Trazodone

Generic name	Trazodone
Available brand	None
Available strengths and formulations	50-mg, 100-mg, 150-mg, and 300-mg tablets
Available in generic	Yes

General Information

Trazodone is an antidepressant that was approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder and originally marketed under the trade name Desyrel. However, at the high dosages needed to treat depression, most people could not tolerate trazodone's pronounced daytime sedation and drowsiness. With the advent of **selective serotonin reuptake inhibitor** (**SSRI**) antidepressants, such as fluoxetine (Prozac) and other newer antidepressants, the use of trazodone for depression rapidly declined. However, for many people, SSRIs caused insomnia and other sleep difficulties. To counter this side effect, practitioners added low doses of trazodone at bedtime. Trazodone is used commonly for insomnia rather than for depression, but this is not an approved indication from the FDA. The use of a medication for its FDA-approved indications is called its *labeled use.* In clinical practice, however, practitioners often prescribe medications for *unapproved indications* (*off-label uses*) when published clinical studies indicate the efficacy, and the standards of practice support the safety, of those treatments. Another off-label use for trazodone includes treatment of aggressive behavior in children and adults with mental retardation, dementia, or Alzheimer's disease.

It has been postulated that trazodone's antidepressant action—although not fully understood—is mediated predominantly by the antagonism of serotonin receptors (5-HT_2) and, to a lesser extent, by inhibition of serotonin reuptake in the brain, similar to the SSRI antidepressants (e.g., fluoxetine [Prozac]). It is not exactly clear how antagonism of 5-HT_2 receptors explains the antidepressant effects of trazodone. It has been hypothesized that this action may reverse (i.e., downregulate) the changes in areas of the brain that cause depression. Also, serotonin reuptake inhibition increases levels of serotonin, and this has been proven to help depression. However, increasing serotonin levels also stimulate other serotonin receptors that causes side effects (e.g., sexual dysfunction associated with the SSRIs). Trazodone's antagonism of 5-HT_2 receptors would theoretically attenuate the undesired actions of stimulating these receptors. Trazodone appears to lack the sexual dysfunction and activating properties (e.g., restlessness, agitation) of SSRIs. Because of this dual action, trazodone is classified as a **serotonin antagonist and reuptake inhibitor** (**SARI**) antidepressant.

Trazodone also strongly blocks histamine receptors, and because of its antihistaminic properties, trazodone is highly sedating. The sedation limits trazodone's usefulness as an antidepressant because patients usually cannot tolerate sedation and drowsiness at higher doses. Practitioners, however, find its sedative property useful as a hypnotic at lower doses with low abuse potential.

Dosing Information

When prescribed for insomnia and sleep disturbance, the usual dose of trazodone is 50–100 mg at bedtime, but some patients may need doses as high as 150–200 mg.

Common Side Effects

The most common side effects associated with trazodone are sedation, drowsiness, dizziness, dry mouth, headaches, nausea, indigestion, and visual disturbance. Nausea and indigestion are more frequent at higher dosages and on an empty stomach. Taking trazodone with food may decrease gastrointestinal side effects.

Dizziness and even fainting may occur in patients taking high doses of trazodone. Elderly patients must be especially cautious of trazodone-induced dizziness, which may cause falling.

Patients may experience visual disturbances—seeing visual trails or afterimages when their eyes move. Generally, these side effects subside over time and are less frequent at lower dosages.

Trazodone is highly sedating and can cause significant drowsiness, especially when starting the medication. Patients should exercise caution when driving or performing tasks that require mental alertness. Avoid or minimize the use of alcohol when taking trazodone, which can intensify somnolence and drowsiness and severely impair one's mental and/or physical ability to function.

Adverse Reactions and Precautions

At higher dosages of trazodone, patients may experience dizziness upon standing from a recumbent position, which may lead to **syncope**, the loss of consciousness resulting from insufficient blood flow to the brain. This is due to the opposing effect of trazodone on blood vessels that normally compensate for a postural change, resulting in a momentary drop in blood pressure. Dizziness ensues when insufficient blood is supplied to the brain. This reaction is known as **orthostatic hypotension** and is occasionally seen with trazodone. Patients generally develop tolerance to orthostatic hypotension, but they should be cautious when rising too quickly, especially when starting therapy or when increasing dosages. Elderly patients and patients taking medications for high blood pressure may be more prone to orthostatic hypotension and are susceptible to syncope (fainting) and falling. Dosage reduction may help ameliorate orthostatic hypotension, but reducing the dosage too much may lead to reemergence of depressive symptoms. Using compression or support stockings may help with blood circulation (i.e., venous return) and offset hypotension. As a precaution, patients should be aware of positional shifts and not rise to their feet suddenly. When lying down, they should get up gradually to a sitting position before standing. If feeling light-headed or dizzy, they should sit and wait for a minute or two before standing up to allow the blood pressure to adjust.

Patients should be cautioned about a reaction known as **serotonin syndrome** when taking trazodone, which is a **serotonergic** medication. Serotonergic medications enhance **serotonin**, a **neurotransmitter** in the central nervous system (CNS). If excessive, serotonin syndrome ensues. Serotonin syndrome is potentially a life-threatening situation requiring immediate cessation of the offending medications and medical attention. Typical symptoms include lethargy, confusion, restlessness, flushing, profuse sweating, tremor, and uncontrollable muscular twitching and jerking. If untreated, serotonin syndrome can progress to elevated temperature and blood pressure, excessive muscle tension, muscle breakdown (rhabdomyolysis), kidney failure, coma, and death. Rare cases of serotonin syndrome have been reported with trazodone, but usually these cases involved taking two or more medications that augmented serotonin.

Trazodone can cause a rare condition in males known as **priapism,** which is an uncontrolled, persistent erection of the penis. The incidence of priapism reported with trazodone is about 1 in 6,000 men. If painful erection persists for more than several hours, the patient should present to the emergency depart-

ment for immediate medical attention. If not treated promptly, priapism may result in damage of vascular structures in the penis and permanent erectile dysfunction.

Rarely, trazodone is associated with a condition known as **syndrome of inappropriate antidiuretic hormone secretion** (**SIADH**). **Antidiuretic hormone** (**ADH**) is a hormone produced by the **hypothalamus** in the brain and transported and stored in the **pituitary gland**, specifically in the posterior portion of the pituitary gland. With change in blood volume (e.g., dehydration), ADH is released from the posterior pituitary gland into the bloodstream and carried to the kidneys, where it exerts its action. One of the primary functions of ADH is to regulate reabsorption and retention of water by the kidneys. By its hormonal action, the kidneys retain and conserve the body's water by reabsorbing it into the bloodstream, resulting in less urinary output. The hypothalamus, in turn, senses the increased volume of the blood by amount of water reabsorbed and thereby decreases secretion of ADH. This feedback loop between the hypothalamus and kidneys is the homeostatic (equilibrium) mechanism of regulating blood volume.

Medications like trazodone may induce excessive release of ADH and therefore an *inappropriate* side effect of treatment. Excessive ADH leads to excessive reabsorption and retention of water by the kidneys, resulting in a higher blood volume (**hypervolemia**). This may lead to a dilutional lowering of the blood's sodium concentration (**hyponatremia**). Depending on the extent of hyponatremia, SIADH may result in a cluster of symptoms (i.e., syndrome). With mild hyponatremia, the patient may experience loss of appetite, headache, nausea, vomiting, muscle weakness, fatigue, and spasms or cramps. With severe hyponatremia, symptoms include irritability, restlessness, confusion, seizures, loss of consciousness or coma, and death if untreated. The diagnosis of drug-induced SIADH can be made by checking the plasma sodium level and urine concentration. When the offending medication is interrupted, these levels return to normal.

Patients should not discontinue trazodone without first consulting their practitioner. It should be discontinued gradually by tapering the dose. Stopping the medication abruptly, especially after taking it regularly for long periods, may trigger **discontinuation** (**withdrawal**) **symptoms**, including headaches, nausea, vomiting, diarrhea, insomnia, tremors, tingling of hands and/or legs (**paresthesia**), and possibly other unpleasant symptoms.

With antidepressant therapy, there may be risks of suicidal thinking and behavior in children and adolescents with depressive disorders and other neuropsychiatric disorders. The risk with antidepressants is age related, associated with patients younger than age 24 years, and higher during the early course of treatment. The FDA advises practitioners to exercise caution when treating pediatric patients and added warnings of suicidal risk to the labeling for all antidepressants.

Risk During Pregnancy and Breast-Feeding

The information on trazodone in human pregnancy is limited. The available data from reported cases of women exposed to trazodone during pregnancy suggest a very low risk of **teratogenicity** (congenital malformations).

It is not recommended that women take trazodone during pregnancy if possible. Use of trazodone during pregnancy may be justified if discontinuing the antidepressant poses greater known risk to the mother than the potential risk to the fetus. Some women may experience a relapse of depression if they stop their antidepressant, and relapse may pose a greater risk to the baby. Women of childbearing age should be cautioned of the potential hazards to the fetus if they become pregnant while taking this drug.

Nursing mothers should not take trazodone because it can pass into breast milk and be ingested by the baby. If stopping the drug is not an alternative, breast-feeding should not be started or should be discontinued.

Potential Drug Interactions

Patients should not take trazodone concomitantly with alcohol or other sedating medications, such as narcotics, barbiturates, sleep medications, and antihistamines. Combining trazodone with alcohol or

these medications can heighten CNS side effects and severely impair physical coordination and mental alertness.

Some medications can interfere with the breakdown (metabolism) of trazodone in the liver, which may therefore increase levels of the drug in the body, increasing the potential of drug toxicity, including oral antifungal agents known as azoles (e.g., itraconazole, ketoconazole, fluconazole), anti-HIV drugs known as protease inhibitors (e.g., indinavir, nelfinavir, ritonavir), and certain antibiotics (e.g., clarithromycin, erythromycin).

Carbamazepine can significantly reduce the blood levels of trazodone when administered together, decreasing the therapeutic effectiveness of the latter.

Antidepressants known as **monoamine oxidase inhibitors** (**MAOIs**; e.g., phenelzine, selegiline, isocarboxazid, tranylcypromine) and the antibiotic linezolid (Zyvox) are contraindicated with trazodone because when combined, their serotonergic actions greatly increase the risk of serotonin syndrome. A washout period of 14 days should be allowed when stopping an MAOI before starting trazodone and similarly when stopping trazodone before introducing an MAOI. Moreover, other drugs that boost serotonin levels in the CNS have an additive effect with trazodone's serotonergic action and can increase risk of serotonin syndrome. Serotonergic drugs, for example, include triptans for migraine headache (e.g., sumatriptan), tramadol, serotonergic antidepressants (e.g., SSRIs, tricyclic antidepressants), and St. John's wort.

Overdose

Overdose with trazodone alone is usually safer than with tricyclic antidepressants (e.g., amitriptyline) or with MAOI antidepressants. Overdoses often involve more than one drug. The combination of CNS depressants (e.g., alcohol, antihistamines, benzodiazepines, narcotics, sleep medications) and trazodone can be fatal, and deaths have been reported from overdose in patients who ingest trazodone with CNS depressants.

Any suspected overdose should be treated as an emergency. The person should be taken to the emergency department for observation and treatment. The prescription bottle of medication (and any other medication suspected in the overdose) should be brought along as well because the information on the prescription label can be helpful to the treating physician in determining the number of pills ingested.

The American Association of Poison Control Centers (www.aapcc.org) can also be contacted via their helpline at 1-800-222-1222, and they can provide the location of the local poison center.

Treatment Summary

The risk of suicide is inherent in depression and may persist until the individual responds to treatment. After starting or changing antidepressant therapy, the person, especially a child or adolescent, should be closely observed for signs of worsening depression, and the family or caregiver should communicate any concerns to the practitioner.

- **Warning:** Always let your practitioner or a family member know if you have suicidal thoughts. Notify your practitioner whenever your depressive symptoms worsen or whenever you feel unable to control suicidal urges or thoughts.
- Do not discontinue trazodone without consulting your practitioner. Trazodone should be discontinued gradually by tapering the dose. Stopping the medication abruptly may trigger discontinuation (withdrawal) symptoms.
- If the trazodone is prescribed for sleep, take it about 1 hour before bedtime. Take only the amount prescribed and only when needed.
- If you miss a dose, take it as soon as possible. If it is close to your next scheduled dose, skip the missed dose and continue on your regular dosing schedule. Do not take double doses.

- Trazodone may be taken with or without food.
- Keep in mind trazodone is very sedating. Be aware of how the medication affects you, and exercise caution when operating a vehicle or performing tasks that require alertness.
- Avoid alcohol while taking trazodone because alcohol can increase the CNS side effects of the medication.
- Be aware that trazodone can induce dizziness and light-headedness upon standing from a recumbent position, which may lead to orthostatic hypotension. This reaction is more prone to occur when starting the medication and in elderly patients. Rise slowly and allow your body to adjust to the change in position.
- Keep in mind that the benefits of trazodone may not be noticeable right away. It may take weeks before the benefits from trazodone are fully achieved.
- Store the medication in its originally labeled, light-resistant container, away from heat and moisture. Heat and moisture may precipitate breakdown of your medication, and the medication may lose its therapeutic effects.
- Keep your medication out of the reach of children.

If you have any questions about your medication, consult your medical practitioner or pharmacist.

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