indexes of somatic health, functional status and social status. In addition, both the PLE (RR = 0.41, 95%CI = 0.24–0.69) and the NLE (RR = 1.95, 95%CI = 1.11–3.45) were significant predictors. More specifically, one (or more) positive event played a strong protective role and two (or more) negative events in the last 12 months played a strong adverse role on the affective level of the oldest old. In this multivariate model, no independent association with affective status was found for gender, age and cognitive level; only a trend was detected for economic condition.

On the whole, these data suggest that the mental health of the oldest old remains susceptible to change from external factors, and recent life events in both directions (either positive or negative) are among its major determinants.

ILDEBRANDO APPOLLONIO
S. Gerardo Hospital
Monza

RENZO ROZZINI
FRANCESCA CASTELLETTI
MARCO TRABUCCHI
Geriatric Research Group
Brescia

REFERENCES

Bazargan, M. and Hamm-Baugh, V. P. (1995) The relationship between chronic illness and depression in a community of urban black elderly persons. *J. Gerontol. (Ser. B)* **50**, S119–S127.

Bowling, A. and Browne, P. D. (1991) Social networks, health, and emotional well-being among the oldest old in London. *J. Gerontol.* **46**. S20–S32.

Katona, C. L. (1992) The epidemiology of depression in old age: The importance of physical illness. *Clin. Neuropharmacol.* **15**(Suppl. 1), 281A–282A.

Kennedy, G. J., Kelman, H. R. and Thomas, C. (1990) The emergence of depressive symptoms in late life: The importance of declining health and increasing disability. *J. Commun. Health* **15**, 93–104.

Kuvela, S. L., Kongas-Saviaro, P., Laippala, P., Pahakala, K. and Kesti, E. (1996) Social and psychosocial factors predicting depression in old age: A longitudinal study. *Int. Psychogeriat.* **8**, 635–644.

Lawton, M. P., De Voe, M. R. and Parmelee, P. (1995) Relationship of events and affect in the daily life of an elderly population. *Psychol. Aging* **10**, 469–477.

Martin, P. (1997) Longevity as a developmental process: Life history and individual perspectives. *Z. Gerontol. Geriat.* **30**, 3–9.

Ravaglia, G., Forti, P., Maioli, F., Boschi, F., Cicognani, A., Bernardi, M., Pratelli, L., Pizzoferrato, A., Porcu, S. and Gasbarrini, G. (1997) Determinants of functional status in healthy Italian nonagenarians and centenarians: A comprehensive functional assessment by the instruments of geriatric practice. *J. Am. Geriatr. Soc.* **45**, 1196–1202.

Mania Associated With Donepezil

Dear Editor

Two depressed women became manic after treatment with donepezil, a new cholinesterase inhibitor for the therapy of Alzheimer's disease. A MEDLINE search did not find similar Reports.

CASE 1

A 78-year-old woman presented with a DSM-IV 6-month duration major depressive episode associated with memory impairment. She needed only minimal family support to function. In the last 3 years she had had other depressive episodes, remitted spontaneously or with fluoxetine. She had never had manic or hypomanic episodes. She had been taking lorazepam, 1 mg/day, for 10 years. In the last few years she had had some episodes of disorientation lasting no more than a day. She had no other medical illness and she had been taking no other drugs. A recent brain CT scan had shown mild cortical atrophy. Treatment was started with nortriptyline, 10 mg/day, and alprazolam, 1 mg/day. Lorazepam was discontinued. Three weeks later mood and memory improved. Then, nortriptyline was increased to 20 mg/day and the

cholinesterase inhibitor donepezil, 5 mg/day, was started. Three days later she became manic, with euphoric mood, severe insomnia, pressured speech, flight of ideas, distractibility, psychomotor agitation, hyperactivity, severe memory impairment and disorientation. She required continuous supervision. Four days later nortriptyline and donepezil were discontinued, while alprazolam dose was increased to 2 mg/day. Mania and cognitive impairment improved during the following days. Ten days later donepezil, 5 mg/day, was restarted, to prove a causal association. The following day mania was more severe, and it was discontinued 2 days later. During the following week mania and cognitive impairment improved significantly.

CASE 2

A 64-year-old woman with DSM-IV bipolar I disorder, depressed, in partial remission for some months with lamotrigine, 50 mg/day, fluoxetine, 20 mg/day, and lorazepam, 1 mg/day, was treated with donepezil, 5 mg/day, to improve memory. One week later she became hypomanic, with euphoric mood, insomnia, hyperactivity, pressured speech and distractibility. She continued to take donepezil for the following 2 months. During this time hypomania continued. She then discontinued donepezil because it was too expensive and hypomania improved significantly in a week. She had been taking for some years the calcium channel blocker verapamil, 60 mg/day, the beta-blocker atenolol, 100 mg/day (for hypertension), and the sulfonylurea gliquidone, 600 mg/day (for diabetes mellitus).

In case 1, mania may have been induced by the antidepressant or it may have had a spontaneous onset. New onset mania in late life is rare (Goodwin and Jamison, 1990). The timing of mania seems to involve donepezil in its onset. Mania appeared soon after nortriptyline dose was increased and donepezil started (pointing against a spontaneous switch), it improved with the discontinuation of both drugs (and the dose increase of alprazolam), it soon worsened when donepezil was restarted and it soon improved after its discontinuation. In case 2, the timing of hypomania suggests a link with donepezil, as its onset and improvement were closely associated with donepezil start and discontinuation. No case of mania was observed during donepezil clinical trials (1997 Pfizer prescribing information). These two case reports seem to run against previous observations reporting that cholinergic agonists may decrease mania and anticholinergic drugs may induce mania (Goodwin and Jamison, 1990; Green *et al*., 1995). Acetylcholine may have interactive relationships with the monoamine systems, which are involved in mood disorders (Goodwin and Jamison, 1990). In case 1, a sudden imbalance in the cholinergic system, caused by the concurrent administration of a cholinergic (donepezil) and an anticholinergic (nortriptyline) drug may have caused mania. In case 2, fluoxetine may have increased blood levels and effects of donepezil by inhibiting (Ereshefsky *et al*., 1997) its metabolism by cytochromes CYP 2D6 and CYP 3A4 (1997 Pfizer prescribing information). A pharmacodynamic interaction with the calcium channel blocker verapamil and the beta-blocker atenolol, two drugs with mood effects (Baldessarini, 1996), might have been involved in the onset of hypomania. Donepezil, despite its cholinergic action, might, however, have some mood-elevating effects, alone or in combination with other psychoactive drugs.

FRANCO BENAZZI
Public Hospital 'Morgagni'
Forli, Italy

REFERENCES

Baldessarini, R. J. (1996) Drugs and the treatment of psychiatric disorders. In *The Pharmacological Basis of Therapeutics*, 9th edn (J. G. Hardman, L. E. Limbird, P. B. Molinoff, R. W. Ruddon and A. Goodman Gilman, Eds). McGraw-Hill, New York.

Ereshefsky, L., Alfaro, C. L. and Lam, Y. W. F. (1997) Treating depression: Potential drug interactions. *Psychiat. Ann.* **27**, 244–258.

Goodwin, F. K. and Jamison, K. R. (1990) *Manic-Depressive Illness*. Oxford University Press, New York.

Green, A. I., Mooney, J. J., Posener, J. A. and Schildkraut, J. J. (1995) Mood disorders: biochemical aspects. In *Comprehensive Textbook of Psychiatry*, 6th edn (H. I. Kaplan and B. J. Sadock, Eds). Williams & Wilkins, Baltimore.