**DONEPEZIL**

**THERAPEUTICS**

**Brands**
- Aricept
- Memac

*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: acetylcholine enzyme inhibitor (ACh-EI)
- Cholinesterase inhibitor (selective acetylcholinesterase inhibitor); cognitive enhancer

**Commonly Prescribed for**
(bold for FDA approved)
- Alzheimer disease (mild, moderate, and severe)
- Memory disorders in other conditions
- Mild cognitive impairment

**How the Drug Works**
- Reversibly but noncompetitively inhibits centrally active acetylcholinesterase (AChE), making more acetylcholine available
- Increased availability of acetylcholine compensates in part for degenerating cholinergic neurons in neocortex that regulate memory
- Does not inhibit butryrylcholinesterase
- May release growth factors or interfere with amyloid deposition

**How Long Until It Works**
- May take up to 6 weeks before any improvement in baseline memory or behavior is evident
- May take months before any stabilization in degenerative course is evident

**If It Works**
- May improve symptoms and slow progression of disease, but does not reverse the degenerative process

**If It Doesn’t Work**
- Consider adjusting dose, switching to a different cholinesterase inhibitor or adding an appropriate augmenting agent
- Reconsider diagnosis and rule out other conditions such as depression or a dementia other than Alzheimer disease

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**SIDE EFFECTS**

**How Drug Causes Side Effects**
- Peripheral inhibition of acetylcholinesterase can cause gastrointestinal side effects
- Central inhibition of acetylcholinesterase may contribute to nausea, vomiting, weight loss, and sleep disturbances

**Notable Side Effects**
- Nausea, diarrhea, vomiting, appetite loss, increased gastric acid secretion, weight loss
- Insomnia, dizziness
- Muscle cramps, fatigue, depression, abnormal dreams

**Life-Threatening or Dangerous Side Effects**
- Rare seizures
- Rare syncope

**Weight Gain**
- Reported but not expected
- Some patients may experience weight loss

**Sedation**
- Reported but not expected

**What to Do About Side Effects**
- Wait
- Wait

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**Best Augmenting Combos for Partial Response or Treatment Resistance**
- Atypical antipsychotics to reduce behavioral disturbances
- Antidepressants if concomitant depression, apathy, or lack of interest
- Memantine for moderate to severe Alzheimer disease
- Divalproex, carbamazepine, or oxcarbazepine for behavioral disturbances
- Not rational to combine with another cholinesterase inhibitor

**Tests**
- None for healthy individuals
DONEPEZIL (continued)

Long-Term Use
- Drug may lose effectiveness in slowing degenerative course of Alzheimer disease after 6 months
- Can be effective in some patients for several years

Habit Forming
- No

How to Stop
- Taper to avoid withdrawal effects
- Discontinuation may lead to notable deterioration in memory and behavior, which may not be restored when drug is restarted or another cholinesterase inhibitor is initiated

Pharmacokinetics
- Metabolized by CYP450 2D6 and CYP450 3A4
- Elimination half-life approximately 70 hours

Drug Interactions
- Donepezil may increase the effects of anesthetics and should be discontinued prior to surgery
- Inhibitors of CYP450 2D6 and CYP450 3A4 may inhibit donepezil metabolism and increase its plasma levels
- Inducers of CYP450 2D6 and CYP450 3A4 may increase clearance of donepezil and decrease its plasma levels
- Donepezil may interact with anticholinergic agents and the combination may decrease the efficacy of both
- May have synergistic effect if administered with cholinomimetics (e.g., bethanechol)
- Bradycardia may occur if combined with beta blockers
- Theoretically, could reduce the efficacy of levodopa in Parkinson’s disease
- Not rational to combine with another cholinesterase inhibitor

Other Warnings/Precautions
- May exacerbate asthma or other pulmonary disease
- Increased gastric acid secretion may increase the risk of ulcers
- Bradycardia or heart block may occur in patients with or without cardiac impairment

Best Augmenting Agents for Side Effects
- Hypnotics or trazodone may improve insomnia
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range
- 5–10 mg at night

Dosage Forms
- Tablet 5 mg, 10 mg, 23 mg
- Orally disintegrating tablet 5 mg, 10 mg

How to Dose
- Initial 5 mg/day; may increase to 10 mg/day after 4–6 weeks

Dosing Tips
- Side effects occur more frequently at higher doses than at lower doses
- Slower titration (e.g., 6 weeks to 10 mg/day) may reduce the risk of side effects
- Food does not affect the absorption of donepezil
- Probably best to utilize highest tolerated dose within the usual dosage range
- Some off-label uses for cognitive disturbances other than Alzheimer disease have anecdotally utilized doses higher than 10 mg/day
- When switching to another cholinesterase inhibitor, probably best to cross-titrate from one to the other to prevent precipitous decline in function if the patient washes out of one drug entirely

Overdose
- Can be lethal; nausea, vomiting, excess salivation, sweating, hypotension, bradycardia, collapse, convulsions, muscle weakness (weakness of respiratory muscles can lead to death)

 Wait
- Take in daytime to reduce insomnia
- Use slower dose titration
- Consider lowering dose, switching to a different agent or adding an appropriate augmenting agent

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THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Once a day dosing
- May be used in vascular dementia
- May work in some patients who do not respond to other cholinesterase inhibitors
- May work in some patients who do not tolerate other cholinesterase inhibitors

Potential Disadvantages
- Patients with insomnia

Primary Target Symptoms
- Memory loss in Alzheimer disease
- Behavioral symptoms in Alzheimer disease
- Memory loss in other dementias

Pearls
- A fixed-dose combination of memantine extended-release and donepezil has been approved for the treatment of moderate to severe Alzheimer’s dementia in patients stabilized on memantine and donepezil
- Dramatic reversal of symptoms of Alzheimer disease is not generally seen with cholinesterase inhibitors
- Can lead to therapeutic nihilism among prescribers and lack of an appropriate trial of a cholinesterase inhibitor

* Perhaps only 50% of Alzheimer patients are diagnosed, and only 50% of those diagnosed are treated, and only 50% of those treated are given a cholinesterase inhibitor, and then only for 200 days in a disease that lasts 7–10 years
- Must evaluate lack of efficacy and loss of efficacy over months, not weeks
- Treats behavioral and psychological symptoms of Alzheimer dementia as well as cognitive symptoms (i.e., especially

SPECIAL POPULATIONS

Renal Impairment
- Few data available but dose adjustment is most likely unnecessary

Hepatic Impairment
- Few data available; may need to lower dose

Cardiac Impairment
- Should be used with caution
- Syncopal episodes have been reported with the use of donepezil

Elderly
- Some patients may tolerate lower doses better
- Use of cholinesterase inhibitors may be associated with increased rates of syncope, bradycardia, pacemaker insertion, and hip fracture in older adults with dementia

Children and Adolescents
- Safety and efficacy have not been established
- Preliminary reports of efficacy as an adjunct in attention deficit hyperactivity disorder (ADHD) (ages 8–17)

Pregnancy
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
* Not recommended for use in pregnant women or women of childbearing potential

Breast Feeding
- Unknown if donepezil is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
* Recommended either to discontinue drug or bottle feed
- Donepezil is not recommended for use in nursing women

Do Not Use
- If there is a proven allergy to donepezil
DONEPEZIL (continued)

- Patients who complain themselves of memory problems may have depression, whereas patients whose spouses or children complain of the patient’s memory problems may have Alzheimer disease
- Treat the patient but ask the caregiver about efficacy
- What you see may depend upon how early you treat
- The first symptoms of Alzheimer disease are generally mood changes; thus, Alzheimer disease may initially be diagnosed as depression
- Women may experience cognitive symptoms in perimenopause as a result of hormonal changes that are not a sign of dementia or Alzheimer disease
- Aggressively treat concomitant symptoms with augmentation (e.g., atypical antipsychotics for agitation, antidepressants for depression)
- If treatment with antidepressants fails to improve apathy and depressed mood in the elderly, it is possible that this represents early Alzheimer disease and a cholinesterase inhibitor like donepezil may be helpful
- What to expect from a cholinesterase inhibitor:
  - Patients do not generally improve dramatically although this can be observed in a significant minority of patients
  - Onset of behavioral problems and nursing home placement can be delayed
  - Functional outcomes, including activities of daily living, can be preserved
  - Caregiver burden and stress can be reduced
  - Delay in progression in Alzheimer disease is not evidence of disease-modifying actions of cholinesterase inhibition
  - Cholinesterase inhibitors like donepezil depend upon the presence of intact targets for acetylcholine for maximum effectiveness and thus may be most effective in the early stages of Alzheimer disease
  - The most prominent side effects of donepezil are gastrointestinal effects, which are usually mild and transient
  - May cause more sleep disturbances than some other cholinesterase inhibitors
  - For patients with intolerable side effects, generally allow a washout period with resolution of side effects prior to switching to another cholinesterase inhibitor
- Weight loss can be a problem in Alzheimer patients with debilitation and muscle wasting
- Women over 85, particularly with low body weights, may experience more adverse effects
- Use with caution in underweight or frail patients
- Cognitive improvement may be linked to substantial (>65%) inhibition of acetylcholinesterase
- Donepezil has greater action on CNS acetylcholinesterase than on peripheral acetylcholinesterase
- Some Alzheimer patients who fail to respond to donepezil may respond to another cholinesterase inhibitor
- Some Alzheimer patients who fail to respond to another cholinesterase inhibitor may respond when switched to donepezil
- To prevent potential clinical deterioration, generally switch from long-term treatment with one cholinesterase inhibitor to another without a washout period
  ✽ Donepezil may slow the progression of mild cognitive impairment to Alzheimer disease
  ✽ May be useful for dementia with Lewy bodies (DLB, constituted by early loss of attentiveness and visual perception with possible hallucinations, Parkinson-like movement problems, fluctuating cognition such as daytime drowsiness and lethargy, staring into space for long periods, episodes of disorganized speech)
  - May decrease delusions, apathy, agitation, and hallucinations in dementia with Lewy bodies
  ✽ May be useful for vascular dementia (e.g., acute onset with slow stepwise progression that has plateaus, often with gait abnormalities, focal signs, imbalance, and urinary incontinence)
  - May be helpful for dementia in Down’s syndrome
  - Suggestions of utility in some cases of treatment-resistant bipolar disorder
  - Theoretically, may be useful for ADHD, but not yet proven
  - Theoretically, could be useful in any memory condition characterized by cholinergic deficiency (e.g., some cases of brain injury, cancer chemotherapy-induced cognitive changes, etc.)
**Suggested Reading**


