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Do patients at high risk of Alzheimer's disease benefit from early treatment?

Evidence-based answer

Yes, but the extent of the benefit is unclear. Treating patients with early-stage Alzheimer's disease yields statistically significant, though perhaps not clinically significant, improvement in cognition and global function (strength of recommendation [SOR]: **A**, consistent evidence from multiple randomized controlled trials [RCTs]). In a few cases, it may delay loss of function and need for long-term care.

Treating patients with mild cognitive impairment (MCI)—the most likely precursor to Alzheimer's disease—with cholinesterase inhibitors seems to have an initial, but perhaps unsustained, benefit over no treatment (SOR: **B**, inconsistent results from few trials). Withdrawing anticholinergic drugs from patients taking them promises to reduce symptoms of MCI, but is unlikely to reduce rates of Alzheimer's (SOR: **C**, well-designed observational study).

Clinical commentary

Remember nondrug interventions

Clinicians often forget the many nonpharmacologic treatments for dementia, including exercise, cognitive stimulation, increased socialization, addressing polypharmacy, and optimizing nutrition. Diagnosing and managing comorbidities such as depression and cardiovascular disease are also important. Primary care physicians who care for the frail elderly should advocate these interventions. In the very elderly, who are all at high risk of developing Alzheimer's disease, these measures may help prevent functional decline and reduce clinically

apparent disease.

All patients diagnosed with early-stage Alzheimer's disease, and possibly patients with MCI, should be offered a trial of pharmacotherapy. However—given the high cost of drug therapy, the modest improvement it produces in patients with Alzheimer's dementia, and the lack of definitive evidence that it benefits patients with MCI—I wouldn't advocate medication for asymptomatic patients at high risk of developing dementia.

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FAST TRACK

Treating early Alzheimer's yields statistically significant—though perhaps not clinically significant—improvement in cognition and global function.

Evidence summary

Alzheimer's disease is characterized by deficits in memory and at least 1 other cognitive domain (aphasia, apraxia, ag-

nosia, or loss of executive function) accompanied by impaired function. As the US population ages, Alzheimer's disease is likely to increase substantially in preva-



lence and cost, from its current 4.5 million people affected and \$100 billion per year in direct expenses.¹

Because the definition of Alzheimer's precludes asymptomatic disease, "early" treatment implies either treating a precursor condition or treating before cognitive and functional impairment force the patient and family to seek medical care. The literature identifies 2 possible prodromal conditions: MCI and personality change. Personality change is proposed as a prodrome based only on a small study that diagnosed Alzheimer's disease at autopsy, so this Clinical Inquiry doesn't address it further.²

Therapy for MCI:

A look at 3 interventions

MCI is a measurable memory deficit, more severe than normal aging changes (slower learning of new material and difficulty retrieving names and places) but not meeting criteria for dementia.³ Researchers differ on a more precise definition; some subdivide MCI into "MCI-amnesic type" and "MCI-multiple cognitive deficits type."⁴ MCI progresses to Alzheimer's disease in anywhere from 10% to 56% of patients.^{4,5}

Three interventions may benefit patients with MCI:

- cholinesterase inhibitors
- exercise
- discontinuation of anticholinergic drugs in patients taking them.

Two recent RCTs of donepezil^{6,7} and 1 of galantamine⁸ showed initial cognitive improvement in MCI patients. However, the only trial carried out for 3 years showed no persistent benefit at that time.⁶

Another study showed that moderate exercise—30 minutes 3 days a week—improves cognition in MCI patients.⁹

A longitudinal cohort study found that patients taking anticholinergic drugs had an 80% prevalence of MCI, compared with a 35% prevalence in a matched population of patients not using these drugs; yet Alzheimer's disease

hadn't increased among the anticholinergic drug users at 8-year follow-up. Attributable risk for MCI from anticholinergic drug use was 19%. Stopping anticholinergic medications may reduce the prevalence of MCI.¹⁰

In established Alzheimer's disease, cholinesterase inhibitors statistically benefit patients with early and moderate disease and probably benefit patients with severe disease.^{11,12} The treatment effect is small, however—3 points on a 70-point cognitive scale. Comparison studies show mixed results; no single agent appears to be most effective.¹²

Are cholinesterase inhibitors cost effective?

The relatively modest benefit of cholinesterase inhibitors—especially given their expense—has raised questions about cost effectiveness. When weighing the choice, consider that donepezil may delay nursing home placement,^{11,13} and the cholinesterase inhibitors may reduce caregiver burden.¹¹ The medications are likely to be cost effective in patients showing a clinically significant response. More effective treatments would clearly be welcome.

Recommendations

The US Preventive Services Task Force (USPSTF) acknowledges that fair to good evidence supports a benefit from treatment of early-stage Alzheimer's disease. However, routine screening for dementia in older adults receives an I-level recommendation (insufficient evidence), both because it's unknown whether diagnosis would be as accurate and treatment as effective in primary care practices and because the benefit from screening is uncertain (coupled with a small treatment benefit).¹⁴

The task force reported finding no good data that treating MCI is beneficial. However, the USPSTF recommendation preceded publication of all 4 RCTs on treatment of MCI addressed in this Clinical Inquiry.

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FAST TRACK

For the very elderly, encourage exercise, cognitive stimulation, and increased socialization, which may help prevent functional decline.

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Physicians published a joint clinical practice guideline in March 2008 that questioned whether the slight benefit of cholinesterase inhibitors surpassed the harm of adverse effects and cost. They recommend counseling each patient about the likely benefits and harms.¹⁵ ■

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