# Mania associated with donepezil

There have been reports of agitation, depression, anxiety, paranoia, and aggression associated with the acetylcholinesterase inhibitor donepezil, used in the treatment of dementia.[1,2] I would like to report 4 patients with dementia who became manic after donepezil treatment. A MEDLINE search found only one similar report.[3]

The 4 patients were aged 78, 64, 74 and 68 years; 3 were women and 1 was a man. They had mild to severe dementia, as well as a major depressive disorder (patient 1), bipolar I disorder (patients 2 and 3), or delusional disorder (patient 4). When donepezil (5 mg per day) was started to improve memory, patients 1 and 2 were depressed, patient 3 was in remission, and patient 4 was delusional.

Other daily medication regimens were as follows:

- Patient 1: alprazolam (1 mg) and nortriptyline (20 mg)
- Patient 2: lamotrigine (50 mg), fluoxetine (20 mg), lorazepam (1 mg), verapamil (60 mg) (a calcium-channel blocker prescribed for hypertension), atenolol (100 mg) (a β-adrenergic blocker prescribed for hypertension), gliquidone (600 mg) (a sulfonylurea prescribed for diabetes mellitus)
- Patient 3: enalapril (2.5 mg) (for hypertension), carbidopa/levodopa (25/250 mg) (for parkinsonism), and lorazepam (1 mg)
- Patient 4: terazosin (5 mg) (a α-1-selective adrenergic receptor blocker prescribed for prostatic enlargement).

After 3 to 7 days of treatment with donepezil (5 mg per day in patients 1, 2 and 4; 10 mg per day in patient 3), mania developed suddenly in patients 1 and 4, and hypomania in patients 2 and 3. The main symptoms were euphoric mood, insomnia, pressured speech, flight of ideas, psychomotor agitation, hyperactivity, disorientation, and marked impairment of functioning in patient 1; euphoric mood, insomnia, hyperactivity, and pressured speech in patient 2; euphoric mood, hyperactivity, agitation, and logorrhea in patient 3; and irritability, aggressivity, insomnia, psychomotor agitation, worsening of delusions, and marked impairment of functioning in patient 4. Donepezil was discontinued after 4 to 7 days in the 2 manic patients, after 2 weeks in one of the hypomanic patients and after 2 months in the other.

After discontinuation of donepezil, the mania and hypomania resolved spontaneously in 1 to 7 days. Ten days to 1 month after remission, donepezil (5 mg per day) was restarted in the 2 patients who had had mania. In both, the mania recurred within a day. Donepezil was discontinued after 2 days, and there was a remission of mania within a week; this was spontaneous in one patient, and associated with antipsychotic treatment in the other.

The close temporal association between the start of donepezil and the appearance of mania or hypomania, the rapid resolution of mania soon after discontinuation of donepezil, and the recurrence of this pattern in a second trial, suggest a causal link. In the 2 patients with bipolar disorder, a spontaneous switch cannot be excluded, but the timing of the mania or hypomania suggests a strong association with donepezil. Cholinomimetic agents can improve mania and cause depression, while anticholinergic agents can have mood-elevating effects.[4] These observations may militate against a causal role of the cholinergic agent donepezil. However, when the central cholinergic system is activated by the cholinesterase inhibitor physostigmine, the noradrenergic and dopaminergic systems can be activated, causing a rebound of manic symptoms.[4] This mechanism might explain the effects of donepezil in these patients. Bipolar vulnerability in 2 patients may have facilitated this action. Pharmacodynamic interactions of donepezil with concurrent psychoactive drugs may also have been involved in the onset of mania or hypomania. As well, the anticholinergic agent nortriptyline, the calcium-channel blocker verapamil, the β-adrenergic blocker atenolol, the α-adrenergic blocker terazosin, and the dopamine agonist levodopa, act on the monoamine and acetylcholine systems, which are involved in mood disorders.[5] These may have interacted with the cholinergic agent donepezil, causing dysfunctions in these systems, and favouring the

onset of mania or hypomania. Delirium with manic features, caused by the combination of medications, might also account for this clinical picture.

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## References

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