NEFAZODONE

THERAPEUTICS

Brands • Dutonin
see index for additional brand names

Generic? Yes

Class • Neuroscience-based Nomenclature: serotonin receptor antagonist
• SARI (serotonin 2 antagonist/reuptake inhibitor); antidepressant

Commonly Prescribed for (bold for FDA approved)
• Depression
• Relapse prevention in major depressive disorder
• Panic disorder
• Posttraumatic stress disorder (PTSD)

How the Drug Works
• Blocks serotonin 2A receptors potently
• Blocks serotonin reuptake pump (serotonin transporter) and norepinephrine reuptake pump (norepinephrine transporter) less potently

How Long Until It Works
• Can improve insomnia and anxiety early after initiating dosing
• Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
• If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all
• May continue to work for many years to prevent relapse of symptoms

If It Works
• The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
• Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
• Continue treatment until all symptoms are gone (remission)
• Once symptoms gone, continue treating for 1 year for the first episode of depression
• For second and subsequent episodes of depression, treatment may need to be indefinite
• Use in anxiety disorders may also need to be indefinite

If It Doesn’t Work
• Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
• Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
• Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
• Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
• Consider psychotherapy, especially cognitive-behavioral psychotherapies, which have been specifically shown to enhance nefazodone’s antidepressant actions
• Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
• Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer

Best Augmenting Combos for Partial Response or Treatment Resistance

✽ Venlafaxine and escitalopram may be the best tolerated when switching or augmenting with a serotonin reuptake inhibitor, as neither is a potent CYP450 2D6 inhibitor (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)
• Modafinil, especially for fatigue, sleepiness, and lack of concentration
• Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
• Benzodiazepines for anxiety, but give alprazolam cautiously with nefazodone as alprazolam levels can be much higher in the presence of nefazodone
• Classically, lithium, buspirone, or thyroid hormone
NEFAZODONE (continued)

**Tests**
- Liver function testing is not required but is often prudent given the small but finite risk of serious hepatotoxicity
- However, to date no clinical strategy, including routine liver function tests, has been identified to reduce the risk of irreversible liver failure

**SIDE EFFECTS**

**How Drug Causes Side Effects**
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- A metabolite of nefazodone, mCPP (meta-chloro-phenyl-piperazine), can cause side effects if its levels rise significantly
- If CYP450 2D6 is absent (7% of Caucasians lack CYP450 2D6) or inhibited (concomitant treatment with CYP450 2D6 inhibitors such as fluoxetine or paroxetine), increased levels of mCPP can form, leading to stimulation of 5HT2C receptors and causing dizziness, insomnia, and agitation
- Most side effects are immediate but often go away with time

**Notable Side Effects**
- Nausea, dry mouth, constipation, dyspepsia, increased appetite
- Headache, dizziness, vision changes, sedation, insomnia, agitation, confusion, memory impairment
- Ataxia, paresthesia, asthenia
- Cough increased
- Rare postural hypotension

**Life-Threatening or Dangerous Side Effects**
- Rare seizures
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Rare priapism (no causal relationship established)
- Hepatic failure requiring liver transplant and/or fatal

**Weight Gain**
- Reported but not expected

**Sedation**
- Many experience and/or can be significant in amount

**What to Do About Side Effects**
- Wait
- Wait
- Wait
- Take once daily at night to reduce daytime sedation
- Lower the dose and try titrating again more slowly as tolerated
- Switch to another agent

**Best Augmenting Agents for Side Effects**
- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Many side effects cannot be improved with an augmenting agent
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of nefazodone

**DOSING AND USE**

**Usual Dosage Range**
- 300–600 mg/day

**Dosage Forms**
- Tablet 50 mg, 100 mg scored, 150 mg scored, 200 mg, 250 mg
How to Dose
• Initial dose 100 mg twice a day; increase by 100–200 mg/day each week until desired efficacy is reached; maximum dose 600 mg twice a day

Dosing Tips
• Take care switching from or adding to SSRIs (especially fluoxetine or paroxetine) because of side effects due to the drug interaction
• Do not underdose the elderly
• Normally twice daily dosing, especially when initiating treatment
• Patients may tolerate all dosing once daily at night once titrated
• Often much more effective at 400–600 mg/day than at lower doses if tolerated
• Slow titration can enhance tolerability when initiating dosing

Overdose
• Rarely lethal; sedation, nausea, vomiting, low blood pressure

Long-Term Use
• Safe

Habit Forming
• No

How to Stop
• Taper is prudent to avoid withdrawal effects, but problems in withdrawal not common

Pharmacokinetics
• Half-life of parent compound is 2–4 hours
• Half-life of active metabolites up to 12 hours
• Inhibits CYP450 3A4

Drug Interactions
• Tramadol increases the risk of seizures in patients taking an antidepressant
• May interact with SSRIs such as paroxetine, fluoxetine, and others that inhibit CYP450 2D6
• Since a metabolite of nefazodone, mCPP, is a substrate of CYP450 2D6, combination of 2D6 inhibitors with nefazodone will raise mCPP levels, leading to stimulation of 5HT2C receptors and causing dizziness and agitation
• Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
• Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing nefazodone
• Via CYP450 3A4 inhibition, nefazodone may increase the half-life of alprazolam and triazolam, so their dosing may need to be reduced by half or more
• Via CYP450 3A4, nefazodone may increase plasma concentrations of buspirone, so buspirone dose may need to be reduced
• Via CYP450 3A4 inhibition, nefazodone could theoretically increase concentrations of certain cholesterol lowering HMG CoA reductase inhibitors, especially simvastatin, atorvastatin, and lovastatin, but not pravastatin or fluvastatin, which would increase the risk of rhabdomyolysis; thus, coadministration of nefazodone with certain HMG CoA reductase inhibitors should proceed with caution
• Via CYP450 3A4 inhibition, nefazodone could theoretically increase the concentrations of pimozide, and cause QTc prolongation and dangerous cardiac arrhythmias
• Nefazodone may reduce clearance of haloperidol, so haloperidol dose may need to be reduced
• It is recommended to discontinue nefazodone prior to elective surgery because of the potential for interaction with general anesthetics

Other Warnings/Precautions
• Hepatotoxicity, sometimes requiring liver transplant and/or fatal, has occurred with nefazodone use. Risk may be one in every 250,000 to 300,000 patient years. Patients should be advised to report symptoms such as jaundice, dark urine, loss of appetite, nausea, and abdominal pain to prescriber immediately. If patient develops signs of hepatocellular injury, such as increased serum AST or serum ALPT levels >3 times the upper limit of normal, nefazodone treatment should be discontinued.
No risk factor yet predicts who will develop irreversible liver failure with nefazodone and no clinical strategy, including routine monitoring of liver function tests, is known to reduce the risk of liver failure.

- Use with caution in patients with history of seizures.
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent.
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart.
- Distribute the brochures provided by the FDA and the drug companies.
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately.
- Monitor patients for activation of suicidal ideation, especially children and adolescents.

**Do Not Use**

- If patient is taking an MAOI.
- If patient has acute hepatic impairment or elevated baseline serum transaminases.
- If patient was previously withdrawn from nefazodone treatment due to hepatic injury.
- If patient is taking pimozide, as nefazodone could raise pimozide levels and increase QTc interval, perhaps causing dangerous arrhythmia.
- If patient is taking carbamazepine, as this agent can dramatically reduce nefazodone levels and thus interfere with its antidepressant actions.
- If there is a proven allergy to nefazodone.

## Cardiac Impairment

- Use in patients with cardiac impairment has not been studied, so use with caution because of risk of orthostatic hypotension.

## Elderly

- Recommended to initiate treatment at half the usual adult dose, but to follow the same titration schedule as with younger patients, including same ultimate dose.
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older.

## Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart.
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment.
- Use with caution, observing for activation of known or unknown bipolar disorder and/ or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients.
- Safety and efficacy have not been established.
- Preliminary research indicates efficacy and tolerability of nefazodone in children and adolescents with depression.

## 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 generally recommended for use during pregnancy, especially during first trimester.
- Must weigh the risk of treatment (first trimester fetal development, third trimester...
Patients with SSRI-induced sexual dysfunction

Potential Disadvantages
- Patients who have difficulty with a long titration period or twice daily dosing
- Patients with hepatic impairment

Primary Target Symptoms
- Depressed mood
- Sleep disturbance
- Anxiety

Pearls
- Preliminary data for efficacy in panic disorder and PTSD
- Fluoxetine and paroxetine may not be tolerated when switching or augmenting
- For elderly patients with early dementia and agitated depression, consider nefazodone in the morning and additional trazodone at night
- Anecdotal reports suggest that nefazodone may be effective in treating PMDD

Risk of hepatotoxicity makes this agent a second-line choice and has led to its withdrawal from some markets, including the withdrawal of Serzone from the US market

Studies suggest that cognitive behavioral psychotherapy enhances the efficacy of nefazodone in chronic depression

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Depressed patients with anxiety or insomnia who do not respond to other antidepressants

Suggested Reading


