

Tricyclic antidepressants

Older antidepressants that raise synaptic noradrenaline and serotonin by blocking their reuptake, but which also antagonise muscarinic, histamine H1 and alpha-1 adrenergic receptors, and which block cardiac fast sodium channels in overdose - the combination that explains both their tolerability problem and their lethality.

Online guide: <https://www.medguideglobal.com/pharmacology/central-nervous-system/tricyclic-antidepressants>

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Quick revision

One Liner: Tricyclics work by blocking monoamine reuptake, but nearly everything a student needs to remember about them comes from the receptors they block by accident and from what happens to the heart when too much is taken.

1. The amitriptyline label describes inhibition of the membrane pump responsible for uptake of noradrenaline and serotonin in adrenergic and serotonergic neurons. [1]
2. Off-target antagonism at muscarinic, histamine H1 and alpha-1 adrenergic receptors generates most of the adverse effects, and none of the antidepressant benefit. [8][10]
3. In poisoning the decisive lesion is cardiac: blockade of fast sodium channels in myocardial cells slows phase 0 of the action potential and widens the QRS complex. [7]
4. A QRS prolonged beyond 100 milliseconds is predictive of seizures, and beyond 160 milliseconds is predictive of arrhythmia. [7]
5. Every agent in the class carries the antidepressant boxed warning on suicidal thinking and behaviour in children, adolescents and young adults. [1][2][3][4]
6. The class divides chemically: amitriptyline, imipramine, doxepin, clomipramine and trimipramine are tertiary amines, while desipramine, nortriptyline and protriptyline are secondary amines. [8]
7. Tricyclics are contraindicated during the acute recovery period after a myocardial infarction, and with monoamine oxidase inhibitors inside a fourteen-day window. [2][4][3]
8. Clomipramine is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder. [4]
9. Amitriptyline is used for nerve pain and to help prevent migraines, and the NHS states the doses used for pain are lower than those used for depression. [12]

Overview

1. Tricyclic antidepressants inhibit the reuptake of serotonin and noradrenaline at presynaptic terminals, raising the concentration of both transmitters in the synaptic cleft. The Pamelor label is unusually frank about the limits of that explanation: the mechanism of mood elevation by tricyclic antidepressants is at present unknown, and what the drug demonstrably does is inhibit the activity of agents as diverse as histamine, 5-hydroxytryptamine and acetylcholine. Reuptake inhibition is the working model, not a proven account of why mood improves. [2][1][8]
2. What displaced these agents from first-line use was not weak efficacy. Tricyclics show equivocal efficacy with SSRIs in major depressive disorder, yet cause more significant adverse effects because of their anticholinergic activity and their lower threshold for overdose. The class also has a narrow therapeutic index. A student who remembers only one thing about tricyclics should remember that the gap between a therapeutic quantity and a dangerous one is small. [8]
3. The adverse-effect profile is receptor pharmacology made visible. Muscarinic blockade produces dry mouth, blurred vision, constipation and urinary retention, and confusion in older people. Histamine H1 blockade produces sedation, increased appetite and weight gain. Alpha-1 adrenergic blockade induces orthostatic hypotension and dizziness. Each of these is an off-target effect of a molecule that was never selective. [8][1]

4. The class has not disappeared. Clomipramine holds a licensed place in obsessive-compulsive disorder, low-dose doxepin is licensed for sleep-maintenance insomnia through H1 antagonism, imipramine remains an option in childhood enuresis, and amitriptyline is widely used for nerve pain and migraine prevention. Reuptake inhibition of noradrenaline and serotonin is believed to underlie the use of tricyclics in neuropathic pain and headache.

[4][6][3][12][8]

Classification and drug examples

Intro: Grouped by the amine on the side chain, because that single structural feature tracks the receptor selectivity and, in the case of desipramine, a measurably lighter anticholinergic load. The secondary amines are also the demethylated metabolites of the tertiary amines they sit beside.

1. Name: Tertiary amine tricyclics

1. Note: Tertiary amines typically exhibit significant serotonin reuptake inhibition. They carry the heavier receptor burden of the two groups, and several of them are demethylated to an active metabolite: amitriptyline to nortriptyline, imipramine to desipramine, clomipramine to desmethylclomipramine.

1. Name: Amitriptyline

Elavil

1. Route: Oral

1. Note: The archetype of the group. Its label states that geriatric patients are particularly sensitive to the anticholinergic side effects of tricyclic antidepressants, listing cognitive impairment, psychomotor slowing, confusion, sedation and delirium among the central effects. [1]

2. Name: Imipramine

Tofranil

2. Route: Oral

2. Note: A tertiary amine similar in structure to amitriptyline, with strong affinities for alpha-1 adrenergic, histamine H1 and muscarinic M1 receptors. It is demethylated by CYP2C19 to desipramine. [10]

3. Name: Clomipramine

Anafranil

3. Route: Oral

3. Note: The most serotonergic member. Its label presumes the effect on obsessions and compulsions comes from serotonergic neuronal transmission, and names desmethylclomipramine as an active metabolite whose contribution in OCD remains unknown. [4]

4. Name: Doxepin

1. Sinequan

2. Silenor

4. Route: Oral

4. Note: A dibenzoxepine with very high affinity at the histamine H1 receptor, quoted in the Silenor label as a K_i below 1 nM. That affinity is the basis of a separate low-dose licence in insomnia. [6]

5. Name: Trimipramine

Surmontil

5. Route: Oral

5. Note: Grouped with the tertiary amines on structure. It has no released medicine page on this site, so it is named here rather than linked. [8] [8][10]

2. Name: Secondary amine tricyclics

2. Note: Secondary amines display heightened inhibition of noradrenaline uptake. Desipramine, compared with tertiary amines such as amitriptyline, is associated with fewer anticholinergic adverse effects - the practical reason this half of the class is often preferred in older patients.

1. Name: Nortriptyline

1. Pamelor

2. Aventyl

1. Route: Oral

1. Note: A secondary amine, and the form amitriptyline is converted into: amitriptyline is metabolised to nortriptyline, which is its active form. Its label warns of a tendency to produce sinus tachycardia and to prolong conduction time.

[10][11][2]

2. Name: Desipramine

Norpramin

2. Route: Oral

2. Note: Classified as a secondary amine and produced from imipramine by CYP2C19. Its own label reports that use in the elderly has been associated with a proneness to falling as well as confusional states. [9][10][5]

3. Name: Protriptyline

Vivactil

3. Route: Oral

3. Note: The third member of the secondary amine group. It shares the group's shift towards noradrenaline reuptake blockade rather than serotonin reuptake blockade. [8] [8][9]

Mechanism of action

Summary: Reuptake inhibition of noradrenaline and serotonin is the intended action; antagonism at muscarinic, histamine H1 and alpha-1 adrenergic receptors is unintended and accounts for the tolerability problem; and blockade of cardiac fast sodium channels is what makes overdose lethal. The labels do not claim more than the evidence supports, and the nortriptyline label states plainly that the mechanism of mood elevation by tricyclic antidepressants is at present unknown.

Target: Presynaptic noradrenaline and serotonin transporters, with off-target antagonism at muscarinic, histamine H1 and alpha-1 adrenergic receptors, and blockade of cardiac fast sodium channels in overdose

Cidal Static: Symptom-modifying rather than curative

Kill Kinetics: Effect builds over weeks of continuous exposure rather than with a single dose

1. Step: 1

1. Title: Inhibition of monoamine reuptake at the presynaptic terminal

1. Detail: These medicines inhibit serotonin and noradrenaline reuptake within the presynaptic terminals, raising the concentration of both transmitters inside the synaptic cleft. The amitriptyline label puts the same action in older language, describing inhibition of the membrane pump mechanism responsible for uptake of noradrenaline and serotonin in adrenergic and serotonergic neurons. [8][1]

2. Step: 2

2. Title: Amine class shifts which transporter dominates

2. Detail: Tertiary amines typically exhibit significant serotonin reuptake inhibition, whereas secondary amines display heightened inhibition of noradrenaline uptake. Researchers propose that secondary amine agents such as desipramine produce greater noradrenaline blockade than the tertiary amines do. [8][9]

3. Step: 3

3. Title: Muscarinic receptor antagonism

3. Detail: The same molecules act as competitive antagonists at postsynaptic muscarinic receptors. That produces the familiar set of blurred vision, constipation, xerostomia, confusion, urinary retention and tachycardia, and it is the single largest reason the class fell out of first-line use. [8]

4. Step: 4

4. Title: Histamine H1 antagonism

4. Detail: Histamine blockade at the H1 receptor may lead to sedation, increased appetite, weight gain and confusion. Doxepin holds the extreme position here, with a binding affinity at H1 quoted as a K_i below 1 nM, and its

sleep-maintenance effect is described in its label as possibly mediated through antagonism of that receptor. [8][6]

5. Step: 5

5. Title: Alpha-1 adrenergic antagonism

5. Detail: Alpha-1 adrenergic receptor blockade can induce orthostatic hypotension and dizziness. Imipramine is documented as having strong affinities for alpha-1 adrenergic, histamine H1 and muscarinic M1 receptors, which is why one molecule can cause postural drops, sedation and dry mouth at the same time. [8][10]

6. Step: 6

6. Title: Cardiac fast sodium-channel blockade in overdose

6. Detail: Blockade of fast sodium channels in myocardial cells slows the action potential and provides a membrane stabilising effect. The characteristic QRS prolongation seen in overdose occurs secondary to prolongation of phase 0 of the myocardial action potential, and separate potassium channel blockade lengthens the QT interval and can generate torsades de pointes. [7]

Major clinical uses

1. Drug: Nortriptyline

1. Organism: Not applicable

1. Indication: Relief of symptoms of depression

1. Line: second-line

1. Note: A secondary amine used where a tricyclic is still wanted for depression. Its label notes it is not a monoamine oxidase inhibitor, and it is not approved for use in paediatric patients. [2]

2. Drug: Clomipramine

2. Organism: Not applicable

2. Indication: Obsessions and compulsions in obsessive-compulsive disorder

2. Line: established

2. Note: The label requires that the obsessions or compulsions cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning. This is the class's most durable psychiatric niche outside depression. [4]

3. Drug: Imipramine

3. Organism: Not applicable

3. Indication: Depression, and temporary adjunctive therapy in childhood enuresis

3. Line: second-line

3. Note: Its label allows use in reducing enuresis in children aged six years and older, after possible organic causes have been excluded by appropriate tests, and warns that one to three weeks of treatment may be needed before optimal antidepressant effect appears. [3]

4. Drug: Amitriptyline

4. Organism: Not applicable

4. Indication: Nerve pain, long-lasting pain, and migraine prevention

4. Line: widely used

4. Note: The NHS describes it as a prescription-only medicine used to treat nerve pain and pain that lasts a long time, and to help prevent migraines, and states that the doses used to treat pain are lower than the doses for depression. This page gives no dose information of any kind. [12]

5. Drug: Doxepin

5. Organism: Not applicable

5. Indication: Insomnia characterised by difficulties with sleep maintenance, at low dose

5. Line: niche

5. Note: A tricyclic repurposed as an antihistamine hypnotic. Its label states the mechanism in sleep maintenance is unclear, but that the effect could be mediated through antagonism of the H1 receptor. [6]

- 6. Drug: Desipramine
- 6. Organism: Not applicable
- 6. Indication: Depression, where anticholinergic load is the limiting concern
- 6. Line: second-line
- 6. Note: Described in its label as an antidepressant drug of the tricyclic type. Compared with tertiary amines such as amitriptyline it is associated with fewer anticholinergic adverse effects, which is the usual reason to reach for it. [5][9]

Pharmacokinetics

- 1. Drug: Imipramine
- 1. Route: Oral
- 1. Absorption: Oral
- 1. Csf Penetration: Not applicable
- 1. Metabolism: CYP2C19 demethylation to desipramine, itself a tricyclic; CYP2D6 handles further hydroxylation
- 1. Elimination: Hepatic
- 1. Half Life: Not stated in the sources cited on this page
- 1. Dose Adjust: Optimal response is generally reported when combined imipramine and desipramine serum levels sit between 150 and 300 ng/mL [10]
- 2. Drug: Amitriptyline
- 2. Route: Oral
- 2. Absorption: Oral
- 2. Csf Penetration: Not applicable
- 2. Metabolism: Metabolised to nortriptyline, described as its active form
- 2. Elimination: Hepatic
- 2. Half Life: Not stated in the sources cited on this page
- 2. Dose Adjust: Its label flags geriatric patients as particularly sensitive to the anticholinergic effects of the class [11][1]
- 3. Drug: Clomipramine
- 3. Route: Oral
- 3. Absorption: Oral
- 3. Csf Penetration: Not applicable
- 3. Metabolism: Demethylated to desmethylclomipramine, an active metabolite
- 3. Elimination: Hepatic
- 3. Half Life: Not stated in the sources cited on this page
- 3. Dose Adjust: The contribution of the metabolite to the effect in OCD is stated in the label to be unknown [4]
- 4. Drug: Desipramine
- 4. Route: Oral
- 4. Absorption: Oral
- 4. Csf Penetration: Not applicable
- 4. Metabolism: CYP2D6 substrate; poor metabolisers reach higher plasma concentrations than expected on usual quantities
- 4. Elimination: Hepatic
- 4. Half Life: Not stated in the sources cited on this page
- 4. Dose Adjust: Adverse effects are more likely in CYP2D6 poor metabolisers because tricyclic plasma concentrations run high [10]
- 1. No dose regimens appear anywhere on this page. Starting, titrating, monitoring or withdrawing a tricyclic is a decision for the treating clinician, working from a current prescribing reference and the individual patient in front of them.
- 2. The metabolite relationships are worth memorising as a pair: amitriptyline yields nortriptyline, and imipramine yields

desipramine. In both cases the tertiary amine is demethylated to a secondary amine that is marketed as a drug in its own right. [11][10]

3. CYP2D6 status matters more here than in most classes, because a narrow therapeutic index leaves little room for an unexpectedly high plasma concentration. [10][8]

Adverse effects

1. Effect: Antimuscarinic effects

1. Detail: Dry mouth and rarely associated sublingual adenitis, blurred vision, disturbance of accommodation, mydriasis, constipation, paralytic ileus, urinary retention, delayed micturition and dilation of the urinary tract. The clomipramine trials quantify the burden: dry mouth in 84% of patients against 17% on placebo, constipation in 47% against 11%, and abnormal vision in 18% against 4%. [2][3][4]

2. Effect: Sedation, increased appetite and weight gain

2. Detail: Histamine H1 blockade may lead to sedation, increased appetite, weight gain and confusion. Weight gain was reported in 18% of patients receiving clomipramine against 1% on placebo. [8][4]

3. Effect: Orthostatic hypotension and dizziness

3. Detail: Alpha-1 adrenergic receptor blockade can induce a postural drop. The imipramine label lists orthostatic hypotension first among its cardiovascular reactions, alongside tachycardia and palpitation, with drowsiness, dizziness, weakness and fatigue listed separately. [8][3]

1. Effect: Suicidal thinking and behaviour in the young

1. Detail: The boxed warning states that antidepressants increased the risk compared with placebo of suicidal thinking and behaviour in children, adolescents and young adults in short-term studies of major depressive disorder and other psychiatric disorders. The pooled figures are expressed per thousand treated: 14 additional cases under 18, 5 additional cases from 18 to 24, one fewer case from 25 to 64, and 6 fewer cases at 65 and above.

1. Action: All patients started on an antidepressant for any indication are to be monitored appropriately and observed closely for clinical worsening, suicidality and unusual changes in behaviour. [1][2][4]

2. Effect: Cardiac conduction disturbance and arrhythmia at therapeutic exposure

2. Detail: Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia and prolongation of the conduction time, and myocardial infarction and stroke have been reported with drugs of this class. Desipramine has been linked with heart block, arrhythmias and sudden death.

2. Action: Labels direct extreme caution in cardiovascular disease, with cardiac surveillance at all levels of exposure rather than only at high ones. [1][3][9]

3. Effect: Cardiotoxicity in overdose

3. Detail: Critical manifestations include cardiac dysrhythmias, severe hypotension, shock, congestive heart failure, pulmonary oedema, convulsions and central nervous system depression including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are the clinically significant indicators of tricyclic toxicity, and the imipramine label calls a maximal limb-lead QRS duration of 0.10 seconds or more the best single indication of severity. Death is most often attributed to hypotension or arrhythmia.

3. Action: This is a medical emergency handled by an emergency service; nothing on this page describes its management. [2][3][8]

4. Effect: Seizures

4. Detail: The clomipramine label reports a cumulative incidence of seizures of 0.64% at 90 days, 1.12% at 180 days and 1.45% at 365 days among exposed patients. In overdose, seizures precede cardiac dysrhythmias and death in some patients, and a QRS beyond 100 milliseconds is predictive of them.

4. Action: A recognised hazard of the class that bears on the choice of agent in anyone with a seizure history. [4][5][7]

5. Effect: Precipitation of angle-closure glaucoma

5. Detail: The pupillary dilation that follows use of many antidepressants including amitriptyline may trigger an angle closure attack in a patient with anatomically narrow angles.

5. Action: Relevant before a tricyclic is chosen for anyone with narrow angles or untreated narrow-angle glaucoma. [1][6]

6. Effect: Confusion, delirium and falls in older people

6. Detail: Central anticholinergic effects include cognitive impairment, psychomotor slowing, confusion, sedation and delirium, and geriatric patients are described as particularly sensitive to them. Use of desipramine in the elderly has been associated with a proneness to falling as well as confusional states.

6. Action: This is the effect that most often ends a tricyclic trial in an older patient, and it is a clinician's judgement to make. [1][5]

1. Drug: Clomipramine

1. Effect: Sexual dysfunction is prominent: 42% of men experienced ejaculatory failure and 20% impotence, against 2.0% and 2.6% respectively on placebo. [4]

2. Drug: Nortriptyline

2. Effect: A tendency to produce sinus tachycardia and to prolong the conduction time, so patients with cardiovascular disease are given it only under close supervision. [2]

3. Drug: Imipramine

3. Effect: Its cardiovascular list runs to heart block, ECG changes, precipitation of congestive heart failure and stroke, which is why cardiac surveillance is specified at every level of exposure. [3]

4. Drug: Doxepin

4. Effect: Even at the low hypnotic strength, constipation and urinary retention are noted above the licensed maximum, and the product is contraindicated in untreated narrow angle glaucoma or severe urinary retention. [6]

5. Drug: Desipramine

5. Effect: Overdose may produce cardiac dysrhythmia, severe hypotension, convulsions, coma, hyperactive reflexes, stupor, drowsiness, hypothermia and confusion. [9]

6. Drug: Amitriptyline

6. Effect: Paralytic ileus and hyperpyrexia sit alongside the ordinary antimuscarinic effects, and hypotension is specifically noted as postural. [1]

Contraindications, precautions and interactions

1. Use with a monoamine oxidase inhibitor intended to treat a psychiatric disorder, or within fourteen days of stopping either agent, is contraindicated because of an increased risk of serotonin syndrome. [2][4][5]

2. The acute recovery period after a myocardial infarction. Every tricyclic label consulted for this page states the same restriction in almost the same words. [2][4][3][1][5]

3. Prior hypersensitivity to the agent or, in the clomipramine label, to other tricyclic antidepressants. [1][4]

4. Low-dose doxepin for insomnia is contraindicated in individuals with untreated narrow angle glaucoma or severe urinary retention. [6]

1. Cardiovascular disease calls for extreme caution, because of the possibility of conduction defects, arrhythmias, congestive heart failure, myocardial infarction, strokes and tachycardia; these patients require cardiac surveillance at all dosage levels. [3]

2. Older patients, in whom sensitivity to anticholinergic effects is heightened and falls and confusional states have been reported. [1][5]

3. A history of urinary retention or angle-closure glaucoma, given the anticholinergic properties of these drugs. [1][5]

4. A history of seizures, which matters most for clomipramine given its measured cumulative seizure incidence. [1][4]

5. CYP2D6 poor metaboliser status, since poor metabolisers reach higher than expected tricyclic plasma concentrations and adverse effects become more likely. [10]

6. A family history of QT interval prolongation or sudden cardiac death is listed among the reasons to avoid this class. [8]

1. With: Monoamine oxidase inhibitors

1. Effect: Hyperpyretic crises or severe convulsive seizures may occur in patients receiving such combinations, and the potentiation of adverse effects can be serious or even fatal. A minimum interval of fourteen days is specified when substituting one for the other. [3][2]
2. With: Other anticholinergic agents
2. Effect: Given together with a tricyclic, close supervision and careful adjustment of dosages are required, because the antimuscarinic burden is additive. [1]
3. With: Sympathomimetics, including adrenaline combined with local anaesthetics
3. Effect: The amitriptyline label singles this combination out as requiring close supervision, which makes it a genuine dental and minor-surgery consideration. [1]
4. With: CYP2D6 inhibitors such as quinidine
4. Effect: Inhibition of CYP2D6 slows tricyclic clearance and drives plasma concentrations up, which is dangerous in a class with a narrow therapeutic index. [5][8]
5. With: Selective serotonin reuptake inhibitors
5. Effect: Combining a tricyclic with an SSRI is listed among the contraindicated pairings for this class. [8]

Comparison tables

Title: Tertiary against secondary amines, and what each member is actually used for

Caption: Structure predicts transporter selectivity and anticholinergic load. Choice of agent is a clinical decision made from a current prescribing reference, not from this table.

1. Key: drug
1. Label: Drug
1. Is Row Header: true
2. Key: amine
2. Label: Amine class
3. Key: selectivity
3. Label: Reuptake emphasis
4. Key: signature
4. Label: Distinguishing feature
1. Drug: Amitriptyline
1. Amine: Tertiary
1. Selectivity: Serotonin-weighted
1. Signature: Heaviest anticholinergic reputation; converted to nortriptyline; widely used for nerve pain and migraine prevention [8][11][12]
2. Drug: Imipramine
2. Amine: Tertiary
2. Selectivity: Serotonin-weighted
2. Signature: Strong alpha-1, H1 and M1 affinity; the enuresis agent; demethylated to desipramine [10][3]
3. Drug: Clomipramine
3. Amine: Tertiary
3. Selectivity: Most serotonergic of the group
3. Signature: Licensed for OCD; measured cumulative seizure incidence; high rates of dry mouth and sexual dysfunction [4][8]
4. Drug: Doxepin
4. Amine: Tertiary
4. Selectivity: Serotonin-weighted
4. Signature: H1 affinity with a K_i below 1 nM; separately licensed at low dose for sleep-maintenance insomnia [6][8]
5. Drug: Nortriptyline

- 5. Amine: Secondary
- 5. Selectivity: Noradrenaline-weighted
- 5. Signature: Active form of amitriptyline; sinus tachycardia and prolonged conduction time are its label's cardiac warnings [11][2][8]
- 6. Drug: Desipramine
- 6. Amine: Secondary
- 6. Selectivity: Noradrenaline-weighted
- 6. Signature: Fewer anticholinergic adverse effects than tertiary amines; falls and confusion still reported in the elderly [9][5]
- 7. Drug: Protriptyline
- 7. Amine: Secondary
- 7. Selectivity: Noradrenaline-weighted
- 7. Signature: The least used member; shares the secondary amine transporter emphasis [8]

High-yield exam pearls

- 1. Pearl: Blockade of fast sodium channels in myocardial cells slows the action potential and gives a membrane stabilising effect, and QRS prolongation follows from prolongation of phase 0.
- 1. Why: It is the mechanistic answer to the most examined question about this class, and it explains why the ECG rather than the plasma level guides severity. [7]
- 2. Pearl: Two QRS thresholds carry prognostic weight in poisoning: beyond 100 milliseconds predicts seizures, beyond 160 milliseconds predicts arrhythmia.
- 2. Why: Numbers this specific are examinable, and they show that a single ECG measurement stratifies two different complications. [7]
- 3. Pearl: Amitriptyline is metabolised to nortriptyline, which is its active form, and imipramine is demethylated by CYP2C19 to desipramine.
- 3. Why: The parent-metabolite pairs also happen to be the tertiary-to-secondary amine pairs, so one fact answers two different question types. [11][10]
- 4. Pearl: Desipramine, compared with tertiary amines such as amitriptyline, is associated with fewer anticholinergic adverse effects.
- 4. Why: It is the reason a secondary amine is the usual pick when a tricyclic is wanted in an older patient. [9]
- 5. Pearl: The three off-target receptors map cleanly onto three symptom groups: muscarinic to dry mouth and retention, H1 to sedation and weight gain, alpha-1 to postural dizziness.
- 5. Why: Examiners test the mapping rather than the list, and the mapping also predicts which patient will not tolerate the drug. [8]
- 6. Pearl: Clomipramine's cumulative seizure incidence was 0.64% at 90 days, 1.12% at 180 days and 1.45% at 365 days.
- 6. Why: It is one of very few places where a tricyclic label quantifies a neurological risk over time rather than describing it. [4]

Common exam traps

- 1. Trap: Saying tricyclics were replaced because SSRIs work better.
- 1. Correction: Efficacy is equivocal with SSRIs in major depressive disorder. What separates them is a heavier anticholinergic burden and a lower threshold for overdose. [8]
- 2. Trap: Attributing overdose deaths mainly to the central nervous system depression.
- 2. Correction: Death is generally attributed to hypotension or arrhythmia, and the ECG change in QRS axis or width is the clinically significant indicator of toxicity. [8][2]
- 3. Trap: Treating the antidepressant suicidality boxed warning as an SSRI-only phenomenon.

3. Correction: It appears on tricyclic labels in identical language, covering children, adolescents and young adults in short-term studies of depression and other psychiatric disorders. [1][3]
4. Trap: Assuming any antidepressant may follow a monoamine oxidase inhibitor immediately.
4. Correction: Hyperpyretic crises or severe convulsive seizures may occur, and a minimum of fourteen days must elapse when substituting one class for the other. [3]
5. Trap: Thinking a tricyclic is safe soon after a heart attack because the patient is stable.
5. Correction: The acute recovery period following myocardial infarction is a stated contraindication across the class, independent of how well the patient appears. [2][4]
6. Trap: Assuming low-dose doxepin for insomnia carries no tricyclic cautions.
6. Correction: It is still contraindicated in untreated narrow angle glaucoma and in severe urinary retention, and within two weeks of a monoamine oxidase inhibitor. [6]

Self-test questions

1. Question: A patient is brought to hospital after a large ingestion of a tricyclic antidepressant. The ECG shows a widened QRS complex. Which mechanism best explains this finding?
 1. Blockade of fast sodium channels prolonging phase 0 of the myocardial action potential
 2. Antagonism of cardiac muscarinic receptors
 3. Blockade of alpha-1 adrenergic receptors in vascular smooth muscle
 4. Inhibition of noradrenaline reuptake at cardiac sympathetic nerve endings

1. Explanation: Blockade of fast sodium channels in myocardial cells slows the action potential and provides a membrane stabilising effect, and the characteristic QRS prolongation occurs secondary to prolongation of phase 0 of the myocardial action potential. [7]
2. Question: In tricyclic antidepressant poisoning, which QRS duration is described as predictive of arrhythmia?
 1. Greater than 160 milliseconds
 2. Greater than 60 milliseconds
 3. Greater than 80 milliseconds
 4. Greater than 200 milliseconds

2. Explanation: Prolongation of the QRS beyond 100 milliseconds is described as predictive of seizures, while a QRS greater than 160 milliseconds is described as predictive of arrhythmia. [7]
3. Question: Which pairing of parent drug and its active metabolite is correct?
 1. Amitriptyline to nortriptyline, and imipramine to desipramine
 2. Nortriptyline to amitriptyline, and desipramine to imipramine
 3. Clomipramine to nortriptyline, and doxepin to desipramine
 4. Imipramine to nortriptyline, and amitriptyline to desipramine

3. Explanation: Amitriptyline is metabolised to nortriptyline, which is its active form, and imipramine is metabolised by CYP2C19 to desipramine, which is itself a tricyclic antidepressant. [11][10]
4. Question: Which group do desipramine, nortriptyline and protriptyline belong to, and what does that predict?
 1. Secondary amines, with heightened inhibition of noradrenaline uptake
 2. Tertiary amines, with heightened inhibition of noradrenaline uptake
 3. Secondary amines, with greater serotonin reuptake inhibition
 4. Tetracyclic agents, with no effect on monoamine transporters

4. Explanation: Desipramine, nortriptyline and protriptyline are categorised as secondary amines, and secondary amines display heightened inhibition of noradrenaline uptake, whereas tertiary amines show significant serotonin reuptake inhibition. [8]
5. Question: A tricyclic antidepressant is being considered three days after a monoamine oxidase inhibitor was stopped. What does the labelling require?
 1. A minimum interval of fourteen days between the two agents

2. An interval of forty-eight hours is sufficient
3. No interval is required if the doses are low
4. A minimum interval of six months between the two agents
5. Explanation: The labels state that concomitant use is contraindicated and that a minimum of fourteen days should elapse when substituting one class for the other, because hyperpyretic crises or severe convulsive seizures may occur. [3][2]
6. Question: Which cardiac situation is a stated contraindication on tricyclic antidepressant labels?
 1. The acute recovery period after a myocardial infarction
 2. Well-controlled hypertension
 3. A single episode of supraventricular tachycardia ten years ago
 4. A resting heart rate at the lower end of normal
6. Explanation: Tricyclic labels state that the drug is contraindicated during the acute recovery period after a myocardial infarction, and separately warn of conduction defects and arrhythmias in cardiovascular disease. [2][4][3]
7. Question: Which receptor effect of the tricyclics best explains sedation, increased appetite and weight gain?
 1. Histamine H1 antagonism
 2. Muscarinic receptor antagonism
 3. Alpha-1 adrenergic antagonism
 4. Serotonin transporter blockade
7. Explanation: Histamine blockade at H1 may lead to sedation, increased appetite, weight gain and confusion, and doxepin's very high H1 affinity is the basis of its separate licence in sleep-maintenance insomnia. [8][6]
8. Question: Which tricyclic antidepressant is licensed for the treatment of obsessions and compulsions in obsessive-compulsive disorder?
 1. Clomipramine
 2. Nortriptyline
 3. Protriptyline
 4. Trimipramine
8. Explanation: Clomipramine is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder, and the label presumes the effect comes from its action on serotonergic neuronal transmission. [4]

Frequently asked questions

1. Question: Why are tricyclic antidepressants second-line if they work as well as SSRIs?
 1. Answer: Because the price of the same benefit is higher. Efficacy is equivocal with SSRIs in major depressive disorder, but tricyclics cause more significant adverse effects through their anticholinergic activity and have a lower threshold for overdose, on top of a narrow therapeutic index. The deciding factor is tolerability and danger in excess, not potency. [8]
 2. Question: What makes a tricyclic overdose so dangerous compared with an SSRI overdose?
 2. Answer: The heart. Beyond the sedation and seizures, these molecules block fast myocardial sodium channels, which slows conduction and widens the QRS complex, and they block potassium channels, which lengthens the QT interval and can produce torsades de pointes. Hypotension and arrhythmia are the usual causes of death. [7][8]
 3. Question: What is the difference between a secondary and a tertiary amine tricyclic?
 3. Answer: It is a difference in the side-chain nitrogen that tracks a difference in behaviour. Amitriptyline, imipramine, clomipramine, doxepin and trimipramine are tertiary amines with greater serotonin reuptake inhibition; desipramine, nortriptyline and protriptyline are secondary amines that block noradrenaline uptake more strongly. Desipramine is also associated with fewer anticholinergic adverse effects than tertiary amines such as amitriptyline. [8][9]
 4. Question: Do tricyclics still have a place in modern practice?
 4. Answer: Yes, in narrower roles. Clomipramine holds a licence in obsessive-compulsive disorder, imipramine remains

an option as temporary adjunctive therapy for enuresis in children aged six and over, low-dose doxepin is licensed for sleep-maintenance insomnia, and amitriptyline is commonly used for nerve pain and migraine prevention with the NHS noting that pain doses are lower than depression doses. [4][3][6][12]

5. Question: Why do older patients tolerate these drugs so poorly?

5. Answer: Geriatric patients are described as particularly sensitive to the anticholinergic effects of the class, and the central ones include cognitive impairment, psychomotor slowing, confusion, sedation and delirium. Add alpha-1 blockade with its postural drop, and the same molecule that dries the mouth also raises the risk of a fall; desipramine's own label records a proneness to falling alongside confusional states. [1][5][8]

6. Question: Does the antidepressant suicidality warning apply to this class too?

6. Answer: It does, in the same wording used across antidepressants: the risk of suicidal thinking and behaviour was increased against placebo in children, adolescents and young adults in short-term studies. The pooled per-thousand figures show 14 additional cases below 18 and 5 from 18 to 24, with fewer cases than placebo at 25 to 64 and at 65 and above. [1][2]

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