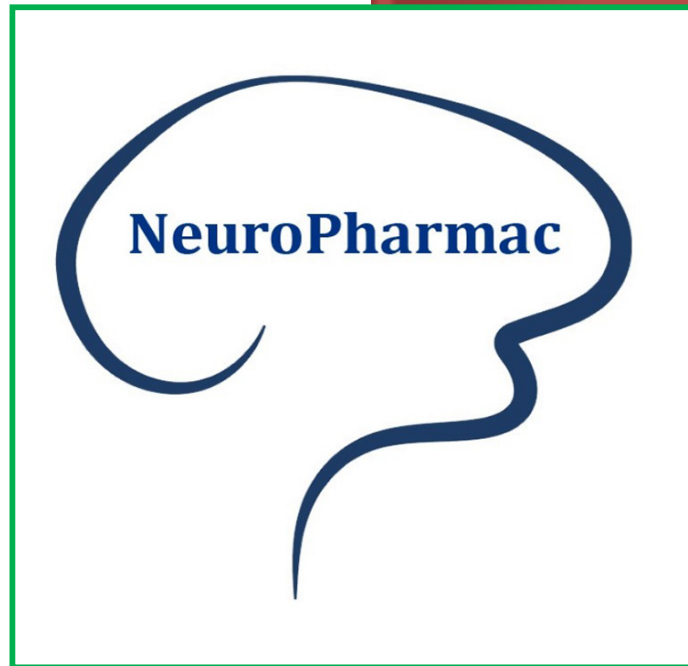


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## Alzheimer's Disease: Pharmacotherapy of subjective cognitive decline

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### ABSTRACT

Alzheimer disease (AD) is a neurodegenerative disorder marked by cognitive and behavioral impairment that significantly interferes with social and occupational functioning. AD is a progressive and fatal dementia of unknown cause characterized by loss of cognitive and physical functioning, commonly with behavior or cognitive symptoms. Cognitive decline is gradual and includes memory loss, aphasia, apraxia, agnosia, disorientation, and impaired executive function. Physicians will often play a major role in diagnosing and treating dementia and related disorders in the community. Accurate treatment of cognitive symptoms is important. Accordingly, we reviewed the available pharmacotherapy in the clinical management of cognitive symptoms of dementia.

### INTRODUCTION

Cognitive decline is gradual and includes memory loss, aphasia, apraxia, agnosia, disorientation, and impaired executive function. Other symptoms include depression, psychotic symptoms, aggression, motor hyperactivity, uncooperativeness, wandering, and combativeness. Patients become increasingly unable to care for themselves. Subjective cognitive decline (SCD) is common in older adults and may be an early marker of future cognitive decline. Research suggests that SCD is more closely related to concurrent symptoms of depression.<sup>1-3</sup> Subjective cognitive decline is indicative of accumulation of early tauopathy in the medial temporal lobe, specifically in the entorhinal cortex, and to a lesser extent, elevated global levels of A $\beta$ . Our findings suggest multiple underlying pathways that motivate SCD that do not necessarily interact to influence SCD endorsement. As such, multiple biological factors must be considered when assessing SCD in clinically healthy older adults.<sup>2-4</sup> Research increasingly suggests that subjective cognitive decline (SCD) in older adults, in the absence of objective cognitive dysfunction or depression, may be a harbinger of non-normative cognitive decline and eventual progression to

dementia.<sup>5</sup> suggest that depressive symptoms, particularly anhedonia and negative affect, are related to cognitive decline in older African Americans.<sup>6-8</sup> Subjective memory complaints (SMCs) represent a type of complaint made by individuals with cognitive symptoms or complaints but no clear impairment on objective psychometric testing.<sup>9-12</sup> Evidence suggests that individuals with SMCs may be at increased risk of dementia, with several studies showing that patients with cognitive complaints have a higher rate of progression to mild cognitive impairment (MCI) or AD than those without.<sup>13-18</sup> Subjective memory impairment (SMI) is receiving increasing attention as a pre-mild cognitive impairment (MCI) condition in the course of the clinical manifestation of Alzheimer disease (AD).<sup>19</sup> The prediction of dementia in AD by SMI with subsequent amnesic MCI supports the model of a consecutive 3-stage clinical manifestation of AD from SMI via MCI to dementia.<sup>20-21</sup> The diagnostic criteria of the National Institute on Aging and the Alzheimer's Association view AD as a spectrum beginning with an asymptomatic preclinical phase progressing to the symptomatic preclinical phase and then to the dementia phase. AD is a clinical diagnosis, based

largely on identified symptoms and difficulty with activities of daily living revealed by patient and caregiver interviews. The Folstein Mini-Mental State Examination (MMSE) can help establish a history of deficits in two or more areas of cognition at baseline against which to evaluate change in severity over time (table 1). The average expected decline in an untreated patient is 2 to 4 points per year.

Table 1: Stages of Alzheimer’s Disease

Satge with score	symptoms
Mild (MMSE score 26–18)	Patient has difficulty remembering recent events. Ability to manage finances, prepare food, and carry out other household activities declines. May get lost while driving. Begins to withdraw from difficult tasks and to give up hobbies. May deny memory problems
Moderate (MMSE score 17–10)	Patient requires assistance with activities of daily living. Frequently disoriented with regard to time (date, year, and season). Recall for recent events is severely impaired. May forget some details of past life and names of family and friends. Agitation, paranoia, and delusions are common
Severe (MMSE score 9–0)	Patient loses ability to speak, walk, and feed self. Incontinent of urine and feces. Requires care 24 hours a day, 7 days a week

MMSE: Mini-Mental Status Examination

**PHARMACOTHERAPY OF COGNITIVE SYMPTOMS**

The mainstay of therapy for patients with Alzheimer disease (AD) is the use of centrally acting cholinesterase inhibitors to attempt to compensate for the depletion of acetylcholine (ACh) in the cerebral cortex and hippocampus. A partial N-methyl-D-aspartate (NMDA) antagonist is approved for treatment of moderate and severe AD. Table 2 summarizes dosing of the cholinesterase inhibitors and memantine. When switching from one cholinesterase inhibitor to another, 1 week washout is generally sufficient. No comparative trials have assessed the effectiveness of one agent over another. Donepezil, rivastigmine, and galantamine are indicated in mild to moderate AD; donepezil is also indicated for severe AD.<sup>22,23</sup>

If the decline in MMSE score is more than 2 to 4 points after treatment for 1 year with the initial agent, it is reasonable to change to a different cholinesterase inhibitor. Otherwise, treatment should be continued with the initial medication throughout the course of the illness. The three cholinesterase inhibitors have similar efficacy in mild to moderate AD, and duration of benefit lasts 3 to 12 months. Because of their short half-lives, if rivastigmine or galantamine treatment is interrupted for several days or longer, retitrate starting at the lowest dose. The most frequent adverse effects include mild to moderate gastrointestinal (GI) symptoms (nausea, vomiting, and diarrhea), urinary incontinence, dizziness, headache, syncope, bradycardia, muscle weakness, salivation, and sweating. Abrupt discontinuation can cause worsening of cognition and behavior in some patients.<sup>24-29</sup>

**Memantine**

Memantine (Namenda) blocks glutamatergic neurotransmission by antagonizing N-methyl-d-aspartate receptors, which may prevent excitotoxic reactions. It is used as monotherapy and in combination with a cholinesterase inhibitor. It is indicated for treatment of moderate to severe AD, but not for mild AD. It is not metabolized by the liver but

is primarily excreted unchanged in the urine. Dosing must be adjusted in patients with renal impairment. It is usually well tolerated; side effects include constipation, confusion, dizziness, and headache. Because of the incidence of side effects and a lack of supporting evidence, neither NSAIDs nor prednisone is recommended for treatment or prevention of AD. Because of limited efficacy data, the potential for adverse effects (eg, nausea, vomiting, diarrhea, headache, dizziness, restlessness, weakness, and hemorrhage), and poor standardization of herbal products, ginkgo biloba is not recommended for prevention or treatment of AD.<sup>30-33</sup>

Table 2: Dosing of Drugs Used for Cognitive Symptoms

Drug	Initial Dose	Usual Range
Cholinesterase inhibitors		
Donepezil	5 mg daily in the evening	5–10 mg daily in mild to moderate AD 10–23 mg daily in moderate to severe AD
Rivastigmine	1.5 mg twice daily (capsule, oral solution) 4.6 mg/day (transdermal patch)	3–6 mg twice a day (capsule, oral solution) 9.5–13.3 mg/day (transdermal patch)
Galantamine	4 mg twice daily (tablet, oral solution) 8 mg daily in the morning (ER capsule)	8–12 mg twice a day (tablet, oral solution) 16–24 mg (extended release capsule)
N-methyl-d-aspartate (NMDA) receptor antagonist		
Memantine	5 mg daily 7 mg daily (ER capsule)	10 mg twice daily 28 mg daily (ER capsule)

### Combination Drugs

Fixed dose combination capsule containing memantine extended-release and donepezil for patients with moderate-to-severe Alzheimer disease currently stabilized on donepezil 10 mg once daily. Administer once daily in the evening. Starting dose is 7 mg/10 mg PO, taken once a day in the evening. Increase dose in 7 mg increments based on the memantine component to the recommended maintenance dose of 28 mg/10 mg once daily.<sup>34</sup>

### Nutritional Supplement

Medical foods are dietary supplements intended to compensate specific nutritional problems caused by a disease or condition. Caprylidene is a prescription medical food that is metabolized into ketone bodies. The brain can use these ketone bodies for energy when its ability to process glucose is impaired, which brain-imaging scans suggest is the case in AD.<sup>35</sup>

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