



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Alzheimer's disease
-July 2019-



Background:

In July 2019, the IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed medications used to treat Alzheimer's disease. The NPTC last reviewed this topic in 2011 at which time donepezil, a cholinesterase inhibitor, was added to the IHS National Core Formulary. After evaluating current treatment guidelines, applicable research, and procurement data, the NPTC voted to **add memantine** to the National Core Formulary.

Discussion:

Alzheimer's disease is a progressive and fatal neurologic condition for which no current pharmacologic therapies prevent, slow or stop deterioration. The pathophysiology of the disease is poorly understood but involves the accumulation of amyloid proteins outside neurons and the formation of tau protein tangles inside neurons which is associated with a localized inflammatory reaction and neuronal atrophy. These changes lead to reduced cerebral synthesis of acetylcholine and pathologic excitation by glutamate on neuronal structures¹.

Alzheimer's disease is classified into three phases; 1) preclinical – which is an asymptomatic phase designated for research purposes, 2) mild cognitive impairment – characterized by development of memory impairment with retained ability to perform activities of daily living (ADL), and 3) dementia – characterized by impairment of both memory and capacity to perform ADLs. The severity of Alzheimer's dementia is further categorized by staging into mild, moderate or severe disease². The definitive diagnosis of Alzheimer's dementia requires histopathology, but most cases are classified as “probable” based on clinical characteristics. Diagnostic parameters include worsening cognition of insidious onset, a cognitive deficit based on objective testing, impairment in two specific areas of function (acquisition of new information, complex reasoning, visuospatial ability, language, personality and/or behavior), and no evidence of another cause for the cognitive decline.

No medications have been approved for the treatment of Alzheimer's disease in the pre-clinical or mild cognitive impairment phases, as studies have failed to show benefit in these populations. For Alzheimer's dementia, two medication classes are approved which modestly reduce cognitive and behavioral symptoms associated with mild, moderate and severe stages: cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and an N-methyl-D-aspartate receptor agonist (memantine)¹.

The American Psychiatric Association^{3,4}, American Neurological Society⁵ and British National Institute for Health and Care Excellence guidelines^{6,7} all recommend starting a cholinesterase inhibitor upon diagnosis of mild, moderate or severe Alzheimer's dementia. Studies have shown similar, mild degrees of improved cognitive function with each of the three approved cholinesterase inhibitors (on average –2.37 points [95% CI –2.73 to –2.02, $p < 0.00001$] on the ADAS-Cog Scale with 6 months of treatment)⁴, though only donepezil has FDA approval for severe Alzheimer's disease. All cholinesterase inhibitors have high discontinuation rates (29%) compared to placebo (18%) due to side effects⁸.

Memantine use, with and without a cholinesterase inhibitor, in moderate to severe Alzheimer's dementia is associated with improvement in several outcomes, including cognitive function (3.11 point improvement on the Severe Impairment Battery, 95% CI 2.42 to 3.92)⁹. The aforementioned guidelines also recommend considering the addition of memantine in clients with moderate to severe dementia. Memantine monotherapy is recommended for patients who cannot tolerate a cholinesterase inhibitor and have moderate to severe Alzheimer's dementia³⁻⁷. Studies have demonstrated no clear benefit of the use of memantine in mild Alzheimer's dementia and the magnitude of benefit in moderate to severe disease is mild at best¹⁰.

Frequent reevaluation of clinical benefit is recommended, with discontinuation of therapy when the patient no longer benefits from therapy, or becomes fully dependent/non-communicative³⁻⁷.

Findings:

Alzheimer's disease remains a condition where available treatments provide nothing to alter the course of the disease, but can provide mild relief of cognitive and behavioral symptoms. Guidelines are consistent in recommending a cholinesterase inhibitor at the time of Alzheimer's dementia diagnosis and considering the addition of memantine in those with moderate to severe staging or as monotherapy in individuals intolerant to cholinesterase inhibitors.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References

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