AMOXAPINE

Therapeutics

Brands • Asendin
see index for additional brand names

Generic? Yes

Class
• Neuroscience-based Nomenclature: norepinephrine, serotonin reuptake inhibitor (SN-RI)
• Tricyclic antidepressant (TCA), sometimes classified as a tetracyclic antidepressant
• Norepinephrine/noradrenaline reuptake inhibitor
• Serotonin 2A antagonist
• Parent drug and especially an active metabolite are dopamine 2 antagonists

Commonly Prescribed for (bold for FDA approved)
• Neurotic or reactive depressive disorder
• Endogenous and psychotic depressions
• Depression accompanied by anxiety or agitation
• Depressive phase of bipolar disorder
• Anxiety
• Insomnia
• Neuropathic pain/chronic pain
• Treatment-resistant depression

How the Drug Works
• Boosts neurotransmitter norepinephrine/noradrenaline
• Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
• Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, amoxapine can thus increase dopamine neurotransmission in this part of the brain
• A more potent inhibitor of norepinephrine reuptake pump than serotonin reuptake pump (serotonin transporter)
• At high doses may also boost neurotransmitter serotonin and presumably increase serotonergic neurotransmission
• Blocks dopamine 2 receptors, reducing positive symptoms of psychosis

How Long Until It Works
• 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
• Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
• 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 for Partial Response or Treatment Resistance
• Lithium, buspirone, thyroid hormone

Tests
• Baseline ECG is recommended for patients over age 50

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AMOXAPINE (continued)

Notable Side Effects
- Blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, heartburn, unusual taste in mouth, weight gain
- Fatigue, weakness, dizziness, sedation, headache, anxiety, nervousness, restlessness
- Sexual dysfunction, sweating
- Can cause extrapyramidal symptoms, akathisia, and theoretically, tardive dyskinesia

Life-Threatening or Dangerous Side Effects
- Paralytic ileus, hyperthermia (TCAs/tetracyclics + anticholinergic agents)
- Lowered seizure threshold and rare seizures
- Orthostatic hypotension, sudden death, arrhythmias, tachycardia
- QTc prolongation
- Hepatic failure, extrapyramidal symptoms
- Increased intraocular pressure
- 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
- Many experience and/or can be significant in amount
- Can increase appetite and carbohydrate craving

Sedation
- Many experience and/or can be significant in amount
- Tolerance to sedative effect may develop with long-term use

What to Do About Side Effects
- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

SIDE EFFECTS

How Drug Causes Side Effects
- Anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
- Sedative effects and weight gain may be due to antihistamine properties
- Blockade of alpha adrenergic 1 receptors may explain dizziness, sedation, and hypotension
- Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels

Since tricyclic and tetracyclic antidepressants are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
- While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antidepressant
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfl oxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

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How to Stop
• Taper to avoid withdrawal effects
• Even with gradual dose reduction some withdrawal symptoms may appear within the first 2 weeks
• Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
• If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics
• Substrate for CYP450 2D6
• Half-life of parent drug approximately 8 hours
  • 7- and 8-hydroxymetabolites are active and possess serotonin 2A and dopamine 2 antagonist properties, similar to atypical antipsychotics
  • Amoxapine is the N-desmethyl metabolite of the conventional antipsychotic loxapine
  • Half-life of the active metabolites approximately 24 hours

Drug Interactions
• Tramadol increases the risk of seizures in patients taking TCAs
• Use of TCAs/tetracyclics with anticholinergic drugs may result in paralytic ileus or hyperthermia
• Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP450 2D6 inhibitors may increase TCA/tetracyclic concentrations
• Cimetidine may increase plasma concentrations of TCAs/tetracyclics and cause anticholinergic symptoms
• Phenothiazines or haloperidol may raise TCA/tetracyclic blood concentrations
• May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
• Use of TCAs/tetracyclics with sympathomimetic agents may increase sympathetic activity
• Methylphenidate may inhibit metabolism of TCAs/tetracyclics
• Activation and agitation, especially following switching or adding antidepressants, 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 amoxapine

**Other Warnings/Precautions**
- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing amoxapine
- Generally, do not use with MAOIs, including 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 amoxapine, but see Pearls
- Use with caution in patients with history of seizure, urinary retention, angle-closure glaucoma, hyperthyroidism
- TCAs/tetracyclics can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit its metabolism via CYP450 2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs/tetracyclics can prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because TCAs/tetracyclics can prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia, or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- 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 recovering from myocardial infarction
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfl oxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA/tetracyclic metabolism, including CYP450 2D6 inhibitors, except by an expert
- If there is reduced CYP450 2D6 function, such as patients who are poor 2D6 metabolizers, except by an expert and at low doses
- If there is a proven allergy to amoxapine or loxapine

**SPECIAL POPULATIONS**

**Renal Impairment**
- Use with caution – may require lower than usual adult dose

**Hepatic Impairment**
- Use with caution – may require lower than usual adult dose

**Cardiac Impairment**
- Baseline ECG is recommended
- TCAs/tetracyclics have been reported to cause arrhythmias, prolongation of conduction time, orthostatic hypotension, sinus tachycardia, and heart failure, especially in the diseased heart
- Myocardial infarction and stroke have been reported with TCAs/tetracyclics
- TCAs/tetracyclics produce QTc prolongation, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering amoxapine
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
- Avoid TCAs/tetracyclics in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
Pregnancy
- Controlled studies have not been conducted in pregnant women
- Some animal studies show adverse effects
- Amoxapine crosses the placenta
- Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations)
- Evaluate for treatment with an antidepressant with a better risk/benefit ratio

Breast Feeding
- Some drug is found in mother’s breast milk
- Recommended either to discontinue drug or bottle feed
- 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
- Evaluate for treatment with an antidepressant with a better risk/benefit ratio

Elderly
- Baseline ECG is recommended for patients over age 50
- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects
- Initial dose 25 mg/day at bedtime; increase by 25 mg/day each week; maximum dose 300 mg/day

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
- 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
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Not generally recommended for use under age 16
- Several studies show lack of efficacy of TCAs/tetracyclics for depression
- May be used to treat enuresis or hyperactive/impulsive behaviors
- Some cases of sudden death have occurred in children taking TCAs/tetracyclics
- Adolescents: initial 25–50 mg/day; increase gradually to 100 mg/day in divided doses or single dose at bedtime

THE ART OF PSYCHOPHARMACOLOGY
Potential Advantages
- Severe or treatment-resistant depression
- Treatment-resistant psychotic depression

Potential Disadvantages
- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients
- Patients with Parkinson’s disease or tardive dyskinesia

Primary Target Symptoms
- Depressed mood

Pearls
- Tricyclic/tetracyclic antidepressants are no longer generally considered a first-line treatment option for depression because of their side effect profile
- Tricyclic/tetracyclic antidepressants continue to be useful for severe or treatment-resistant depression
Because of potential extrapyramidal symptoms, akathisia, and theoretical risk of tardive dyskinesia, first consider other TCAs/tetracyclics for long-term use in general and for treatment of chronic patients
- TCAs may aggravate psychotic symptoms
- Alcohol should be avoided because of additive CNS effects
- Underweight patients may be more susceptible to adverse cardiovascular effects
- Children, patients with inadequate hydration, and patients with cardiac disease may be more susceptible to TCA-induced cardiotoxicity than healthy adults
- For the expert only: although generally prohibited, a heroic but potentially dangerous treatment for severely treatment-resistant patients is to give a tricyclic/tetracyclic antidepressant other than clomipramine simultaneously with an MAOI for patients who fail to respond to numerous other antidepressants
- Use of MAOIs with clomipramine is always prohibited because of the risk of serotonin syndrome and death
- Amoxapine may be the preferred tricyclic/tetracyclic antidepressant to combine with an MAOI in heroic cases due to its theoretically protective 5HT2A antagonist properties
- If this option is elected, start the MAOI with the tricyclic/tetracyclic antidepressant simultaneously at low doses after appropriate drug washout, then alternately increase doses of these agents every few days to a week as tolerated
- Although very strict dietary and concomitant drug restrictions must be observed to prevent hypertensive crises and serotonin syndrome, the most common side effects of MAOI/tricyclic or tetracyclic combinations may be weight gain and orthostatic hypotension
- Patients on TCAs/tetracyclics should be aware that they may experience symptoms such as photosensitivity or blue-green urine
- SSRIs may be more effective than TCAs/tetracyclics in women, and TCAs/tetracyclics may be more effective than SSRIs in men
- May cause some motor effects, possibly due to effects on dopamine receptors
- Amoxapine may have a faster onset of action than some other antidepressants
- May be pharmacologically similar to an atypical antipsychotic in some patients
- At high doses, patients who form high concentrations of active metabolites may have akathisia, extrapyramidal symptoms, and possibly develop tardive dyskinesia
- Structurally and pharmacologically related to the antipsychotic loxapine
- Since tricyclic/tetracyclic antidepressants are substrates for CYP450 2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of 2D6, such patients may not safely tolerate normal doses of tricyclic/tetracyclic antidepressants and may require dose reduction
- Phenotypic testing may be necessary to detect this genetic variant prior to dosing with a tricyclic/tetracyclic antidepressant, especially in vulnerable populations such as children, elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe side effects at normal or low doses may have this phenotypic CYP450 2D6 variant and require low doses or switching to another antidepressant not metabolized by 2D6

Suggested Reading


