

SNRIs and other antidepressants

The antidepressants that are neither SSRIs nor tricyclics: the dual serotonin-noradrenaline reuptake inhibitors, the receptor-modulating atypicals, the selective noradrenaline reuptake inhibitor reboxetine, and the monoamine oxidase inhibitors, grouped here because each raises monoamine signalling by a different route and each carries its own signature hazard.

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

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Quick revision

One Liner: These agents raise monoamine signalling by four different routes, and each member earns its place in an examination through one safety fact that the others do not share.

1. Serotonin-noradrenaline reuptake inhibitors potentiate both transmitters by blocking their reuptake, although the venlafaxine label calls the antidepressant mechanism itself unclear. [1][3]
2. Venlafaxine produced dose-related increases in systolic and diastolic blood pressure in controlled trials, together with cases of sustained hypertension. [1]
3. Duloxetine carries a hepatic caution: hepatic failure, sometimes fatal, has been reported, and its label bars use where there is substantial alcohol use or evidence of chronic liver disease. [3]
4. Bupropion is contraindicated in seizure disorder and in current or prior anorexia nervosa or bulimia, because seizure is its defining hazard. [6]
5. Mirtazapine blocks central alpha-2 autoreceptors and heteroreceptors and antagonises 5-HT₂, 5-HT₃ and histamine H₁ receptors, which is why sedation and appetite gain dominate its profile. [5]
6. Irreversible MAO inhibition lets dietary tyramine escape breakdown and precipitate hypertensive crisis, so aged, fermented and air-dried foods are restricted. [10][9]
7. Moclobemide inhibits MAO-A reversibly, so a rising tyramine load displaces the drug from the enzyme and tyramine potentiation is negligible. [12]
8. Every antidepressant on this page carries the same boxed warning on suicidal thoughts and behaviours in children, adolescents and young adults. [6][3][8]
9. Stopping abruptly provokes withdrawal reactions, and the MHRA names venlafaxine among the agents linked with a greater frequency of them. [11]

Overview

1. This class is defined partly by exclusion. It holds the antidepressants that are neither selective serotonin reuptake inhibitors nor tricyclics, which in practice means the dual serotonin-noradrenaline reuptake inhibitors, a small group of receptor-modulating atypicals, one selective noradrenaline reuptake inhibitor, and the monoamine oxidase inhibitors. What unites them is that all of them raise the synaptic availability of one or more monoamines, and that all of them share the antidepressant boxed warning on suicidal thoughts and behaviours in young people. [1][6]
2. The SNRIs block the serotonin and noradrenaline transporters together. Regulators are careful about how far that explains the clinical effect: the venlafaxine label says the mechanism of action in depression, generalised anxiety, social anxiety and panic disorder is unclear, but is thought to relate to potentiation of serotonin and noradrenaline through inhibition of their reuptake. The added noradrenergic action brings a cost the SSRIs largely avoid, which is a measurable effect on blood pressure and heart rate. [1][4]
3. The atypicals reach the same end by acting at receptors rather than only at transporters. Mirtazapine antagonises presynaptic alpha-2 receptors and several postsynaptic serotonin and histamine receptors; trazodone combines serotonin reuptake inhibition with 5-HT₂ antagonism; vilazodone adds partial agonism at 5-HT_{1A} to serotonin reuptake

blockade; bupropion is a relatively weak inhibitor of noradrenaline and dopamine uptake that does not touch serotonin at all. Reboxetine sits apart again as a selective inhibitor of the noradrenaline transporter. [5][8][7][6][13]

4. The monoamine oxidase inhibitors are the oldest members and the most constrained. Tranylcypromine inhibits the enzyme irreversibly, so its effect outlasts the drug in the plasma and its contraindication list runs to a page of serotonergic and sympathomimetic agents. The dietary problem follows from the same chemistry, because tyramine in aged and fermented food is normally destroyed before it reaches the circulation. Moclobemide, a reversible inhibitor of MAO-A, was designed to keep the antidepressant effect while removing that constraint. [10][12]

Classification and drug examples

Intro: Grouped by molecular action, because that is what predicts both the therapeutic reach of an agent and the accident it is most likely to cause.

1. Name: Serotonin-noradrenaline reuptake inhibitors (SNRIs)

1. Note: Dual transporter blockade. Their labels share warnings on serotonin syndrome, on blood pressure, and on withdrawal reactions after abrupt cessation, and all of them require a gap either side of a monoamine oxidase inhibitor.

1. Name: Venlafaxine

Effexor XR

1. Route: Oral

1. Note: Licensed in adults for major depressive disorder, generalised anxiety disorder, social anxiety disorder and panic disorder. Controlled trials showed dose-related increases in systolic and diastolic blood pressure and cases of sustained hypertension. [1]

2. Name: Desvenlafaxine

1. O-desmethylvenlafaxine

2. Pristiq

2. Route: Oral

2. Note: Described by its own label as the major active metabolite of venlafaxine, marketed for major depressive disorder in adults. Blood pressure is monitored during treatment, and pre-existing hypertension should be controlled before it is started. [2]

3. Name: Duloxetine

Cymbalta

3. Route: Oral

3. Note: The broadest licence of the group, reaching beyond mood into diabetic peripheral neuropathic pain, fibromyalgia and chronic musculoskeletal pain. Its distinguishing caution is hepatic. [3]

4. Name: Milnacipran

Savella

4. Route: Oral

4. Note: Inhibits noradrenaline uptake with roughly threefold higher potency in vitro than serotonin. In the United States it is licensed only for the management of fibromyalgia and is expressly not approved for major depressive disorder. [4] [1][3][4]

2. Name: Selective noradrenaline reuptake inhibitor

2. Note: A single-transporter agent, useful in teaching because it isolates the noradrenergic contribution to antidepressant action from the serotonergic one.

Name: Reboxetine

Edronax

Route: Oral

Note: The first commercially available noradrenaline reuptake inhibitor, with high affinity and selectivity for the human noradrenaline transporter over the serotonin and dopamine transporters. It beat placebo in five of twelve controlled studies reviewed, and its efficacy has stayed contested. [13] [13]

3. Name: Noradrenaline-dopamine reuptake inhibitor

3. Note: The only antidepressant here with no serotonergic action at all, which shapes both its adverse-effect profile and its interaction list.

Name: Bupropion

Wellbutrin XL

Route: Oral

Note: Its label calls the mechanism of action unknown, while stating that the effect is presumed to be noradrenergic or dopaminergic, and that bupropion is a relatively weak inhibitor of neuronal uptake of noradrenaline and dopamine which does not inhibit monoamine oxidase or serotonin reuptake. [6] [6]

4. Name: Receptor-modulating atypicals

4. Note: These act on postsynaptic and presynaptic receptors as well as, or instead of, transporters. Their labels are unusually candid that the net effect on serotonergic transmission is not understood.

1. Name: Mirtazapine

1. Remeron

2. RemeronSolTab

1. Route: Oral, including an orally disintegrating tablet

1. Note: An antagonist at central presynaptic alpha-2 adrenergic autoreceptors and heteroreceptors, at 5-HT₂ and 5-HT₃ receptors, and at histamine H₁ receptors. The label still describes the mechanism in depression as unclear. [5]

2. Name: Trazodone

Serotonin antagonist and reuptake inhibitor

2. Route: Oral

2. Note: Both a selective serotonin reuptake inhibitor and a 5-HT₂ receptor antagonist, with the label stating that the net result on serotonergic transmission and its role in the antidepressant effect are unknown. Sedation, orthostatic hypotension and QT prolongation follow it around. [8]

3. Name: Vilazodone

Viiibryd

3. Route: Oral

3. Note: Combines selective serotonin reuptake inhibition with partial agonism at 5-HT_{1A} receptors, though the label says the net consequence of the 5-HT_{1A} action is unknown. Exposure depends heavily on food. [7] [5][8][7]

5. Name: Monoamine oxidase inhibitors

5. Note: Raise monoamine levels by disabling their catabolic enzyme rather than their transporter. Whether the block is irreversible or reversible is the single fact that decides how safe the diet has to be.

1. Name: Phenelzine

Nardil

1. Route: Oral

1. Note: A potent inhibitor of monoamine oxidase whose label reserves it for depressed patients characterised as atypical, nonendogenous or neurotic, and warns that hypertensive crises are the most important reaction associated with it. [9]

2. Name: Tranylcypromine

Parnate

2. Route: Oral

2. Note: Licensed for major depressive disorder in adults who have not responded adequately to other antidepressants, acting through irreversible inhibition of monoamine oxidase. Enzyme inhibition may persist for up to ten days after the last dose. [10]

3. Name: Moclobemide

1. Reversible inhibitor of MAO-A

2. RIMA

3. Route: Oral

3. Note: The only reversible MAO-A inhibitor in clinical use. Because the drug can be displaced from the enzyme when substrate concentrations rise, reversible inhibitors carry a built-in safety factor against ingested tyramine. [12]
[10][9][12]

Mechanism of action

Summary: Four distinct routes to the same endpoint of increased monoamine signalling: blockade of the serotonin and noradrenaline transporters, blockade of the noradrenaline and dopamine transporters, antagonism or partial agonism at monoamine receptors, and inhibition of the enzyme that degrades monoamines.

Target: The serotonin, noradrenaline and dopamine transporters; alpha-2 adrenergic, 5-HT1A, 5-HT2, 5-HT3 and histamine H1 receptors; and monoamine oxidase A and B.

Cidal Static: Symptom-modifying rather than curative

Kill Kinetics: Clinical benefit builds over weeks despite immediate pharmacological action

1. Step: 1

1. Title: Dual transporter blockade raises serotonin and noradrenaline together

1. Detail: The SNRIs bind both the serotonin and the noradrenaline transporter, so reuptake into the presynaptic terminal falls and synaptic concentrations of both transmitters rise. The venlafaxine label states that the mechanism of action in its licensed indications is unclear, but is thought to be related to potentiation of serotonin and noradrenaline through inhibition of their reuptake, and the duloxetine and desvenlafaxine labels use the same guarded wording.

[1][2][3]

2. Step: 2

2. Title: The balance between the two transporters differs between agents

2. Detail: Dual action is not a single quantity. Milnacipran inhibits noradrenaline uptake with approximately threefold higher potency in vitro than serotonin uptake, while reboxetine has high affinity and selectivity for the noradrenaline transporter over the serotonin and dopamine transporters. That gradient is one reason the group contains both an agent licensed for a pain syndrome and an agent licensed only for depression. [4][13]

3. Step: 3

3. Title: Bupropion works on catecholamines and leaves serotonin alone

3. Detail: Bupropion is a relatively weak inhibitor of the neuronal uptake of noradrenaline and dopamine, and does not inhibit monoamine oxidase or the reuptake of serotonin. Its label goes further and states plainly that the mechanism of action is unknown, presuming only that the effect is mediated by noradrenergic or dopaminergic mechanisms. [6]

4. Step: 4

4. Title: Alpha-2 blockade disinhibits transmitter release

4. Detail: Mirtazapine antagonises central presynaptic alpha-2 adrenergic autoreceptors and heteroreceptors. Those receptors normally act as a brake on further release, so blocking them increases noradrenergic and serotonergic output without any transporter being touched. The same molecule antagonises 5-HT2 and 5-HT3 receptors, which steers the released serotonin away from the receptors that generate nausea and sexual dysfunction. [5]

5. Step: 5

5. Title: Receptor antagonism explains the sedation and appetite effects

5. Detail: Histamine H1 antagonism accompanies mirtazapine's other receptor actions and accounts for the prominence of drowsiness and increased appetite in its adverse-effect table. Trazodone pairs serotonin reuptake inhibition with 5-HT2 antagonism, and vilazodone pairs it with 5-HT1A partial agonism; both labels state that the net result of the receptor action on serotonergic transmission is unknown. [5][8][7]

6. Step: 6

6. Title: Enzyme inhibition raises monoamines from the other end

6. Detail: Monoamine oxidase deaminates monoamines after they re-enter the neuron, MAO-A showing greater affinity for hydroxylated amines such as noradrenaline and serotonin. Tranylcypromine inhibits the enzyme irreversibly, so new

enzyme must be synthesised before activity returns, and inhibition may persist for up to ten days after the drug is stopped. [10][12]

7. Step: 7

7. Title: Reversibility is what removes the dietary trap

7. Detail: If a reversible inhibitor occupies MAO-A, a rising concentration of substrate drives the inhibitor off its binding site, so the enzyme is available again exactly when it is most needed. That built-in safety factor is why tyramine potentiation with moclobemide and the other reversible agents is negligible, and why the cheese reaction belongs to the irreversible drugs. [12]

Major clinical uses

1. Drug: Venlafaxine

1. Organism: Not applicable

1. Indication: Major depressive disorder, generalised anxiety disorder, social anxiety disorder and panic disorder in adults

1. Line: widely used

1. Note: The broadest psychiatric licence in the group, and the reason venlafaxine turns up in anxiety questions as often as in depression questions. The extended-release product is not approved for paediatric patients. [1]

2. Drug: Duloxetine

2. Organism: Not applicable

2. Indication: Major depressive disorder, generalised anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia and chronic musculoskeletal pain

2. Line: widely used

2. Note: The generalised anxiety indication extends to paediatric patients aged seven years and older, and the fibromyalgia indication to those aged thirteen and older. Its use in neuropathic pain rests on the noradrenergic component of descending inhibition. [3]

3. Drug: Desvenlafaxine

3. Organism: Not applicable

3. Indication: Major depressive disorder in adults

3. Line: alternative

3. Note: Giving the active metabolite directly bypasses the CYP2D6 step that converts venlafaxine to it, which is the usual rationale offered for a separate product. [2][1]

4. Drug: Milnacipran

4. Organism: Not applicable

4. Indication: Management of fibromyalgia

4. Line: specialist

4. Note: An SNRI that is not an antidepressant in the regulatory sense in the United States, since its label states it is not approved for use in the treatment of major depressive disorder. [4]

5. Drug: Mirtazapine

5. Organism: Not applicable

5. Indication: Major depressive disorder in adults

5. Line: widely used

5. Note: Chosen in practice when sedation and appetite stimulation are wanted rather than tolerated, although the licence itself is narrow. [5]

6. Drug: Bupropion

6. Organism: Not applicable

6. Indication: Major depressive disorder, and prevention of seasonal affective disorder

6. Line: widely used

6. Note: The seasonal indication is preventive rather than acute, which distinguishes it from every other entry in this table. [6]
7. Drug: Trazodone
7. Organism: Not applicable
7. Indication: Major depressive disorder in adults
7. Line: alternative
7. Note: The licensed indication is depression, and the sedative profile described in its own warnings section is what drives its wider off-label reputation. [8]
8. Drug: Vilazodone
8. Organism: Not applicable
8. Indication: Major depressive disorder in adults
8. Line: alternative
8. Note: Taken once daily with food, because exposure in the fasted state falls substantially compared with the fed state. [7]
9. Drug: Tranylcypromine
9. Organism: Not applicable
9. Indication: Major depressive disorder in adults who have not responded adequately to other antidepressants
9. Line: reserve
9. Note: The licence itself places this agent after failure of other treatment, which is the regulatory expression of its interaction and dietary burden. [10]
10. Drug: Phenelzine
10. Organism: Not applicable
10. Indication: Depression characterised on the label as atypical, nonendogenous or neurotic
10. Line: reserve
10. Note: The wording is old but examinable, and is the origin of the teaching association between MAOIs and atypical depressive features. [9]

Pharmacokinetics

1. Drug: Venlafaxine
1. Route: Oral
1. Absorption: Absorbed then subject to extensive presystemic metabolism in the liver
1. Csf Penetration: Not applicable
1. Metabolism: Converted primarily to O-desmethylvenlafaxine by CYP2D6, and also to N-desmethylvenlafaxine
1. Elimination: Hepatic metabolism to an active metabolite
1. Dose Adjust: Poor CYP2D6 metabolisers were shown to have increased venlafaxine and reduced metabolite concentrations [1]
2. Drug: Desvenlafaxine
2. Route: Oral
2. Absorption: Given as an extended-release tablet
2. Csf Penetration: Not applicable
2. Metabolism: Administered as the metabolite itself, so no CYP2D6 conversion step is required
2. Elimination: Not detailed on this page
2. Dose Adjust: Blood pressure is monitored during treatment and pre-existing hypertension controlled beforehand [2]
3. Drug: Duloxetine
3. Route: Oral, as delayed-release capsules
3. Absorption: Formulated with delayed release
3. Csf Penetration: Not applicable

3. Metabolism: Hepatic
3. Elimination: Hepatic
3. Dose Adjust: Its label bars use in patients with substantial alcohol use or evidence of chronic liver disease [3]
4. Drug: Vilazodone
4. Route: Oral
4. Absorption: Markedly food-dependent: in the fasted state the area under the curve falls by roughly half and peak concentration by about sixty per cent compared with the fed state
4. Csf Penetration: Not applicable
4. Metabolism: Not detailed on this page
4. Elimination: Not detailed on this page
4. Dose Adjust: Administration with food is part of the licensed instruction rather than a comfort measure [7]
5. Drug: Tranylcypromine
5. Route: Oral
5. Absorption: Not detailed on this page
5. Csf Penetration: Not applicable
5. Metabolism: Not detailed on this page
5. Elimination: Pharmacological effect outlasts the plasma drug because the enzyme block is irreversible
5. Dose Adjust: Monoamine oxidase inhibition may persist for as long as ten days after the drug is discontinued [10]
6. Drug: Moclobemide
6. Route: Oral
6. Absorption: Not detailed on this page
6. Csf Penetration: Not applicable
6. Metabolism: Not detailed on this page
6. Elimination: Enzyme function returns as the inhibitor dissociates rather than as new enzyme is made
6. Dose Adjust: Reversibility means a rising substrate load itself relieves the inhibition [12]
1. No dose regimens appear on this page. Choice of agent, titration, monitoring and withdrawal all belong to the treating clinician working from a current prescribing reference, because they depend on diagnosis, age, comorbidity and every other medicine the patient is taking.
2. Two handling facts carry most of the examination weight here: the CYP2D6 conversion of venlafaxine into its active metabolite, and the persistence of enzyme blockade after an irreversible MAOI has been stopped. [1][10]
3. Vilazodone is the outlier for absorption, since its exposure depends on whether it is taken with food to an extent that changes the dose actually delivered. [7]

Adverse effects

1. Effect: Gastrointestinal upset
1. Detail: Nausea leads the tables for the serotonergic agents. For vilazodone the commonest reactions occurring in at least five per cent of patients and at twice the placebo rate were diarrhoea, nausea, vomiting and insomnia, with diarrhoea reported in roughly a quarter of those treated. [7]
2. Effect: Sedation and drowsiness
2. Detail: Somnolence was reported in 54 per cent of patients given mirtazapine against 18 per cent on placebo, and led to discontinuation in 10.4 per cent against 2.2 per cent. Trazodone's label warns that it may cause somnolence or sedation sufficient to impair performance of hazardous tasks. [5][8]
3. Effect: Increased appetite and weight gain
3. Detail: Appetite increase was recorded in 17 per cent of adults on mirtazapine against 2 per cent on placebo, and a weight gain of at least seven per cent of body weight in 7.5 per cent against none on placebo. [5]
4. Effect: Cardiovascular effects of noradrenergic drive
4. Detail: SNRIs have been associated with reports of increased blood pressure and increased heart rate, which is why

the milnacipran label directs that both be measured before treatment starts and periodically thereafter. [4][3]

1. Effect: Suicidal thoughts and behaviours in young people

1. Detail: The boxed warning shared across this class states that antidepressants increased the risk of suicidal thoughts and behaviour in children, adolescents and young adults in short-term trials. The venlafaxine label quantifies the risk difference as fourteen additional patients per thousand treated under eighteen years, and five per thousand aged eighteen to twenty-four.

1. Action: Close monitoring for clinical worsening and for emerging suicidal thinking is required, particularly early in treatment; assessment and any change of treatment rest with the treating clinician. [1][6][4]

2. Effect: Serotonin syndrome

2. Detail: Serotonin-noradrenaline reuptake inhibitors can precipitate serotonin syndrome, described in the labels as a potentially life-threatening condition, and the risk rises when they are combined with other serotonergic agents. Serotonin toxicity is the classical outcome of combining an irreversible MAOI with a drug that elevates synaptic serotonin.

2. Action: Recognition depends on the combination of mental-state change, autonomic instability and neuromuscular signs; management and any withdrawal of the offending agents rest with the treating clinician. [1][3][12]

3. Effect: Hypertensive crisis with an irreversible MAOI

3. Detail: The phenelzine label calls hypertensive crises the most important reaction associated with the drug and records that they have sometimes been fatal. The described picture is occipital headache that may radiate forwards, palpitation, neck stiffness, nausea and vomiting, sweating, dilated pupils and photophobia, with either tachycardia or bradycardia and sometimes constricting chest pain.

3. Action: The label directs immediate discontinuation and immediate treatment to lower blood pressure, with phentolamine recommended on present evidence; this is an emergency handled by the attending clinical team. [9]

4. Effect: Seizure

4. Detail: Bupropion can cause seizure, and the risk is dose-related. The reported incidence was approximately 0.1 per cent, one patient in a thousand, at the maximum recommended dose of the sustained-release formulation, and approximately 0.4 per cent, thirteen of three thousand two hundred, in the higher immediate-release dose range.

4. Action: The label restricts the maximum daily dose and requires gradual increases; prescribing decisions and any dose change rest with the treating clinician. [6]

5. Effect: Hepatic failure

5. Detail: Reports of hepatic failure, sometimes fatal, have occurred in patients treated with duloxetine. The label directs that treatment be discontinued in anyone who develops jaundice or other evidence of clinically significant liver dysfunction.

5. Action: Liver-related symptoms warrant prompt medical assessment; the decision to stop or resume treatment rests with the treating clinician. [3]

6. Effect: Priapism

6. Detail: Cases of priapism, defined on the trazodone label as painful erection lasting more than six hours, have been reported in men taking the drug. If it is not treated promptly it can cause irreversible damage to erectile tissue.

6. Action: This is a urological emergency requiring immediate attention rather than watchful waiting. [8]

7. Effect: Agranulocytosis and severe neutropenia

7. Detail: Two of 2,796 patients in the mirtazapine development programme developed agranulocytosis and a third developed severe neutropenia.

7. Action: Fever, sore throat or other signs of infection during treatment call for urgent assessment of the blood count by a clinician. [5]

8. Effect: QT interval prolongation

8. Detail: Trazodone prolongs the QT and QTc interval, and its label advises avoiding the drug in patients with known QT prolongation or alongside inhibitors of CYP3A4.

8. Action: Cardiac and interaction screening before use is a prescribing decision for the treating clinician. [8]

9. Effect: Hyponatraemia

9. Detail: Hyponatraemia can occur as a result of treatment with SNRIs, and the venlafaxine label carries it as a distinct warning.

9. Action: Confusion, unsteadiness or seizures in an older patient recently started on treatment warrant urgent measurement of serum sodium by a clinician. [1]

10. Effect: Abnormal bleeding

10. Detail: Drugs that interfere with serotonin reuptake may increase the risk of bleeding events, and the same association is described for trazodone, with reported events ranging from ecchymosis and haematoma to life-threatening haemorrhage.

10. Action: The added risk matters most alongside anticoagulants, antiplatelet agents and non-steroidal anti-inflammatory drugs, and weighing it is a clinician's task. [1][8]

11. Effect: Angle-closure glaucoma

11. Detail: The pupillary dilatation that follows many antidepressants, venlafaxine included, may trigger an angle-closure attack in an eye with a narrow anatomical angle.

11. Action: Sudden eye pain with visual blurring and a red eye needs same-day ophthalmological assessment. [1]

1. Drug: Venlafaxine

1. Effect: Blood pressure. Across all clinical studies 1.4 per cent of treated patients had a rise in diastolic pressure of at least 15 mmHg to a level of at least 105 mmHg, against 0.9 per cent on placebo, and 1 per cent had a systolic rise of at least 20 mmHg to at least 180 mmHg, against 0.3 per cent. [1]

2. Drug: Duloxetine

2. Effect: Hepatic injury. This is the caution that separates duloxetine from the other SNRIs and the reason its label refuses the drug to patients with substantial alcohol use or chronic liver disease. [3]

3. Drug: Bupropion

3. Effect: Seizure, at a dose-related incidence, in a drug whose contraindications are written almost entirely around lowering that risk. [6]

4. Drug: Mirtazapine

4. Effect: Somnolence and weight gain, both traceable to the receptor profile rather than to transporter blockade, plus the rare haematological reactions recorded during development. [5]

5. Drug: Trazodone

5. Effect: Priapism, orthostatic hypotension with syncope, and QT prolongation, a combination no other agent on this page shares. [8]

6. Drug: Phenelzine and tranylcypromine

6. Effect: Tyramine-triggered hypertensive crisis. Tranylcypromine's boxed warning states that excessive consumption of food or drink with significant tyramine content can precipitate it. [10][9]

7. Drug: Vilazodone

7. Effect: Diarrhoea, reported far more often than with most antidepressants and prominent enough to head its list of common reactions. [7]

8. Drug: Milnacipran

8. Effect: Increases in heart rate as well as blood pressure, both of which its label asks to be measured before and during treatment. [4]

Contraindications, precautions and interactions

1. Bupropion is contraindicated in patients with a seizure disorder, with a current or prior diagnosis of bulimia or anorexia nervosa, undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs, taking a monoamine oxidase inhibitor within fourteen days, or with known hypersensitivity to the drug. [6]

2. Tranylcypromine must not be given with other MAOIs, SSRIs, SNRIs, tricyclic antidepressants, amphetamines and other sympathomimetics, triptans, buspirone, carbamazepine, dextromethorphan, dopamine, levodopa, meperidine,

methyl dopa, rasagiline, reserpine, tapentadol, tetrabenazine or tryptophan, and is contraindicated in pheochromocytoma and paraganglioma. [10]

3. Phenelzine should not be used in patients hypersensitive to it, nor in pheochromocytoma, congestive heart failure, severe renal impairment or abnormal liver function tests, and its label likewise prohibits sympathomimetics, serotonergic agents, meperidine, other MAOIs, buspirone, dextromethorphan and bupropion. [9]

1. Pre-existing hypertension is controlled before desvenlafaxine is started, and blood pressure is monitored regularly during treatment because increases were seen in the clinical studies. [2]

2. Duloxetine is withheld where there is substantial alcohol use or evidence of chronic liver disease, and stopped if jaundice or clinically significant liver dysfunction appears. [3]

3. Trazodone is avoided in known QT prolongation and in combination with CYP3A4 inhibitors, and its capacity to cause orthostatic hypotension and syncope matters most in frail or older patients. [8]

4. Any narrow anatomical angle in the eye is a reason for caution with these drugs, since antidepressant-induced pupillary dilatation may precipitate an angle-closure attack. [1]

5. New fever or infection during mirtazapine treatment is taken seriously because agranulocytosis and severe neutropenia were both seen during its development programme. [5]

1. With: Monoamine oxidase inhibitors

1. Effect: Every agent here specifies a gap around an MAOI, and the gaps are not symmetrical. At least fourteen days must elapse after an MAOI before venlafaxine is started, and at least seven days after venlafaxine before an MAOI. Duloxetine and milnacipran require fourteen days one way and five days the other, while bupropion requires fourteen days in both directions. [1][3][4][6]

2. With: Fluoxetine and other long-acting serotonergic drugs

2. Effect: The washout is set by the half-life of the drug being stopped, not by a fixed number. At least five weeks must elapse between stopping fluoxetine and starting phenelzine, and the tranylcypromine label asks for four to five half-lives of the previous antidepressant or its active metabolite. [9][10]

3. With: Tyramine-containing food and drink

3. Effect: Aged cheeses, air-dried meats and sausages, pickled herring, broad bean pods, tap beer, concentrated yeast extract, sauerkraut and most soybean products are restricted with an irreversible MAOI. The restriction continues for two weeks after tranylcypromine is stopped, because the enzyme block outlasts the drug. [10][9]

4. With: CYP2D6 inhibitors and CYP2D6 genotype

4. Effect: Formation of venlafaxine's active metabolite is catalysed by CYP2D6, and poor metabolisers had raised parent-drug and lowered metabolite concentrations in a clinical study, which shifts the ratio of the two active species a patient is exposed to. [1]

5. With: Anticoagulants, antiplatelet agents and NSAIDs

5. Effect: Agents that block serotonin reuptake may add to bleeding risk, an effect described from bruising and haematoma through to life-threatening haemorrhage. [1][8]

6. With: Food, in the case of vilazodone

6. Effect: Not an interaction between drugs, but one that changes exposure as much as many of them do: fasted administration cuts the area under the curve by roughly half and the peak concentration by about sixty per cent. [7]

Comparison tables

1. Title: One mechanism, one signature hazard

1. Caption: Read across each row: the molecular action on the left predicts the safety problem on the right. Choice of agent for a given patient belongs to the treating clinician.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: mechanism

2. Label: Molecular action

3. Key: signature

3. Label: Signature safety point

1. Drug: Venlafaxine

1. Mechanism: Serotonin and noradrenaline reuptake inhibition

1. Signature: Dose-related rise in blood pressure and cases of sustained hypertension [1]

2. Drug: Desvenlafaxine

2. Mechanism: The active metabolite of venlafaxine, given directly

2. Signature: Pre-existing hypertension controlled before treatment begins [2]

3. Drug: Duloxetine

3. Mechanism: Serotonin and noradrenaline reuptake inhibition

3. Signature: Hepatic failure, sometimes fatal; refused in chronic liver disease or substantial alcohol use [3]

4. Drug: Milnacipran

4. Mechanism: Reuptake inhibition weighted about threefold towards noradrenaline

4. Signature: Blood pressure and heart rate measured before and during treatment; not approved for depression in the United States [4]

5. Drug: Reboxetine

5. Mechanism: Selective noradrenaline transporter inhibition

5. Signature: Superior to placebo in only five of twelve reviewed controlled studies [13]

6. Drug: Bupropion

6. Mechanism: Weak noradrenaline and dopamine uptake inhibition, no serotonergic action

6. Signature: Dose-related seizure; contraindicated in seizure disorder and in eating disorders [6]

7. Drug: Mirtazapine

7. Mechanism: Alpha-2, 5-HT₂, 5-HT₃ and H₁ antagonism

7. Signature: Somnolence in over half of treated patients, and weight gain [5]

8. Drug: Trazodone

8. Mechanism: Serotonin reuptake inhibition with 5-HT₂ antagonism

8. Signature: Priapism lasting more than six hours, plus QT prolongation [8]

9. Drug: Vilazodone

9. Mechanism: Serotonin reuptake inhibition with 5-HT_{1A} partial agonism

9. Signature: Diarrhoea heads the common reactions, and food changes exposure sharply [7]

10. Drug: Phenelzine

10. Mechanism: Potent monoamine oxidase inhibition

10. Signature: Hypertensive crisis, sometimes fatal, is the most important reaction on the label [9]

11. Drug: Tranylcypromine

11. Mechanism: Irreversible monoamine oxidase inhibition

11. Signature: Enzyme block persisting up to ten days, with a very long contraindication list [10]

12. Drug: Moclobemide

12. Mechanism: Reversible inhibition of MAO-A

12. Signature: Tyramine potentiation is negligible, so the dietary trap largely disappears [12]

2. Title: Why reversibility changes everything about an MAOI

2. Caption: The same enzyme, two kinds of block, two entirely different day-to-day risks.

1. Key: feature

1. Label: Feature

1. Is Row Header: true

2. Key: irreversible

2. Label: Irreversible MAOI

3. Key: reversible

3. Label: Reversible MAO-A inhibitor

1. Feature: Binding to the enzyme

1. Irreversible: Permanent for the life of that enzyme molecule; tranylcypromine acts this way

1. Reversible: Occupancy that can be displaced when substrate concentration rises [10][12]

2. Feature: Behaviour when tyramine arrives

2. Irreversible: No spare enzyme capacity, so the amine passes into the circulation and releases stored noradrenaline

2. Reversible: The inhibitor is driven off its site, restoring capacity exactly when the load appears [12]

3. Feature: Dietary restriction

3. Irreversible: Aged, fermented, pickled, smoked and air-dried foods are avoided, and for two weeks after stopping

3. Reversible: Tyramine potentiation is described as negligible with moclobemide and the other reversible agents [10][12]

4. Feature: Duration of effect after the last dose

4. Irreversible: Inhibition may persist for up to ten days

4. Reversible: Effect ends as the drug leaves the enzyme rather than waiting on enzyme resynthesis [10][12]

High-yield exam pearls

1. Pearl: Blood pressure is the SNRI observation, and the venlafaxine label puts numbers on it: rises in diastolic and systolic pressure were dose-related and cases of sustained hypertension occurred.

1. Why: It is the cleanest way to separate an SNRI from an SSRI in a stem that offers both, and it explains why the labels ask for blood pressure to be measured before treatment. [1]

2. Pearl: Bupropion's contraindications are a list of seizure-threshold problems: seizure disorder, current or previous anorexia nervosa or bulimia, and abrupt withdrawal of alcohol, benzodiazepines, barbiturates or antiepileptics.

2. Why: Examiners rarely ask what bupropion does; they ask who must not receive it, and the eating-disorder entry is the one most often forgotten. [6]

3. Pearl: Milnacipran is an SNRI that is licensed in the United States for fibromyalgia and expressly not approved for major depressive disorder.

3. Why: A stem that calls it an antidepressant and asks about its depression licence is testing exactly this distinction. [4]

4. Pearl: Mirtazapine's sedation and appetite effects are receptor effects, not transporter effects: H1 antagonism sits alongside alpha-2, 5-HT2 and 5-HT3 blockade.

4. Why: Once the receptor list is remembered the adverse-effect profile can be reconstructed rather than memorised. [5]

5. Pearl: The tranylcypromine label states that monoamine oxidase inhibition may persist for as long as ten days after the drug has been discontinued.

5. Why: It is the reason a washout is counted in weeks rather than days, and the reason the tyramine restriction continues after the last tablet. [10]

6. Pearl: Washouts are asymmetric. Fourteen days are required after an MAOI before venlafaxine, but only seven days after venlafaxine before an MAOI.

6. Why: Candidates who memorise a single number get half of these questions wrong; the direction of the switch is the point. [1]

7. Pearl: The MHRA notes that paroxetine and venlafaxine appear to be associated with a greater frequency of withdrawal reactions than other agents, and that reactions are less severe when the dose is tapered over several weeks.

7. Why: It converts a vague statement about discontinuation into a named, sourced comparison, which is what a written answer needs. [11]

Common exam traps

1. Trap: Assuming every monoamine oxidase inhibitor demands a tyramine-free diet.
1. Correction: That constraint belongs to irreversible inhibition. With moclobemide and the other reversible MAO-A inhibitors, tyramine potentiation is described as negligible, because rising substrate displaces the inhibitor from the enzyme. [12][10]
2. Trap: Treating bupropion as a serotonergic drug and expecting it to behave like an SSRI.
2. Correction: Its label records that bupropion does not inhibit monoamine oxidase or the reuptake of serotonin, and describes the antidepressant mechanism itself as unknown. [6]
3. Trap: Saying that duloxetine and venlafaxine share the same distinguishing warning.
3. Correction: They share the class warnings, but the hepatic one is duloxetine's. Reports of hepatic failure, sometimes fatal, sit in its label, along with a bar on use in substantial alcohol use or chronic liver disease. [3][1]
4. Trap: Explaining mirtazapine's action as serotonin reuptake inhibition.
4. Correction: No transporter is involved. It antagonises central presynaptic alpha-2 autoreceptors and heteroreceptors along with 5-HT₂, 5-HT₃ and H₁ receptors, and the label still calls the mechanism in depression unclear. [5]
5. Trap: Claiming that a receptor action explains a clinical effect when the label refuses to.
5. Correction: Both trazodone and vilazodone state that the net result of their receptor action on serotonergic transmission, and its role in the antidepressant effect, is unknown. An answer should not be more confident than the regulator. [8][7]
6. Trap: Restricting the antidepressant suicidality warning to the SSRIs.
6. Correction: It is a class warning that appears on the bupropion, mirtazapine, trazodone, milnacipran and MAOI labels alike, covering children, adolescents and young adults in short-term studies. [6][5][10]

Self-test questions

1. Question: A patient started on an antidepressant for major depressive disorder is found at review to have a diastolic pressure 18 mmHg higher than at baseline, having risen after each increase in dose. Which agent best fits?
 1. Venlafaxine
 2. Mirtazapine
 3. Trazodone
 4. Moclobemide
1. Explanation: Controlled trials of venlafaxine showed dose-related increases in systolic and diastolic blood pressure and cases of sustained hypertension, which is the characteristic cardiovascular signature of the drug. [1]
2. Question: Which history is an absolute contraindication to bupropion according to its label?
 1. A current or previous diagnosis of bulimia or anorexia nervosa
 2. Treated hypothyroidism
 3. A first-degree relative with epilepsy
 4. Previous poor response to an SSRI
2. Explanation: The label lists a current or prior diagnosis of bulimia or anorexia nervosa among the contraindications, alongside a seizure disorder and abrupt withdrawal of alcohol, benzodiazepines, barbiturates or antiepileptic drugs, because each raises seizure risk. [6]
3. Question: Why does an irreversible MAO inhibitor make aged cheese dangerous while moclobemide largely does not?
 1. Reversible inhibitors are displaced from the enzyme as tyramine concentrations rise, restoring the capacity to break it down
 2. Moclobemide destroys tyramine directly in the gut lumen
 3. Moclobemide blocks the noradrenaline transporter so stored transmitter cannot be released
 4. Irreversible inhibitors increase intestinal absorption of tyramine

3. Explanation: Reversibility gives a built-in safety factor: if substrate rises, the inhibitor dissociates from its binding site and enzyme activity returns, which is why tyramine potentiation with the reversible agents is negligible. [12]

4. Question: Which antidepressant label warns of hepatic failure, sometimes fatal, and states that the drug should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease?

1. Duloxetine
2. Desvenlafaxine
3. Reboxetine
4. Vilazodone

4. Explanation: Hepatotoxicity is the caution specific to duloxetine among the SNRIs, and its label also directs discontinuation if jaundice or other clinically significant liver dysfunction develops. [3]

5. Question: A man taking an antidepressant for depression attends with a painful erection lasting eight hours. Which drug is most likely to be responsible?

1. Trazodone
2. Bupropion
3. Milnacipran
4. Phenelzine

5. Explanation: The trazodone label records cases of priapism, defined as painful erection greater than six hours in duration, and warns that irreversible damage to erectile tissue can follow if treatment is delayed. [8]

6. Question: How many days must elapse after stopping venlafaxine before a monoamine oxidase inhibitor is started, according to the venlafaxine label?

1. At least seven days
2. At least fourteen days
3. At least five weeks
4. No interval is specified

6. Explanation: The label requires at least fourteen days between stopping an MAOI and starting venlafaxine, but at least seven days in the opposite direction, which is why the direction of the switch has to be read carefully. [1]

7. Question: Which combination of receptor actions is described on the mirtazapine label?

1. Antagonism at alpha-2 adrenergic, 5-HT₂, 5-HT₃ and histamine H₁ receptors
2. Partial agonism at 5-HT_{1A} with serotonin reuptake inhibition
3. Irreversible inhibition of monoamine oxidase A and B
4. Selective inhibition of the noradrenaline transporter

7. Explanation: Mirtazapine is described as an antagonist at central presynaptic alpha-2 adrenergic autoreceptors and heteroreceptors and at 5-HT₂, 5-HT₃ and H₁ receptors; the H₁ action accounts for the drowsiness that dominates its profile. [5]

8. Question: Which statement about milnacipran matches its United States label?

1. It is indicated for the management of fibromyalgia and is not approved for major depressive disorder
2. It is indicated for major depressive disorder only
3. It is a selective serotonin reuptake inhibitor with no noradrenergic action
4. It requires no blood pressure monitoring

8. Explanation: Milnacipran is licensed there for fibromyalgia, its label states it is not approved for the treatment of major depressive disorder, and it inhibits noradrenaline uptake with about threefold higher in vitro potency than serotonin. [4]

Frequently asked questions

1. Question: What actually makes an SNRI different from an SSRI?

1. Answer: The added noradrenergic action, and its consequences. Blocking the noradrenaline transporter as well as the serotonin transporter is what brings blood pressure and heart rate into the monitoring plan and what underlies the

use of duloxetine in neuropathic and musculoskeletal pain. The labels are careful to say the antidepressant mechanism itself remains unclear. [1][3][4]

2. Question: Why are so many unrelated drugs bundled into one class page?

2. Answer: Because they are defined by what they are not. The SSRIs and the tricyclics each form a coherent family with a shared mechanism and a shared toxidrome; everything else that raises monoamine signalling ends up here. Grouping them by molecular action is still worthwhile, since it is that action, rather than the label indication, that predicts the hazard each one carries. [6][5][10]

3. Question: Are monoamine oxidase inhibitors still worth learning?

3. Answer: Yes, and not only for history. Tranylcypromine holds a licence for major depressive disorder in adults who have not responded adequately to other antidepressants, so it remains a real option after failure. It is also the cleanest teaching example of a drug whose pharmacological effect outlasts its presence in the plasma. [10]

4. Question: What is serotonin syndrome and which combinations bring it on?

4. Answer: It is a potentially life-threatening state that the SNRI labels warn can be precipitated by these drugs, with risk rising when they are given alongside other serotonergic agents. The classic trigger is an irreversible MAOI combined with a drug that raises synaptic serotonin, which is why the MAOI contraindication lists are so long and the washout periods so specific. [1][12][10]

5. Question: What happens when one of these drugs is stopped suddenly?

5. Answer: Withdrawal reactions. The venlafaxine label lists agitation, anxiety, confusion, impaired coordination and balance, dizziness, dysphoric mood, fatigue, flu-like symptoms, headache, insomnia, nausea, nightmares and sensory disturbances including shock-like electrical sensations. The MHRA adds that such reactions are less severe when the dose is reduced gradually over several weeks, and any tapering plan is set by the treating clinician. [1][11]

6. Question: Is the suicidality warning a reason not to prescribe these drugs to young people?

6. Answer: It is a reason for monitoring rather than a prohibition. The boxed warning describes an increased risk of suicidal thoughts and behaviour in children, adolescents and young adults in short-term trials, and asks for close observation for clinical worsening and for emergent suicidal thinking. Whether to treat, and with what, is a judgement for the clinician who knows the patient. [1][6]

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