**THERAPEUTICS**

**Brands**
- Razadyne
- Razadyne ER

*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: acetylcholine multi-modal; enzyme inhibitor; receptor PAM (ACh-MM)
- Cholinesterase inhibitor (acetylcholinesterase inhibitor); also an allosteric nicotinic cholinergic modulator; cognitive enhancer

**Commonly Prescribed for**
(bold for FDA approved)
- Alzheimer disease (mild to moderate)
- Memory disturbances in other dementias
- Memory disturbances in other conditions
- Mild cognitive impairment

**How the Drug Works**
- Reversibly and competitively 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
- Modulates nicotinic receptors, which enhances actions of acetylcholine
- Nicotinic modulation may also enhance the actions of other neurotransmitters by increasing the release of dopamine, norepinephrine, serotonin, GABA, and glutamate
- Does not inhibit butyrylcholinesterase
- 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

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**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

**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

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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
- Headache, dizziness
- Fatigue, depression

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

**Weight Gain**
- Reported but not expected
- Some patients may experience weight loss
**Overdose**
- Can be lethal; nausea, vomiting, excess salivation, sweating, hypotension, bradycardia, collapse, convulsions, muscle weakness (weakness of respiratory muscles can lead to death)

**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 not necessary
- 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**
- Terminal elimination half-life approximately 7 hours
- Metabolized by CYP450 2D6 and 3A4

**Drug Interactions**
- Galantamine may increase the effects of anesthetics and should be discontinued prior to surgery
- Inhibitors of CYP450 2D6 and CYP450 3A4 may inhibit galantamine metabolism and raise galantamine plasma levels
- Galantamine may interact with anticholinergic agents and the combination may decrease the efficacy of both
- Cimetidine may increase bioavailability of galantamine
- 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
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
- Animal studies do not show adverse effects
  ✽ Not recommended for use in pregnant women or in women of childbearing potential

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

Potential Advantages
- Alzheimer disease with cerebrovascular disease
- Theoretically, nicotinic modulation may provide added therapeutic benefits for memory and behavior in some Alzheimer patients
- Theoretically, nicotinic modulation may also provide efficacy for cognitive disorders other than Alzheimer disease

Potential Disadvantages
- Patients who have difficulty taking a medication twice daily

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

Pearls
- 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 apathy, disinhibition, delusions, anxiety, cooperation, pacing)
• 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 galantamine 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 galantamine 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 galantamine are gastrointestinal effects, which are usually mild and transient
• 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

* Galantamine is a natural product present in daffodils and snowdrops
• New extended-release formulation allows for once daily dosing

* Novel dual action uniquely combines acetylcholinesterase inhibition with allosteric nicotine modulation
* Novel dual action should theoretically enhance cholinergic actions but incremental clinical benefits have been difficult to demonstrate
* Actions at nicotinic receptors enhance not only the release of acetylcholine but also that of other neurotransmitters, which may boost attention and improve behaviors caused by deficiencies in those neurotransmitters in Alzheimer disease
• Some Alzheimer patients who fail to respond to another cholinesterase inhibitor may respond when switched to galantamine
• Some Alzheimer patients who fail to respond to galantamine may respond to another cholinesterase inhibitor
• To prevent potential clinical deterioration, generally switch from long-term treatment with one cholinesterase inhibitor to another without a washout period

* Galantamine may slow the progression of mild cognitive impairment to Alzheimer disease

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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


