Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder

PAULA V. NUNES, ORESTES V. FORLENZA and WAGNER F. GATTAZ

Summary Bipolar disorder is associated with increased risk for dementia. We compared the prevalence of Alzheimer's disease between 66 elderly euthymic patients with bipolar disorder who were on chronic lithium therapy and 48 similar patients without recent lithium therapy. The prevalence of dementia in the whole sample was 19% *v.* 7% in an age-comparable population. Alzheimer's disease was diagnosed in 3 patients (5%) on lithium and in 16 patients (33%) who were not on lithium ($P<0.001$). Our case–control data suggest that lithium treatment reduced the prevalence of Alzheimer's disease in patients with bipolar disorder to levels in the general elderly population. This is in accordance with reports that lithium inhibits crucial processes in the pathogenesis of Alzheimer's disease.

Declaration of interest None. Funding detailed in Acknowledgements.

At therapeutic concentrations, lithium inhibits glycogen synthase kinase-3, a key enzyme in the metabolism of amyloid precursor protein and the phosphorylation of tau protein (Klein & Melton, 1996; Lovestone *et al*, 1999) which are critical steps in the formation of neuritic plaques and neurofibrillary tangles, the pathological hallmarks of Alzheimer's disease. Therefore, we examined whether exposure to chronic lithium treatment might protect elderly patients with bipolar disorder against Alzheimer's disease.

METHOD

Patients were recruited at the Institute of Psychiatry, University of São Paulo (which granted ethical approval for the study as a whole) and Santa Casa Medical School, Brazil. Inclusion criteria were: a DSM–IV diagnosis of bipolar disorder (American Psychiatric Association, 1994); 60 years of age or more; continuous treatment for bipolar disorder for at least the previous 6 months; and euthymia in the past month (scores on the Hamilton Rating Scale for Depression (Hamilton, 1960), and the Young Mania Rating Scale (Young *et al*, 1978) of less than 8 and 5 respectively). Exclusion criteria were: electroconvulsive therapy in the previous 6 months; acute physical illness; organic brain syndromes; and comorbidity with other major psychiatric syndromes. Informed consent was obtained from patients and a first-degree relative.

Through hospital chart review we detected 184 patients who fulfilled the first three criteria. Twenty-seven patients could not be located, 10 had died and 12 refused to participate; 17 patients were excluded for not being euthymic or meeting exclusion criteria. Thus, 118 patients with bipolar disorder (64%; 37 male, 81 female; mean age 68.2 years, s.d.=5) underwent cognitive assessment with the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX; Roth *et al*, 1986) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Jorm & Korten, 1988). Patients were classified, as having normal cognitive function, mild cognitive impairment (Petersen, 2004) and DSM–IV dementia (American Psychiatric Association, 1994) by assessors masked to treatment groups. The group with dementia were further classified as Alzheimer's disease (McKhann *et al*, 1984) and vascular dementia (Roman *et al*, 1993).

Statistical analysis

Parametric (Pearson's χ^2, Fisher's exact test, *t*-test for two independent samples and with one-way analysis of variance, corrected for multiple comparisons by the Tukey test) and, when indicated, non-parametric tests (Mann–Whitney test, Kruskal–Wallis test, corrected for multiple comparisons by the Dunn test) were used. A multinomial logistic regression with backward selection of variables was performed addressing variables with $P<0.10$ in the univariate model.

RESULTS

From the total sample (n=118), 70 patients (59%) had normal cognitive function, 25 (21%) had mild cognitive impairment, and 23 (19%) had dementia. Among those with dementia, 19 (16% of the total sample) had Alzheimer's disease and 4 had vascular dementia. The latter were excluded, leaving 114 patients for further analysis. Results of the cognitive assessment are available from the authors upon request.

Patients were allocated to two groups: 66 patients (28 male, 38 female; mean age 67.4 years, s.d.=4.7) continuous treatment on lithium for a mean of 71.2 months (s.d.=71.7); 48 patients (10 male, 38 female; mean age 69.1 years, s.d.=4.6) treated with other mood-stabilising drugs for at least the past 6 months, 15 of whom had never received lithium and 33 who had received lithium in the past (mean use of 54.1 months, s.d.=55.4) but were off lithium for a mean of 59.4 months (s.d.=55.7).

The prevalence of Alzheimer's disease was 5% in the group on continuous lithium treatment (3 out of 66 patients) and 33% (16 out of 48 patients) in the group without recent lithium therapy ($P<0.001$). The prevalence of mild cognitive impairment was 20% and 25% respectively ($P<0.10$). Cognitive assessments of the 33 patients who had been treated with lithium in the past were: normal function, 14 patients (42%), mild cognitive impairment, 9 patients (27%), and Alzheimer's disease, 10 patients (30%); this was very similar to assessments of the remaining 15 patients in the group who had never used lithium (40%, 20% and 40% respectively, P=0.77).

Within the group that had received continuous lithium therapy for the past 6 months, there were no differences according to cognitive function in the mean daily dose and mean serum levels of lithium (0.81 (s.d.=0.18), 0.78 (s.d.=0.17) and 0.69 (s.d.=0.15) mEq/l, P=0.50) throughout treatment.

Patients with Alzheimer's disease were older (mean age 71.5 years, s.d.=5.4) than those with mild cognitive impairment (mean age 67.2 years, s.d.=4.0, P=0.006) and those with normal cognitive function (mean age 67.4 years, s.d.=4.4, P=0.002). Consequently patients with Alzheimer's disease also had a higher duration of bipolar disorder (P=0.015) and more previous depressive episodes (P=0.030) than those

with normal cognitive function. These differences disappeared after correction for age. No other differences were found regarding the remaining socio-demographic and clinical variables. Significantly fewer patients with Alzheimer's disease had received recent continuous lithium treatment compared with those with mild cognitive impairment or normal cognitive function ($P<0.001$). The use of antidepressants, benzodiazepines, antipsychotics, valproate, carbamazepine and other anticonvulsants did not differ with cognitive function (data available on request).

Logistic regression revealed that only the influences of age ($P<0.01$) and lithium use ($P<0.001$) on cognitive outcomes remained significant. After controlling for age, lithium use remained associated with a smaller risk of Alzheimer's disease (OR=0.079; 95% CI 0.020–0.321, $P<0.001$).

When we excluded patients with Alzheimer's disease from the analysis, no negative effects of long-term lithium treatment on cognition were observed, as no differences were found between the lithium and the comparison groups in the extensive assessment of their neuropsychological performance (data available on request).

DISCUSSION

In the present cross-sectional study of elderly patients with bipolar disorder, the prevalence of dementia was 19%, which is almost three times that expected in the elderly Brazilian population (7%; Herrera *et al*, 2002). This prevalence is similar to that in other studies which report an increased risk for dementia in patients with affective disorders and that this risk increases with the number and duration of previous affective episodes (Kessing & Nilsson, 2003; Thompson *et al*, 2005).

In our study, only patients in the group without recent continuous lithium treatment showed an increased prevalence of Alzheimer's disease (33%) and a trend toward increased mild cognitive impairment, which is a risk factor for Alzheimer's disease (Petersen, 2004). Conversely, the prevalence of Alzheimer's disease in the lithium group (5%) was similar to that reported in the elderly general population in Brazil. These findings suggest that lithium treatment might reduce the risk of dementia in patients with bipolar disorder. The mechanisms by which lithium might exert this effect need clarification. Because the risk for dementia may increase with the number of previous affective episodes, lithium might protect against dementia by reducing the lifetime number of affective relapses. This, however, does not hold true in our sample, because the differences between the lithium and the non-lithium groups regarding the number of previous depressive and manic episodes were not significant (depression: 10.4 (s.d.=10.3) and 13.9 (s.d.=13.1) respectively, $P=0.436$; mania: 7.8 (s.d.=8.9) and 11.7 (s.d.=12.9) respectively, $P=0.253$).

There are reports of negative effects of short-term lithium therapy on cognition (for a review see Pachet & Wisniewski, 2003). One could argue that psychiatrists, aware of these possible negative effects, would avoid prescribing lithium to patients with dementia and this could explain the increased prevalence of Alzheimer's disease in our comparison group. However, this is unlikely because most of our patients had previously undiagnosed and mild Alzheimer's disease (mean Mini-Mental State Examination score 21; Folstein *et al*, 1975). Moreover, the mean duration of bipolar disorder in our sample was more than 25 years. Even our patients with cognitive impairment who were taking lithium had taken it continuously for the past 6 years. We feel therefore that the decision to prescribe lithium was based on the clinical response and thus was independent of the cognitive status of our patients, and an *a priori* selection seems unlikely.

It thus seems possible that a protective effect of lithium against Alzheimer's disease in patients with bipolar disorder might be a result of its intrinsic biological properties in the brain. Preliminary data from our laboratory indicate that lithium inhibits the transcription of the glycogen synthase kinase-3 gene. Through this pathway lithium may inhibit crucial processes in the pathogenesis of disease, such as the overproduction of amyloid-β and tau hyperphosphorylation (Klein & Melton, 1996).

PAULA V. NUNES, MD, PhD, ORESTES V. FORLENZA, MD, PhD, WAGNER F. GATTAZ, MD, PhD, Laboratory of Neuroscience – LIM27, Department and Institute of Psychiatry, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil

Correspondence: Professor Wagner F. Gattaz, Department & Institute of Psychiatry, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil. Email: gattaz@usp.br

(First received 14 August 2006, final version 22 November 2006, accepted 8 January 2007)

ACKNOWLEDGEMENTS

We thank Stevin Zung and Priscilla Wacker for help in data collection and Valentim Gentil, MD, PhD, for comments on a previous draft of this work. The Laboratory of Neuroscience – LIM27 receives financial support from ABADHS (Associação Beneficente Alzira Denise Herzog da Silva) and FAPESP (Fundação do Amparo à Pesquisa do Estado de So Paulo, project 02/13633-7). P.V.N. was supported by CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).

REFERENCES

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM–IV). APA.

Folstein, M. F., Folstein, S. E. & McHugh, P. R. (1975) 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, **12**, 189–198.

Hamilton, M. (1960) Rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, **23**, 56–62.

Herrera, E., Caramelli, P., Silveira, A. S., *et al* (2002) Epidemiologic survey of dementia in a community-dwelling Brazilian population. *Alzheimer Disease and Associated Disorders*, **16**, 103–108.

Jorm, A. F. & Korten, A. E. (1988) Assessment of cognitive decline in the elderly by informant interview. *British Journal of Psychiatry*, **152**, 209–213.

Kessing, L. V. & Nilsson, F. M. (2003) Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. *Journal of Affective Disorders*, **73**, 261–269.

Klein, P. S. & Melton, D. A. (1996) A molecular mechanism for the effect of lithium on development. *Proceedings of the National Academy of Sciences of the United States of America*, **93**, 8455–8459.

Lovestone, S., Davis, D. R., Webster, M. T., *et al* (1999) Lithium reduces tau phosphorylation: effects in living cells and in neurons at therapeutic concentrations. *Biological Psychiatry*, **45**, 995–1003.

McKhann, G., Drachman, D., Folstein, M., *et al* (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, **34**, 939–944.

Pachet, A. K. & Wisniewski, A. M. (2003) The effects of lithium on cognition: an updated review. *Psychopharmacology*, **170**, 225–234.

Petersen, R. C. (2004) Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, **256**, 183–194.

Roman, G. C. Tatemichi, T. K., Erkinjuntti, T., *et al* (1993) Vascular Dementia: diagnostic criteria for research studies. Report of the NINDS–AIREN International Workshop. *Neurology*, **43**, 250–260.

Roth, M., Tym, E., Mountjoy, C. Q., *et al* (1986) CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *British Journal of Psychiatry*, **149**, 698–709.

Thompson, J. M., Gallagher, P., Hughes, J. H., *et al* (2005) Neurocognitive impairment in euthymic patients with bipolar affective disorder. *British Journal of Psychiatry*, **186**, 32–40.

Young, R. C., Biggs, J. T., Ziegler, V. E., *et al* (1978) A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry*, **133**, 429–435.

https://doi.org/10.1192/bjp.bp.106.029868 Published online by Cambridge University Press