DOXEPIN

**Brands**
- Sinequan
  see index for additional brand names

**Generic?**
Yes

**Class**
- Tricyclic antidepressant (TCA); serotonin and norepinephrine/noradrenaline reuptake inhibitor

**Commonly Prescribed For**
(FDA approved in bold)
- Psychoneurotic patient with depression and/or anxiety
- Depression and/or anxiety associated with alcoholism
- Depression and/or anxiety associated with organic disease
- Psychotic depressive disorders with associated anxiety
- Involutional depression
- Manic–depressive disorder
- Insomnia
- Pruritus/itching (topical)
- Dermatitis, atopic (topical)
- Lichen simplex chronicus (topical)
- Anxiety
- Neuropathic pain/chronic pain
- Treatment-resistant depression

**How the Drug Works**
At antidepressant doses:
- Boosts neurotransmitters serotonin and norepinephrine/noradrenaline
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably by desensitizes both serotonin 1A receptors and beta-adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, doxepin can thus increase dopamine neurotransmission in this part of the brain
- May be effective in treating skin conditions because of its strong antihistamine properties at low doses (1–6 mg/day)
- Selectively and potently blocks histamine 1 receptors, presumably decreasing wakefulness and thus promoting sleep, also, somewhat blocks histamine 2 receptors

**How Long until It Works**
- May have immediate effects in treating insomnia or anxiety
- 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 of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of insomnia is to improve quality of sleep, including effects on total wake time and number of nighttime awakenings
- The goal of treatment of chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but is not a cure since symptoms can recur after medicine stopped
- Treatment of chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms 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
- Use in insomnia, anxiety disorders, chronic pain, and skin conditions may also need to be indefinite, but long-term treatment is not well studied in these conditions

**If It Doesn’t Work**
- Many depressed patients only have a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed 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
If insomnia does not improve after 7–10 days, it may be a manifestation of a primary psychiatric or physical illness such as obstructive sleep apnea or restless leg syndrome, which requires independent evaluation
Best Augmenting Combos for Partial Response or Treatment-Resistance
Lithium, buspirone, thyroid hormone (for depression)
Trazodone, GABA-ergic sedative hypnotics (for insomnia)
Gabapentin, tiagabine, other antiepileptics, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)
Tests
None for healthy individuals
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 in an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–25 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
ECGs 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, sparfloxacin, etc.)
Patients at risk for electrolyte disturbances (e.g. patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements

ADVERSE EFFECTS (AEs)

How Drug Causes AEs
At antidepressant doses, anticholinergic activity may explain sedative effects, dry mouth, constipation, and blurred vision
Sedative effects and weight gain may be due to antihistamine properties
At antidepressant doses, blockade of alpha-1-adrenergic receptors may explain dizziness, sedation, and hypotension
Cardiac arrhythmias and seizures, especially in overdose, may be caused by blockade of ion channels
Notable AEs
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
Topical: burning, stinging, itching, or swelling at application site
Few AEs at low doses (1–6 mg/day)

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

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

What to Do about AEs
- Wait
- Wait
- Wait
- Lower the dose
- Switch to an SSRI or newer antidepressant

Best Augmenting Agents for AEs
- Many AEs cannot be improved with an augmenting agent

### DOSING AND USE

**Usual Dosage Range**
- 75–150 mg/day for depression
- 1–6 mg at bedtime for insomnia (possible with liquid formulation)

**Dosage Forms**
- Capsule: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg
- Solution: 10 mg/mL
- Topical: 5%

**How to Dose**
- Initial 25 mg/day at bedtime; increase by 25 mg every 3–7 days
- 75 mg/day; increase gradually until desired efficacy is achieved; can be dosed once a day at bedtime or in divided doses; maximum dose 300 mg/day
- Topical: apply thin film 4 times a day (or every 3–4 hours while awake)

**Dosing Tips**
- If given in a single antidepressant dose, should generally be administered at bedtime because of its sedative properties
- If given in split antidepressant doses, largest dose should generally be given at bedtime because of its sedative properties
- If patients experience nightmares, split antidepressant dose and do not give large dose at bedtime
- Patients treated for chronic pain may only require lower doses
- Patients treated for insomnia may benefit from doses of 1–6 mg at bedtime
- 1 mg, 3 mg, and 6 mg doses are in late-stage clinical development for the treatment of insomnia
- Liquid formulation should be diluted with water or juice, excluding grape juice
- 150-mg capsule available only for maintenance use, not initial therapy
- Topical administration is absorbed systematically and can cause the same systematic AEs as oral administration
- If intolerable anxiety, insomnia, agitation, akathisia, or activation occur upon dosing initiation or discontinuation, consider the possibility of activated bipolar disorder, and switch to a mood stabilizer or an atypical antipsychotic

**Overdose**
- Death may occur; convulsions, cardiac dysrhythmias, severe hypotension, CNS depression, coma, changes in ECG

**Long-Term Use**
- Safe

**Habit Forming**
- No

**How to Stop**
- At antidepressant doses, 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
- Taper not necessary for low doses (1–6 mg/day)

**Pharmacokinetics**
- Substrate for CYP2D6
- Half-life approximately 8–24 hours
Drug Interactions

- Tramadol increases the risk of seizures in patients taking TCAs
- Use of TCAs with anticholinergic drugs may result in paralytic ileus or hyperthermia
- Fluoxetine, paroxetine, bupropion, duloxetine, and other CYP2D6 inhibitors may increase TCA concentrations
- Cimetidine may increase plasma concentrations of TCAs and cause anticholinergic symptoms
- Phenothiazines or haloperidol may raise TCA blood concentrations
- May alter effects of antihypertensive drugs; may inhibit hypotensive effects of clonidine
- Use with sympathomimetic agents may increase sympathetic activity
- Methylphenidate may inhibit metabolism of TCAs
- Most drug interactions may be less likely at low doses (1–6 mg/day) due to the lack of effects on receptors other than the histamine 1 receptors
- 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 doxepin

Other Warnings/Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing doxepin
- Generally, do not use with MAOIs, including 14 days after MAOIs are stopped; do not start an MAOI until 2 weeks after discontinuing doxepin, but see Pearls
- Use with caution in patients with history of seizures, urinary retention, narrow angle-closure glaucoma, hyperthyroidism
- TCAs can increase QTc interval, especially at toxic doses, which can be attained not only by overdose but also by combining with drugs that inhibit TCA metabolism via CYP2D6, potentially causing torsade de pointes-type arrhythmia or sudden death
- Because TCAs 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 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 hypomagnesemia (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 AEs 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, sparfloxacin)
- If it is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is taking drugs that inhibit TCA metabolism, including CYP2D6 inhibitors, except by an expert
- If there is reduced CYP2D6 function, such as patients who are poor CYP2D6 metabolizers, except by an expert and at low doses
- If patient has narrow angle-closure glaucoma
- If there is a proven allergy to doxepin

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Use with caution; may need lower than usual adult dose

Cardiac Impairment

- TCAs 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
TCAs 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 doxepin.

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 in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure.

TCAs may cause a sustained increase in heart rate in patients with ischemic heart disease and may worsen (decrease) heart rate variability, an independent risk of mortality in cardiac populations.

Since SSRIs may improve (increase) heart rate variability in patients following a myocardial infarction and may improve survival as well as mood in patients with acute angina or following a myocardial infarction, these are more appropriate agents for cardiac populations than tricyclic/tetracyclic antidepressants.

Risk/benefit ratio may not justify use of TCAs in cardiac impairment.

**Elderly**

- May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects.
- Low-dose doxepin (1–6 mg/day) has been studied and found effective for insomnia in elderly patients and is in late-stage clinical development.
- Reduction in 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 guardian of this risk so they can help observe child or adolescent patients.
- Not recommended for use in children under age 12.

**Pregnancy**

- Risk Category C (some animal studies show AEs; no controlled studies in humans).
- Crosses the placenta.
- AEs have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations).
- Not generally recommended for use during pregnancy, especially during 1st trimester.
- Must weigh the risk of treatment (1st trimester fetal development, 3rd 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.
- Significant drug levels have been detected in some nursing infants.
- 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 3rd 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 PAIN PHARMACOLOGY**

**Potential Advantages**

- Patients with insomnia.
- Severe or treatment-resistant depression.
- Patients with neurodermatitis and itching.
Potential Disadvantages
- Pediatric and geriatric patients
- Patients concerned with weight gain
- Cardiac patients

Primary Target Symptoms
- Depressed mood
- Anxiety
- Disturbed sleep, energy
- Somatic symptoms
- Itching skin

Pearls
- Only TCA available in topical formulation
- Topical administration may reduce symptoms in patients with various neurodermatitis syndromes, especially itching
- TCAs are often a first-line treatment option for chronic pain
- TCAs are no longer generally considered a first-line option for depression because of their AE profile
- TCAs continue to be useful for severe or treatment-resistant depression
- 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
- Phase III trials of low-dose doxepin (1–6 mg/day) for insomnia have been completed and show effectiveness in adult and elderly populations
- At these low doses doxepin is selective for the histamine 1 receptor and thus can improve sleep without causing AEs associated with other neurotransmitter systems
- In particular, low-dose doxepin does not appear to cause anticholinergic symptoms, memory impairment, or weight gain, nor is there evidence of tolerance, rebound insomnia, or withdrawal effects
- 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
- 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 AEs of MAOI/tricyclic or tetracyclic combinations may be weight gain and orthostatic hypotension
- Patients on TCAs should be aware that they may experience symptoms such as photosensitivity or blue–green urine
- SSRIs may be more effective than TCAs in women, and TCAs may be more effective than SSRIs in men
- Since tricyclic/tetracyclic antidepressants are substrates for CYP2D6, and 7% of the population (especially Caucasians) may have a genetic variant leading to reduced activity of CYP2D6, 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, the elderly, cardiac populations, and those on concomitant medications
- Patients who seem to have extraordinarily severe AEs at normal or low doses may have this phenotypic CYP2D6 variant and require low doses or switching to another antidepressant not metabolized by CYP2D6
- Potent antagonist actions at both H1 and H2 receptors
Suggested Reading


