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LETTER TO THE EDITOR

Donepezil-induced manic episodes in two patients with different types of dementia

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Dear Editor,

The efficacy of acetylcholinesterase inhibitors (AChEIs) in managing the cognitive and neuropsychiatric symptoms of Alzheimer's disease (AD) is well documented (1). While it is acknowledged that these medications can potentially induce psychiatric adverse effects, the prevalence of mood disturbances remains documented only in case reports (2). Given the established correlation between acetylcholine and depression, AChEIs are not expected to cause mania (3).

Two cases of donepezil-induced manic episodes in patients diagnosed with different types of dementia are presented. One of the cases represents the oldest patient documented to date, while the other is the only patient reported with Lewy body dementia (LBD).

Case 1 – A 95-year-old female patient was admitted to our outpatient clinic with a recent diagnosis of AD. The patient exhibited symptoms including euphoric mood, hyperactivity, pressured speech, hypersexuality, insomnia, agitation, violent behavior, and new-onset alcohol consumption. This symptomatology began six weeks after the administration of 5 mg/day donepezil. Escitalopram, which she had been taking at 10 mg/day for years, was stopped, and olanzapine 5 mg/day was initiated immediately by her psychiatrist at the fourth week after symptom onset. Two weeks later, she was admitted to the neurology clinic due to worsening symptoms. Donepezil was suspected to have induced her new symptoms and was discontinued immediately. Her symptoms fully remitted within six weeks. Her past medical history included bipolar I disorder, which had been in full remission for a significant period with valproic acid 1 g/day, aripiprazole 5 mg/day, and escitalopram 10 mg/day. Aripiprazole was discontinued three years ago, and valproic acid was stopped 21 months ago by her psychiatrist. There was no family history of psychiatric disorders.

Case 2 – A 66-year-old male with a diagnosis of LBD was admitted to our outpatient clinic with elevated mood, increased visual hallucinations, delusions, behavioral disorganization, pressured speech, hypersexuality, insomnia, agitation, and increased preoccupation with poetry writing. His medication regimen comprised the following daily doses for approximately one year: donepezil (5 mg), memantine (28 mg), pramipexole (1.5 mg), and rasagiline (1 mg). One and a half months earlier, the dosage of pramipexole had been reduced and then discontinued due to visual hallucinations, which diminished by more than 50%, while motor symptoms remained stable. After discontinuation of pramipexole, aripiprazole 5 mg/day was initiated, resulting in a further decrease in hallucinations. Two weeks later, the donepezil dosage was increased to 10 mg/day, and two days afterward the patient exhibited symptoms consistent with mania, which progressively worsened. The donepezil dosage was then reduced to 5 mg/day, resulting in gradual improvement that became fully apparent within a few days, without any need for additional treatment of the symptoms. His medical

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history included hypertension, with no reported personal or familial psychiatric disorders.

The thought processes of both patients were conducive to flight of ideas and occasional loosening of associations, with content marked by grandiose ideation. Montreal Cognitive Assessment scores were 14 and 12 out of 30 on admission, respectively. Physical examination and detailed laboratory investigations did not reveal any abnormalities. Delirium was excluded based on clinical symptoms. No fluctuations were observed. The Young Mania Rating Scale scores of the patients were 46 and 40, respectively. As both patients scored 8 on the Naranjo Adverse Drug Reaction Probability Scale, the symptoms were evaluated as "probable" in terms of drug relation. The mood of both individuals has remained stable, with no recurrence of manic symptoms for one year of follow-up. Written informed consents were obtained from the patients' relatives.

Donepezil-induced mania was first reported by Benazzi in 1998 (4). The temporal relationship between the initiation of donepezil, the onset of manic symptoms, and the subsequent improvement of symptoms when donepezil is ceased or discontinued points to the possible mood-elevating properties of donepezil. The cholinergic-adrenergic hypothesis posits that increased acetylcholine is associated with depressive symptoms (1). It is conceivable that the initiation of donepezil therapy may have triggered a shift in the acetylcholine-serotonin balance toward serotonin dominance, culminating in a recurrence of hypomania. The findings and observations presented here suggest that neurotransmitter balance plays a critical role and supports the hypothesis that donepezil is the primary precipitating agent.

Of the 12 previously documented patients, who exhibited a range of cognitive impairment types and degrees and were between 50 and 81 years of age, nine were receiving donepezil treatment, and seven had mood disorders (4, 5). The time to manic episode exhibited variability, ranging from three days to three weeks after initiation or dose escalation of donepezil. Resolution of symptoms was observed within two weeks of cessation or discontinuation of the AChEI, either spontaneously or following treatment with an antipsychotic agent (4, 5).

It has been reported that bipolar disorder may be encountered in advanced age, particularly in the context of a neurodegenerative process, and may be aggravated by AChEIs. The condition is most commonly seen in cases of frontotemporal dementia, is the second most common in vascular dementia, and is least common in AD (6–8).

The presence of drug-induced mania should be considered in cases where there is a temporal correlation between the initiation of donepezil treatment and the onset of a new manic episode or following a dose increase. AChEIs must be used with caution in patients with a documented history of mood disorders, particularly bipolar I disorder.

Informed Consent: Written informed consents were obtained from the patients' relatives for the publication of anonymized case details.

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