Therapeutic Class Overview  
Alzheimer’s Agents

Therapeutic Class
- **Overview/Summary:** Alzheimer’s disease is a progressive neurodegenerative disorder in older adults that affects cognition, behavior and activities of daily living.\(^1\) It is the most common form of dementia and the average life expectancy from the onset of symptoms to death is approximately 8 to 10 years.\(^1\) Diagnostic features include memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.\(^1\)

The pathophysiologic mechanisms are not entirely understood; however, the disease is characterized by the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in various regions of the brain. Inflammation and free radical processes lead to neuron dysfunction and death. It is thought that memory loss is partially the result of a deficiency of cholinergic neurotransmission.\(^2,3\) Glutamate, an excitatory neurotransmitter, may also play a role in the pathophysiology of Alzheimer’s disease. Glutamate activates N-methyl-D-aspartate (NMDA) receptors and is involved in learning and memory. However, excessive amounts of glutamate in the brain may lead to excitotoxicity and cell death.\(^3\)

There are five agents approved for the treatment of Alzheimer’s disease, including cholinesterase inhibitors (donepezil, galantamine and rivastigmine), an NMDA receptor antagonist (memantine) and a combination product (memantine extended release [ER]/donepezil).\(^4\)\(^\text{—}^\text{13}\) Although none of the agents delay the progression of neurodegeneration, they do delay the progression of symptoms. The cholinesterase inhibitors enhance cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Memantine blocks NMDA receptors and inhibits their overstimulation by glutamate. Currently, memantine ER (Namenda XR\(^\text{®}\)) and memantine ER/donepezil (Namzaric\(^\text{®}\)) are the only products not available generically.

Table 1. Medications Included Within the Therapeutic Class Review\(^4\)\(^\text{—}^\text{13}\)

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<th>Generic (Trade Name)</th>
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| Donepezil\(^*\) (Aricept\(^\text{®*}\)) | Mild-to-moderate dementia of the Alzheimer’s type  
Moderate-to-severe dementia of the Alzheimer’s type | Orally disintegrating tablet:  
5 mg  
10 mg  
Tablet:  
5 mg  
10 mg  
23 mg | yes |
| Galantamine (Razadyne\(^\text{®*}\), Razadyne ER\(^\text{®*}\)) | Mild-to-moderate dementia of the Alzheimer’s type | Extended release capsule:  
8 mg  
16 mg  
24 mg  
Tablet:  
4 mg  
8 mg  
12 mg | yes |
| Rivastigmine (Exelon\(^\text{®*}\), Exelon Patch\(^\text{®*}\)) | Mild-to-moderate dementia of the Alzheimer’s type (capsule and solution)  
Mild, moderate, and severe dementia of the Alzheimer’s type (transdermal) | Capsule:  
1.5 mg  
3 mg  
4.5 mg  
6 mg | yes |
**Generic (Trade Name)** | **Food and Drug Administration Approved Indications** | **Dosage Form/Strength** | **Generic Availability**
--- | --- | --- | ---
patch) | Mild-to-moderate dementia associated with Parkinson’s disease | Solution: 2 mg/mL | 
 | | Transdermal patch: 4.6 mg/24 hours | |
 | | 9.5 mg/24 hours | 
 | | 13.3 mg/24 hours | 

**Memantine** (Namenda®*, Namenda XR®, Namenda Titration Pack®*, Namenda XR Titration Pack®)  
Moderate-to-severe dementia of the Alzheimer’s type  
Extended release capsule: 7 mg, 14 mg, 21 mg, 28 mg  
Solution: 10 mg/5 mL  
Tablet: 5 mg, 10 mg

**Combination Products**

**Memantine ER/donepezil (Namzaric®)**  
Moderate to severe dementia of the Alzheimer’s type for patients stabilized on memantine and donepezil  
Capsule: 14 mg/10 mg, 28 mg/10 mg  

ER=extended-release

*Generic is available in at least one dosage form or strength.

**Evidence-based Medicine**
- Clinical trials have demonstrated the safety and efficacy of the Alzheimer’s agents.  
- Overall there is limited head to head data available comparing the efficacy of the different agents used to treat Alzheimer’s disease. Several different outcomes have been assessed using more than forty different instruments, including cognition, global function, behavior and quality of life. There is inconsistent evidence from well-designed trials that donepezil, galantamine, rivastigmine and memantine positively affect cognition and global function, although the improvements are modest. These findings are less consistent for other outcomes, including behavior and quality of life. In most cases, the duration of well-designed clinical trials were less than one year. There are very few studies that directly compare their various agents. Most of the trials have compared active treatment to placebo or no treatment. The published studies also differ with regards to design, patient population and treatment duration, which make it difficult to directly compare the results.

**Key Points within the Medication Class**
- According to Current Clinical Guidelines:  
  - Supports use of the cholinesterase inhibitors as first-line agents for mild-moderate Alzheimer’s disease.  
  - Memantine is effective in the treatment of moderate-to-severe Alzheimer’s disease.  
  - Memantine may be added to a cholinesterase inhibitor.  
  - Evidence does not show clinically meaningful advantages to administering higher doses of donepezil; however, higher doses of rivastigmine patch may be associated with greater benefit.
  - Other Key Facts:  
    - Memantine ER (Namenda XR®) and memantine ER/donepezil (Namzaric®) are the only products not available generically.
o Rivastigmine is uniquely indicated for symptoms of dementia in Parkinson’s disease patients.

References


