The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.

Should we treat patients with very mild Alzheimer disease with a cholinesterase inhibitor?

A 63-year-old lawyer consulted a memory clinic because of memory complaints over the past 12 months and difficulties in planning his cases for court. His father had Alzheimer disease starting at age 70. His Mini Mental State Examination score was 29/30, and his Montreal Cognitive Assessment was 25/30. Magnetic resonance imaging (MRI) revealed atrophy of both hippocampi, single photon emission computed tomography (SPECT) showed hypoperfusion of parietotemporal areas bilaterally, and fluorodeoxyglucose positron emission tomography (FDG-PET) revealed hypometabolism of these areas. He received a diagnosis of "very early Alzheimer disease" and was able to leave work with full medical disability. He wanted to be involved with clinical trials aiming to arrest disease progression, but wanted to take donepezil immediately.

There is an ongoing effort to diagnose Alzheimer disease in its earliest stages, when there are only cognitive complaints and mild impairment on testing, with no functional impact on daily life. The principal motivation for such an early diagnosis is the hope that drugs acting on specific pathophysiological components of the disease (e.g., amyloid deposition, tau hyperphosphorylation, inflammatory response, apoptosis) will be able to arrest its progression. New diagnostic criteria have been proposed and are undergoing validation. All 3 of the following must be present: memory complaints for at least 6 months, objective evidence of impaired episodic memory, and atrophy of medial temporal structures on MRI or abnormal spinal fluid biomarkers tau and β42 or specific metabolic patterns on SPECT or PET.[1] These diagnostic criteria were meant to be used only for research and not for widespread clinical practice for the following reasons: there is a risk of a catastrophic reaction in someone with full insight into the prognosis of Alzheimer disease, there are concerns about the extra costs of the diagnostic tests and there are no treatments proven to help substantially at this early stage of Alzheimer disease.

Some clinical trials evaluating the use of donepezil in amnestic mild cognitive impairment (aMCI) suggest a slight cognitive benefit, but the effects are small, and there is no evidence that cholinesterase inhibitors (ChEI) delay progression to dementia. In places where patients with very early Alzheimer disease (before functional impairment) have the possibility of being enrolled in clinical trials, they may be kept off ChEI if they wish until they reach a clinical stage of dementia. This would allow participation in placebo-controlled studies with a survival design (e.g., time to clinical dementia) aiming to slow progression of the disease. The reality is that in North America it will be very difficult not to prescribe a ChEI at that stage unless we can offer, immediately after the diagnosis, an opportunity to join a clinical trial with a promising symptomatic or disease-modifying agent. Otherwise, a patient's request for immediate pharmacological treatment should be accepted, after giving best available advice, which includes control of vascular risk factors, treatment of associated depression, planning for finances and advance directives.

Will regulators accept the diagnosis of "very early Alzheimer disease" rather than aMCI as an indication for new drugs? This is likely since aMCI is not a specific diagnosis but rather a risk state toward dementia. Can we arrest progression of Alzheimer disease if treated early enough? I certainly hope so, and new research criteria that make the earlier diagnosis of Alzheimer disease possible are a big step in the right direction, although they do create new challenges for clinicians and patients.

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Reference

1. Dubois M, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology* 2007;6:734–46.

Psychopharmacology for the Clinician columns are usually based on a case report that illustrates a point of interest in clinical psychopharmacology. They are about 500–650 words long and do not include references. Columns can include a bibliography which will be available only at the journal website and can be accessed through a link at the bottom of the column.
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