MEMANTINE

THERAPEUTICS

Brands • Namenda
• Namenda XR

see index for additional brand names

Generic? Yes

Class
• Neuroscience-based Nomenclature:
  Glutamate receptor antagonist (Glu-RAn)
• NMDA receptor antagonist; N-methyl-d-
aspartate (NMDA) subtype of glutamate
  receptor antagonist; cognitive enhancer

Commonly Prescribed for
(bold for FDA approved)
• Alzheimer disease (moderate to severe)
• Alzheimer disease (mild to moderate)
• Memory disorders in other conditions
• Mild cognitive impairment
• Chronic pain

How the Drug Works
✽ Is a low to moderate affinity
  noncompetitive (open-channel) NMDA
  receptor antagonist, which binds
  preferentially to the NMDA receptor-
  operated cation channels
• Presumably interferes with the postulated
  persistent activation of NMDA receptors by
  excessive glutamate release in Alzheimer
disease

How Long Until It Works
• Memory improvement is not expected and
  it may take months before any stabilization
  in degenerative course is evident

If It Works
• May slow progression of disease, but does
  not reverse the degenerative process

If It Doesn’t Work
• Consider adjusting dose, switching to
  a cholinesterase inhibitor or adding a
  cholinesterase inhibitor
• 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
✽ May be combined with cholinesterase
  inhibitors
• Divalproex, carbamazepine, or
  oxcarbazepine for behavioral disturbances

Tests
• None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects
• Presumably due to excessive actions at
  NMDA receptors

Notable Side Effects
• Dizziness, headache
• Constipation

Life-Threatening or
Dangerous Side Effects
• Seizures (rare)

Weight Gain
• Reported but not expected

Sedation
• Reported but not expected
• Fatigue may occur

What to Do About Side Effects
• Wait
• Wait
• Wait
• Consider lowering dose or switching to a
different agent

Best Augmenting Agents for Side
Effects
• Many side effects cannot be improved with
  an augmenting agent

DOSING AND USE

Usual Dosage Range
• 10 mg twice daily
• 28 mg once daily (extended-release)
MEMANTINE (continued)

Dosage Forms
- Tablet 5 mg, 10 mg
- Oral solution 2 mg/mL
- Extended-release capsule 7 mg, 14 mg, 21 mg, 28 mg

How to Dose
- Initial 5 mg/day; can increase by 5 mg each week; doses over 5 mg should be divided; maximum dose 10 mg twice daily
- Extended-release: initial 7 mg once daily; can increase by 7 mg each week; maximum dose 28 mg once daily

Drug Interactions
- No interactions with drugs metabolized by CYP450 enzymes
- Drugs that raise the urine pH (e.g., carbonic anhydrase inhibitors, sodium bicarbonate) may reduce elimination of memantine and raise plasma levels of memantine
- No interactions with cholinesterase inhibitors

Other Warnings/Precautions
- Use cautiously if coadministering with other NMDA antagonists such as amantadine, ketamine, and dextromethorphan

Do Not Use
- If there is a proven allergy to memantine

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Dosing Tips
- Despite very long half-life, is generally dosed twice daily, although some data suggest once daily is safe and tolerable
- Both the patient and the patient’s caregiver should be instructed on how to dose memantine since patients themselves have moderate to severe dementia and may require assistance
- Memantine is unlikely to affect pharmacokinetics of acetylcholinesterase inhibitors
- Absorption not affected by food

Overdose
- No fatalities have been reported; restlessness, psychosis, visual hallucinations, sedation, stupor, loss of consciousness

Long-Term Use
- Drug may lose effectiveness in slowing degenerative course of Alzheimer disease after 6 months

Habit Forming
- No

How to Stop
- No known withdrawal symptoms
- Theoretically, discontinuation could lead to notable deterioration in memory and behavior which may not be restored when drug is restarted or a cholinesterase inhibitor is initiated

Pharmacokinetics
- Little metabolism; mostly excreted unchanged in the urine

Terminal elimination half-life approximately 60–80 hours
- Minimal inhibition of CYP450 enzymes

Renal Impairment
- No dose adjustment in mild or moderate impairment
- Reduce dose in severe impairment

Hepatic Impairment
- Not likely to require dosage adjustment

Cardiac Impairment
- Not likely to require dosage adjustment

Elderly
- Pharmacokinetics similar to younger adults

Children and Adolescents
- Memantine use has not been studied in children or adolescents

SPECIAL POPULATIONS

Renal Impairment
- No dose adjustment in mild or moderate impairment
- Reduce dose in severe impairment

Hepatic Impairment
- Not likely to require dosage adjustment

Cardiac Impairment
- Not likely to require dosage adjustment

Elderly
- Pharmacokinetics similar to younger adults

Children and Adolescents
- Memantine use has not been studied in children or adolescents
Memantine’s actions are somewhat like the natural inhibition of NMDA receptors by magnesium, and thus memantine is a sort of “artificial magnesium.” Theoretically, NMDA antagonism of memantine is strong enough to block chronic low-level overexcitation of glutamate receptors associated with Alzheimer disease, but not strong enough to interfere with periodic high level utilization of glutamate for plasticity, learning, and memory. Structurally related to the antiparkinsonian and anti-influenza agent amantadine, which is also a weak NMDA antagonist. Memantine is well tolerated with a low incidence of adverse effects. Antagonist actions at 5HT3 receptors have unknown clinical consequences but may contribute to low incidence of gastrointestinal side effects. 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. Treat the patient but ask the caregiver about efficacy. Delay in progression of Alzheimer disease is not evidence of disease-modifying actions of NMDA antagonism. May or may not be effective in vascular dementia. Under investigation for dementia associated with HIV/AIDS. May or may not be effective in chronic neuropathic pain. Theoretically, could be useful for any condition characterized by moderate overactivation of NMDA glutamate receptors (possibly neurodegenerative conditions or even bipolar disorder, anxiety disorders, or chronic neuropathic pain), but this is not proven.

**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
- Animal studies do not show adverse effects

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

**The Art of Psychopharmacology**

**Potential Advantages**
- In patients with more advanced Alzheimer disease

**Potential Disadvantages**
- Unproven to be effective in mild to moderate Alzheimer disease
- 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
Suggested Reading


