### TRAZODONE

#### Therapeutics

**Brands**
- Desyrel
- Oleptro

*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: serotonin receptor antagonist (S-MM)
- SARI (serotonin 2 antagonist/reuptake inhibitor); antidepressant; hypnotic

**Commonly Prescribed for**
*bold for FDA approved*
- Depression
- Insomnia (primary and secondary)
- Anxiety

**How the Drug Works**
- Blocks serotonin 2A receptors potently
- Blocks serotonin reuptake pump (serotonin transporter) less potently

**How Long Until It Works**

- Onset of therapeutic actions in insomnia are immediate if dosing is correct
- Onset of therapeutic actions in depression usually not immediate, but often delayed 2–4 weeks whether given as an adjunct to another antidepressant or as a monotherapy
- 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 in depression and to reduce symptoms of chronic insomnia

**If It Works**

- For insomnia, use possibly can be indefinite as there is no reliable evidence of tolerance, dependence, or withdrawal, but few long-term studies
- For secondary insomnia, if underlying condition (e.g., depression, anxiety disorder) is in remission, trazodone treatment may be discontinued if insomnia does not reemerge
- The goal of treatment for depression is complete remission of current symptoms of depression as well as prevention of future relapses

- Treatment most often reduces or even eliminates symptoms of depression, but is not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms of depression are gone (remission)
- Once symptoms of depression are 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

**If It Doesn’t Work**

- For insomnia, try escalating doses or switch to another agent
- Many patients have only a partial antidepressant 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
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent for treatment of depression
- Consider psychotherapy
- 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**

- Trazodone is not frequently used as a monotherapy for insomnia, but can be combined with sedative hypnotic benzodiazepines in difficult cases
- Trazodone is most frequently used in depression as an augmenting agent to numerous psychotropic drugs
- Trazodone can not only improve insomnia in depressed patients treated with antidepressants, but can also be an effective booster of antidepressant actions of other antidepressants (use combinations of antidepressants with caution as this...
TRAZODONE

What to Do About Side Effects
- Wait
- Wait
- Wait
- Take larger dose at night to prevent daytime sedation
- Switch to another agent

Best Augmenting Agents for Side Effects
- Most side effects cannot be improved with an augmenting agent
- 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 trazodone

Trazodone can also improve insomnia in numerous other psychiatric conditions (e.g., bipolar disorder, schizophrenia, alcohol withdrawal) and be added to numerous other psychotropic drugs (e.g., lithium, mood stabilizers, antipsychotics)

Tests
- None for healthy individuals

SIDE EFFECTS

How Drug Causes Side Effects
- Sedative effects may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Most side effects are immediate but often go away with time

Notable Side Effects
- Nausea, vomiting, edema, blurred vision, constipation, dry mouth
- Dizziness, sedation, fatigue, headache, incoordination, tremor
- Hypotension, syncope
- Occasional sinus bradycardia (long-term)
- Rare rash

Life-Threatening or Dangerous Side Effects
- Rare priapism
- 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)

Weight Gain
- Reported but not expected

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

DOSING AND USE

Usual Dosage Range
- 150–600 mg/day
- 150–375 mg/day (extended-release)

Dosage Forms
- Tablet 50 mg scored, 100 mg scored, 150 mg, 150 mg with povidone scored, 300 mg with povidone scored
- Extended-release tablet 150 mg scored, 300 mg scored

How to Dose
- Depression as a monotherapy: initial 150 mg/day in divided doses; can increase every 3–4 days by 50 mg/day as needed; maximum 400 mg/day (outpatient) or 600 mg/day (inpatient), split into 2 daily doses
- Insomnia: initial 25–50 mg at bedtime; increase as tolerated, usually to 50–100 mg/day, but some patients may require up to full antidepressant dose range
- Augmentation of other antidepressants in the treatment of depression: dose as recommended for insomnia
- Extended-release: initial 150 mg once daily; may be increased by 75 mg/day every 3 days; maximum dose generally 375 mg/day

Dosing Tips
- Start low and go slow
Patients can have carryover sedation, ataxia, and intoxicated-like feeling if dosed too aggressively, particularly when initiating dosing.

Do not discontinue trials if ineffective at low doses (<50 mg) as many patients with difficult cases may respond to higher doses (150–300 mg, even up to 600 mg in some cases).

- For relief of daytime anxiety, can give part of the dose in the daytime if not too sedating.
- Although use as a monotherapy for depression is usually in divided doses due to its short half-life, use as an adjunct is often effective and best tolerated once daily at bedtime.

**Overdose**

- Rarely lethal; sedation, vomiting, priapism, respiratory arrest, seizure, EKG changes.

**Long-Term Use**

- Safe.

**Habit Forming**

- No.

**How to Stop**

- Taper is prudent to avoid withdrawal effects, but tolerance, dependence, and withdrawal effects have not been reliably demonstrated.

**Pharmacokinetics**

- Metabolized by CYP450 3A4.
- Half-life is biphasic; first phase is approximately 3–6 hours; second phase is approximately 5–9 hours.

**Drug Interactions**

- Tramadol increases the risk of seizures in patients taking an antidepressant.
- Fluoxetine and other SSRIs may raise trazodone plasma levels.
- Trazodone may block the hypotensive effects of some antihypertensive drugs.
- Trazodone may increase digoxin or phenytoin concentrations.
- Trazodone may interfere with the antihypertensive effects of clonidine.
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped.

**Other Warnings/Precautions**

- Possibility of additive effects if trazodone is used with other CNS depressants.
- Treatment should be discontinued if prolonged penile erection occurs because of the risk of permanent erectile dysfunction.
- Advise patients to seek medical attention immediately if painful erections occur lasting more than 1 hour.
- Generally, priapism reverses spontaneously, while penile blood flow and other signs being monitored, but in urgent cases, local phenylephrine injections or even surgery may be indicated.
- 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, but see Pearls.
- If there is a proven allergy to trazodone.

**SPECIAL POPULATIONS**

**Renal Impairment**

- No dose adjustment necessary.

**Hepatic Impairment**

- Drug should be used with caution.

**Reports of increased and decreased prothrombin time in patients taking warfarin and trazodone.**
CARDIAC IMPAIRMENT
- Trazodone may be arrhythmogenic
- Monitor patients closely
- Not recommended for use during recovery from myocardial infarction

ELDERLY
- Elderly patients may be more sensitive to adverse effects and may require lower doses
- 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, but trazodone has been used for behavioral disturbances, depression, and night terrors
- Children require lower initial dose and slow titration
- Boys may be even more sensitive to having prolonged erections than adult men

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 (PLLRR 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
- Avoid use during first trimester

Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy

BREAST FEEDING
- Some drug is found in mother's breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstituted late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- For insomnia when it is preferred to avoid the use of dependence-forming agents
- As an adjunct to the treatment of residual anxiety and insomnia with other antidepressants
- Depressed patients with anxiety
- Patients concerned about sexual side effects or weight gain

Potential Disadvantages
- For patients with fatigue, hypersomnia
- For patients intolerant to sedating effects

Primary Target Symptoms
- Depression
- Anxiety
- Sleep disturbances

Pearls
- May be less likely than some antidepressants to precipitate hypomania or mania
• Preliminary data suggest that trazodone may be effective treatment for drug-induced dyskinesias, perhaps in part because it reduces accompanying anxiety
• Trazodone may have some efficacy in treating agitation and aggression associated with dementia

✽ May cause sexual dysfunction only infrequently
• Can cause carryover sedation, sometimes severe, if dosed too high
• Often not tolerated as a monotherapy for moderate to severe cases of depression, as many patients cannot tolerate high doses (>150 mg)
• Do not forget to try at high doses, up to 600 mg/day, if lower doses well tolerated but ineffective

✽ For the expert psychopharmacologist, trazodone can be used cautiously for insomnia associated with MAOIs, despite the warning – must be attempted only if patients closely monitored and by experts experienced in the use of MAOIs
• Priapism may occur in 1 in 8,000 men
• Early indications of impending priapism may be slow penile detumescence when awakening from REM sleep
• When using to treat insomnia, remember that insomnia may be a symptom of some other primary disorder, and not a primary disorder itself, and thus warrant evaluation for comorbid psychiatric and/or medical conditions
• Rarely, patients may complain of visual “trails” or after-images on trazodone

Suggested Reading


