THERAPEUTICS

Brands • Prothiaden
see index for additional brand names

Generic? In UK

Class
• Neuroscience-based Nomenclature: serotonin, norepinephrine multi-modal (SN-MM)
• Tricyclic antidepressant (TCA)
• Serotonin and norepinephrine/noradrenaline reuptake inhibitor

Commonly Prescribed for
(bold for FDA approved)
• Major depressive disorder
• Anxiety
• Insomnia
• Neuropathic pain/chronic pain
• Treatment-resistant depression

How the Drug Works
• Boosts neurotransmitters serotonin and norepinephrine/noradrenaline
• Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotoninergic neurotransmission
• Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
• Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
• Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, dothiepin can increase dopamine neurotransmission in this part of the brain

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 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 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 anxiety disorders and chronic pain 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 have only 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
**Best Augmenting Combos for Partial Response or Treatment Resistance**

- Lithium, buspirone, thyroid hormone (for depression)
- Gabapentin, tiagabine, other anticonvulsants, even opiates if done by experts while monitoring carefully in difficult cases (for chronic pain)

**Tests**

- Baseline ECG is recommended for patients over age 50
  - 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

**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

**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

**Life-Threatening or Dangerous Side Effects**

- 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
- 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
DREFERRED TO AS DOThIEPINA

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 EKG

Long-Term Use
• Safe

Habit Forming
• No

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 approximately 14–40 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 CYP450 2D6 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 of TCAs with sympathomimetic agents may increase sympathetic activity
• Methylphenidate may inhibit metabolism of TCAs
• 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 dothiepin

Other Warnings/Precautions

- Add or initiate other antidepressants with caution for up to 2 weeks after discontinuing dothiepin
- 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 dothiepin, but see Pearls
- Use with caution in patients with history of seizures, urinary retention, angle-closure glaucoma, hyperthyroidism, and in patients recovering from myocardial infarction
- 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 CYP450 2D6, 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 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, sparfloxacin)
- 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 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 dothiepin

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Use with caution

Cardiac Impairment

- Baseline ECG is recommended
- 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 dothiepin
- 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 infarct 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 population than tricyclic/tetracyclic antidepressants.

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

Baseline ECG is recommended for patients over age 50.

May be more sensitive to anticholinergic, cardiovascular, hypotensive, and sedative effects.

Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older.

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.

Not recommended for use in children under age 18.

Several studies show lack of efficacy of TCAs for depression.

May be used to treat enuresis or hyperactive/impulsive behaviors.

Some cases of sudden death have occurred in children taking TCAs.

Controlled studies have not been conducted in pregnant women.

Crosses the placenta.

Adverse effects have been reported in infants whose mothers took a TCA (lethargy, withdrawal symptoms, fetal malformations).

Not generally recommended for use during pregnancy, especially 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.

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.

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.

Patients with insomnia.

Severe or treatment-resistant depression.

Anxious depression.

Pediatric and geriatric patients.

Patients concerned with weight gain.

Cardiac patients.

Depressed mood.

Chronic pain.
**Pearls**

- Close structural similarity to amitriptyline
- 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 side effect 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
- For the expert only: a heroic treatment (but potentially dangerous) for severely treatment-resistant patients is to give simultaneously with MAOIs for patients who fail to respond to numerous other antidepressants, but generally recommend a different TCA than dothiepin for this use
- 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 and tricyclic/tetracyclic antidepressant 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 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

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**Suggested Reading**


