clin Psychopharmacol 1988;8:207–212
37. Zerbi F, Clemente J, Bezzi G, et al. Memory performances in depressed patients during prophylactic treatment with lithium salts. Biol Psychiatry 1981;161:190–196
38. Goldberg JF, Burdick KE. Cognitive side effects of anticonvulsants. J Clin Psychiatry 2001;62(suppl 14):27–33
39. Meador KJ, Loring DW, Ray PG, et al. Differential cognitive and behavioral effects of carbamazepine and lamotrigine. Neurology 2001;56: 1177–1182
40. Stip E, Dufresne J, Lussier I, et al. A double-blind, placebo-controlled study of the effects of lithium on cognition in healthy subjects: mild and selective effects on learning. J Affect Disord 2000;60:147–157
41. Martin R, Meador K, Turrentine L, et al. Comparative cognitive effects of carbamazepine and gabapentin in healthy senior adults. Epilepsia 2001; 42:764–771
42. Meador KJ, Loring DW, Moore EE, et al. Comparative cognitive effects of phenobarbital, phenytoin, and valproate in healthy adults. Neurology 1995;45:1494–1499
43. Dalby JT, Williams R. Preserved reading and spelling ability in psychotic disorders. Psychol Med 1986;16:171–175
44. Morice R. Cognitive inflexibility and pre-frontal dysfunction in schizophrenia and mania. Br J Psychiatry 1990;157:50–54
45. Murphy FC, Sahakian BJ, Rubinsztein JS, et al. Emotional bias and inhibitory control processes in mania and depression. Psychol Med 1999;29: 1307–1321
46. Rubinsztein JS, Michael A, Paykel ES, et al. Cognitive impairment in remission in bipolar affective disorder. Psychol Med 2000;30:1025–1036
47. Sweeney JA, Kmiec JA, Kupfer DJ. Neuropsychological impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. Biol Psychiatry 2000;48:674–685

48. Gilvarry C, Takei N, Russell A, et al. Premorbid IQ in patients with functional psychosis and their first-degree relatives. Schizophr Res 2000;41: 417–429
49. Goldberg TE, Gold JM, Greenberg R, et al. Contrasts between patients with affective disorders and patients with schizophrenia on a neuropsychological test battery. Am J Psychiatry 1993;150:1355–1362
50. Mojtabai R, Bromet EJ, Harvey EJ, et al. Neuropsychological differences between first admission schizophrenia and psychotic affective disorders. Am J Psychiatry 2000;157:1453–1460
51. Denicoff KD, Ali SO, Mirsky AF, et al. Relationship between prior course of illness and neuropsychological functioning in patients with bipolar disorder. J Affect Disord 1999;56:67–73
52. Hoff AL, Shukla S, Aronson T, et al. Failure to differentiate bipolar disorder from schizophrenia on measures of neuropsychological function. Schizophr Res 1990;3:253–260
53. Wolfe J, Granholm E, Butters N, et al. Verbal memory deficits associated with major affective disorders: a comparison of unipolar and bipolar patients. J Affect Disord 1987;13:83–92
54. Gourovitch ML, Torrey EF, Gold JM, et al. Neuropsychological performance of monozygotic twins discordant for bipolar disorder. Biol Psychiatry 1999;45:639–646
55. Keri S, Kelemen O, Benedek G, et al. Different trait markers for schizophrenia and bipolar disorder: a neurocognitive approach. Psychol Med 2001;31:915–922