

SSRI antidepressants

Antidepressants that block the neuronal reuptake of serotonin, sharing a boxed warning on suicidal thoughts and behaviours in younger patients and a class burden of serotonin syndrome, hyponatraemia, bleeding and withdrawal reactions, while differing sharply from one another in cytochrome inhibition, half-life and QT liability.

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

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Quick revision

One Liner: Every SSRI shares one mechanism and one boxed warning, so what separates them in an examination and at the bedside is enzyme inhibition, half-life and the QT interval.

1. The shared action is blockade of neuronal serotonin reuptake; the sertraline label states that the drug potentiates serotonergic activity in the central nervous system through inhibition of neuronal reuptake of serotonin. [1]
2. The boxed warning is age-restricted, not general: antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. [1]
3. In the pooled trial analysis the excess appeared under 18 and between 18 and 24, while patients aged 25 to 64 and those 65 and older showed fewer such events than on placebo. [1]
4. Fluoxetine, paroxetine and fluvoxamine are the prominent enzyme inhibitors; the first two act on CYP2D6 and fluvoxamine on CYP1A2 among others. Sertraline inhibits CYP2D6 as well, though its label records a less prominent inhibitory effect on 2D6 at lower doses than some others in the class. [2][3][6][1]
5. Citalopram causes dose-dependent QTc prolongation, an ECG abnormality that has been associated with Torsade de Pointes, and its labelled maximum dosage is capped for that reason. [4]
6. Fluoxetine and its active metabolite norfluoxetine are eliminated so slowly that active drug substance will persist in the body for weeks after dosing stops. [2]
7. A fourteen-day gap in either direction separates most SSRIs from an MAOI, but at least five weeks should be allowed after stopping fluoxetine before starting one. [1][2]
8. Hyponatraemia is often mediated by inappropriate antidiuretic hormone secretion, and cases with serum sodium lower than 110 mmol/L have been reported. [5][3]
9. Withdrawal reactions follow any SSRI, but UK regulators state that paroxetine and venlafaxine seem to be associated with a greater frequency of them than other SSRIs. [8]

Overview

1. Selective serotonin reuptake inhibitors are defined by a single pharmacological action. Sertraline is described in its label as potentiating serotonergic activity through inhibition of neuronal reuptake of serotonin, and the fluoxetine label attributes its antidepressant, antiobsessive compulsive and antitubercular actions to inhibition of central neuronal uptake of serotonin. Labels are careful about how far that action explains the clinical benefit: the citalopram label says the mechanism of action of citalopram is unclear, but is presumed to be related to potentiation of serotonergic activity. A student should reproduce that hedge rather than remove it. [1][2][4]
2. Because the mechanism is shared, the class warnings are shared too. All of these agents carry the boxed warning on suicidal thoughts and behaviours in younger patients, all can precipitate serotonin syndrome, all can cause hyponatraemia and increase bleeding risk, and all may produce symptoms when stopped. Learning the class therefore means learning one common block of warnings once, then learning what is specific to each member. [1][5][8]
3. Three properties do the separating. The first is cytochrome inhibition: fluoxetine inhibits CYP2D6, paroxetine inhibits it irreversibly, and fluvoxamine inhibits CYP1A2 alongside CYP2C9, CYP3A4 and CYP2C19. The second is elimination:

fluoxetine's long half-life and its active metabolite make its washout measured in weeks, whereas the shorter-acting agents produce more prominent withdrawal reactions. The third is cardiac: the citalopram label reports dose-dependent QTc prolongation, and UK regulators responded by lowering the permitted maximum daily doses of citalopram and escitalopram. [2][3][6][4][7]

Classification and drug examples

Intro: Every member blocks the same transporter, so the useful division is by the property that most constrains how each one is used. Several agents would qualify for more than one group; each sits in the group that governs its prescribing.

1. Name: SSRIs that markedly inhibit cytochrome P450 enzymes

1. Note: The interaction-heavy members. Whenever an examination question pairs an SSRI with an unexpected rise in another drug's level, the answer is almost always drawn from this group.

1. Name: Fluoxetine

Prozac

1. Route: Oral

1. Note: Its label states that fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. It is contraindicated with pimozide and with thioridazine. [2]

2. Name: Paroxetine

1. Paxil

2. Seroxat

2. Route: Oral

2. Note: The label describes paroxetine's irreversible inhibition of CYP2D6, and warns that the efficacy of tamoxifen may be reduced with concomitant use as a result of it and of lower blood levels of tamoxifen. [3]

3. Name: Fluvoxamine

Faverin

3. Route: Oral

3. Note: Inhibits several isoenzymes including CYP1A2, CYP2C9, CYP3A4 and CYP2C19, while in vitro data describe it as a relatively weak inhibitor of CYP2D6. Coadministration with tizanidine, thioridazine, alosetron or pimozide is contraindicated. [6] [2][3][6]

2. Name: SSRIs with dose-dependent QT interval prolongation

2. Note: The racemate and its active enantiomer. Their cardiac liability, rather than any interaction profile, is what dictates the ceiling on how much may be given.

1. Name: Citalopram

Cipramil

1. Route: Oral

1. Note: The label states plainly that citalopram causes dose-dependent QTc prolongation, and directs that the drug be discontinued in patients found to have persistent QTc measurements above 500 ms. [4]

2. Name: Escitalopram

1. Cipralex

2. Lexapro

2. Route: Oral

2. Note: Described in its label as the S-enantiomer of racemic citalopram. Its thorough QT study reported a mean difference from placebo of 4.5 msec at the usual starting dose and 10.7 msec at a supratherapeutic dose. [5] [4][5][7]

3. Name: SSRIs licensed across depressive, anxiety and obsessive-compulsive disorders

3. Note: Grouped here by breadth of licensed use, which is what most often puts these agents in front of a student in a psychiatry attachment.

Name: Sertraline

1. Zoloft

2. Lustral

Route: Oral

Note: Licensed for major depressive disorder, obsessive-compulsive disorder from six years of age, panic disorder, post-traumatic stress disorder, social anxiety disorder and premenstrual dysphoric disorder. Its label also identifies it as a CYP2D6 inhibitor, so concomitant use with a CYP2D6 substrate may increase that substrate's exposure. [1] [1]

Mechanism of action

Summary: One target, stated the same way across the labels: the neuronal serotonin transporter. Blocking reuptake raises serotonergic tone in the synapse, and every feature of the class follows from that, including the toxic extreme of serotonin syndrome and the effects outside the brain on antidiuretic hormone and on haemostasis. The labels themselves stop short of claiming the mechanism explains the therapeutic benefit.

Target: The presynaptic neuronal serotonin (5-HT) transporter

Cidal Static: Symptom-modifying rather than curative

Kill Kinetics: Effect depends on sustained transporter occupancy over weeks of treatment

1. Step: 1

1. Title: Blockade of neuronal serotonin reuptake

1. Detail: Sertraline potentiates serotonergic activity in the central nervous system through inhibition of neuronal reuptake of serotonin (5-HT). Paroxetine's action is described in the same terms, as potentiation of serotonergic activity resulting from inhibition of neuronal reuptake of serotonin. [1][3]

2. Step: 2

2. Title: The link to clinical benefit is presumed, not established

2. Detail: The citalopram label states that the mechanism of action of citalopram is unclear, but is presumed to be related to potentiation of serotonergic activity. The fluoxetine label likewise says its antidepressant, antiobsessive compulsive and antibulimic actions are presumed to be linked to inhibition of central neuronal uptake of serotonin. [4][2]

3. Step: 3

3. Title: Stereochemistry concentrates the activity in one enantiomer

3. Detail: Escitalopram is the S-enantiomer of racemic citalopram, and its antidepressant action is attributed to the same potentiation of serotonergic activity through inhibition of neuronal serotonin reuptake. The pair therefore share a mechanism and share the cardiac liability that goes with it. [5][7]

4. Step: 4

4. Title: Excess serotonergic activity produces serotonin syndrome

4. Detail: SSRIs can precipitate serotonin syndrome, a potentially life-threatening condition, and the risk rises when another serotonergic drug is added or when metabolism of serotonin is impaired by a monoamine oxidase inhibitor. That is the pharmacological reason the MAOI washout interval exists rather than a mere labelling formality. [1][5]

5. Step: 5

5. Title: Consequences outside the central nervous system

5. Detail: Hyponatraemia may follow treatment, and in many cases appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion. Separately, drugs that interfere with serotonin reuptake increase the risk of bleeding events, which is why concurrent antiplatelet or anticoagulant therapy matters. [5]

Major clinical uses

1. Drug: Sertraline

1. Organism: Not applicable

1. Indication: Major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder and premenstrual dysphoric disorder

1. Line: licensed indications

1. Note: The obsessive-compulsive disorder licence extends to patients from six years of age, which is the youngest paediatric licence among the agents described on this page. [1]

2. Drug: Fluoxetine

2. Organism: Not applicable

2. Indication: Major depressive disorder, obsessive-compulsive disorder, moderate to severe bulimia nervosa, and panic disorder with or without agoraphobia

2. Line: licensed indications

2. Note: The bulimia nervosa licence is distinctive: the label describes acute and maintenance treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa. [2]

3. Drug: Paroxetine

3. Organism: Not applicable

3. Indication: Major depressive disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder and post-traumatic stress disorder in adults

3. Line: licensed indications

3. Note: All six licensed indications in this label are adult indications, and the choice is further shaped by the withdrawal profile and by the CYP2D6 interaction burden. [3][8]

4. Drug: Escitalopram

4. Organism: Not applicable

4. Indication: Major depressive disorder in adults and patients from twelve years of age, and generalised anxiety disorder in adults and patients from seven years of age

4. Line: licensed indications

4. Note: The two licensed indications are narrower than sertraline's, and the permitted daily maximum is lower in older patients and in hepatic impairment because of the QT effect. [5][7]

5. Drug: Fluvoxamine

5. Organism: Not applicable

5. Indication: Obsessions and compulsions in patients with obsessive-compulsive disorder

5. Line: licensed indication

5. Note: The narrowest licence of the group in this label, and the agent whose enzyme inhibition most often forces a change of plan when another medicine is already established. [6]

Pharmacokinetics

1. Drug: Fluoxetine

1. Route: Oral

1. Absorption: Oral

1. Csf Penetration: Not applicable

1. Metabolism: Extensively metabolised in the liver to the active metabolite norfluoxetine; inhibits CYP2D6

1. Elimination: Hepatic, with slow clearance of both parent drug and metabolite

1. Half Life: One to three days after acute dosing and four to six days on chronic dosing; norfluoxetine four to sixteen days

1. Dose Adjust: Because of the long half-lives, changes in dose will not be fully reflected in plasma for several weeks [2]

2. Drug: Paroxetine

2. Route: Oral

2. Absorption: Oral

2. Csf Penetration: Not applicable

2. Metabolism: Metabolism mediated in part by CYP2D6, which paroxetine also inhibits irreversibly

2. Elimination: Metabolites primarily excreted in the urine and to some extent in the faeces
2. Half Life: Short relative to fluoxetine
2. Dose Adjust: Reduction of a co-prescribed CYP2D6 substrate may be warranted; the label advises gradual dosage reduction rather than abrupt stopping [3]
3. Drug: Fluvoxamine
3. Route: Oral
3. Absorption: Oral
3. Csf Penetration: Not applicable
3. Metabolism: Hepatic; inhibits CYP1A2, CYP2C9, CYP3A4 and CYP2C19, and is a relatively weak inhibitor of CYP2D6
3. Elimination: Hepatic
3. Half Life: Short relative to fluoxetine
3. Dose Adjust: Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers [6]
4. Drug: Citalopram
4. Route: Oral
4. Absorption: Oral
4. Csf Penetration: Not applicable
4. Metabolism: Hepatic, with a contribution from CYP2C19
4. Elimination: Hepatic
4. Half Life: Intermediate
4. Dose Adjust: The labelled maximum is lower in CYP2C19 poor metabolisers, in hepatic impairment and in patients over sixty, all because exposure and therefore QTc rise [4]
5. Drug: Escitalopram
5. Route: Oral
5. Absorption: Oral
5. Csf Penetration: Not applicable
5. Metabolism: Hepatic, with CYP2C19 relevant to exposure
5. Elimination: Hepatic
5. Half Life: Intermediate
5. Dose Adjust: Exposure at the suprathreshold dose used in the QT study is similar to steady-state concentrations expected in CYP2C19 poor metabolisers at the maximum therapeutic dose [5]
1. This page carries no dose regimens. Choice of agent, titration, monitoring and any tapering plan belong to the treating clinician working from a current prescribing reference and the individual patient's circumstances.
2. Half-life is the single most useful pharmacokinetic fact in this class, because it predicts both how quickly a switch can be made and how prominent the symptoms will be when treatment stops. [2][8]
3. The fluoxetine label notes that plasma concentrations of fluoxetine and norfluoxetine decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug. [2]

Adverse effects

1. Effect: Sexual dysfunction
 1. Detail: The sertraline label states that use of SSRIs may cause symptoms of sexual dysfunction, listing ejaculatory delay, decreased libido and erectile dysfunction in males, and decreased libido and delayed or absent orgasm in females. [1]
2. Effect: Symptoms on stopping or reducing treatment
 2. Detail: Reported reactions include dysphoric mood, irritability, agitation, dizziness, sensory disturbances such as electric shock sensations, anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania. UK regulators add dizziness, numbness and tingling, gastrointestinal disturbance, headache, sweating, anxiety and sleep

disturbance as the commonest. [5][8]

1. Effect: Suicidal thoughts and behaviours in younger patients

1. Detail: The boxed warning states that antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. In the pooled analyses there were roughly 14 additional patients per 1,000 under 18 years and 5 additional per 1,000 aged 18 to 24, whereas those aged 25 to 64 showed one fewer per 1,000 and those 65 and older six fewer per 1,000 than on placebo. UK regulators frame the same finding as an increased risk in young people aged up to 25 years.

1. Action: The boxed warning directs close monitoring of all antidepressant-treated patients for clinical worsening and for emergence of suicidal thoughts and behaviors; any change of treatment rests with the treating clinician. [1][8]

2. Effect: Serotonin syndrome

2. Detail: A potentially life-threatening condition that SSRIs can precipitate, with mental status change, autonomic instability, neuromuscular signs, seizures and gastrointestinal symptoms. Risk is increased with other serotonergic drugs and with drugs that impair serotonin metabolism.

2. Action: The sertraline label directs that treatment and any concomitant serotonergic agents be discontinued immediately if such symptoms occur, and that supportive symptomatic treatment be started. [1][5]

3. Effect: Hyponatraemia

3. Detail: Hyponatraemia may occur as a result of SSRI treatment, in many cases as a result of the syndrome of inappropriate antidiuretic hormone secretion, and cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk. Signs include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness.

3. Action: Those non-specific symptoms in an older patient recently started on an SSRI are the reason a serum sodium is checked; interpretation and management belong to the treating clinician. [3][5][4]

4. Effect: Abnormal bleeding

4. Detail: Drugs that interfere with serotonin reuptake inhibition increase the risk of bleeding events, and the labels warn that concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, warfarin, and other anticoagulants may add to the risk.

4. Action: The combination of an SSRI with an NSAID or an anticoagulant is the situation the labels single out, and it is a standard prompt to review whether both are still needed. [5][1]

5. Effect: QT interval prolongation and torsade de pointes

5. Detail: This is not a whole-class effect. The citalopram label states that the drug causes dose-dependent QTc prolongation, an ECG abnormality that has been associated with Torsade de Pointes, and UK regulators report that cases have occurred mainly in women, in people with hypokalaemia, and in those with pre-existing QT prolongation or other cardiac disease.

5. Action: The label directs discontinuation in patients found to have persistent QTc measurements above 500 ms, and regulators advise correcting hypokalaemia and hypomagnesaemia before treatment. [4][7]

6. Effect: Activation of mania or hypomania

6. Detail: Activation of mania or hypomania has been reported in a small proportion of patients with major affective disorder treated with antidepressants, which is why the labels direct screening for bipolar disorder before treatment begins.

6. Action: Screening for a personal and family history of bipolar disorder is the labelled step, because an antidepressant may precipitate a mixed or manic episode in a susceptible patient. [2][1]

7. Effect: Angle-closure glaucoma

7. Detail: The pupillary dilation that can follow antidepressant use may precipitate an angle-closure attack in a patient whose anatomically narrow angles have not been treated.

7. Action: The sertraline label advises avoiding use of antidepressants in patients with untreated anatomically narrow angles. [1]

1. Drug: Fluoxetine

1. Effect: The longest washout in the class. Its active metabolite norfluoxetine has an elimination half-life of four to sixteen days, and the label warns this is of potential consequence when drug discontinuation is required or when interacting drugs are prescribed after fluoxetine has been stopped. [2]
2. Drug: Paroxetine
2. Effect: Withdrawal reactions of greater frequency than other SSRIs, and a pregnancy signal: exposure in the first trimester is associated with a less than 2-fold increase in the rate of cardiovascular malformations. [8][3]
3. Drug: Fluvoxamine
3. Effect: A cluster of absolute interaction bars. Coadministration with tizanidine, thioridazine, alosetron or pimozide is contraindicated, chiefly because of its potency at CYP1A2. [6]
4. Drug: Citalopram
4. Effect: Dose-dependent QTc prolongation, with a mean increase of about 8.5 msec at the lower dose studied and about 18.5 msec at one and a half times the labelled maximum. [4]
5. Drug: Escitalopram
5. Effect: The same cardiac liability in milder form: a mean difference from placebo of 4.5 msec at the usual starting dose and 10.7 msec at a supratherapeutic dose in the thorough QT study. [5]
6. Drug: Sertraline
6. Effect: Its oral solution contains 12% alcohol, so that formulation is contraindicated with disulfiram. The label also advises caution in patients with a seizure disorder, who were excluded from the clinical studies. [1]

Contraindications, precautions and interactions

1. Sertraline and paroxetine are contraindicated in patients taking, or within 14 days of stopping, MAOIs, including the MAOIs linezolid and intravenous methylene blue, because of an increased risk of serotonin syndrome. [1][3]
2. Fluoxetine follows the same fourteen-day rule after an MAOI is stopped, but in the other direction at least 5 weeks should be allowed after stopping it before starting an MAOI. [2]
3. Fluoxetine is contraindicated with pimozide, and thioridazine should not be given with it or within a minimum of five weeks after it has been discontinued. [2]
4. Coadministration of tizanidine, thioridazine, alosetron or pimozide with fluvoxamine is contraindicated. [6]
5. UK regulators state that citalopram and escitalopram should not be used in patients with congenital long QT syndrome or known pre-existing QT interval prolongation, nor in combination with other medicines known to prolong the QT interval. [7]
1. Older patients are singled out twice over: they may be at greater risk of hyponatraemia, and the permitted maximum daily doses of citalopram and escitalopram are lower beyond 65 years and in hepatic impairment. [5][7]
2. Electrolyte disturbances such as hypokalaemia and hypomagnesaemia should be corrected before treatment with citalopram or escitalopram is started. [7]
3. Patients should be screened for bipolar disorder before an antidepressant is started, since a mixed or manic episode may be precipitated. [1]
4. Antidepressants are best avoided in patients with untreated anatomically narrow angles because of the risk of an angle-closure attack. [1]
5. Sertraline has not been systematically evaluated in patients with seizure disorders, who were excluded from the clinical studies, so the label advises caution where a seizure disorder is present. [1]
6. Where an antidepressant is being stopped, withdrawal reactions are less severe when the dose is gradually decreased or tapered off over several weeks, and the paroxetine label directs gradual reduction rather than abrupt stopping wherever possible. [8][3]
1. With: Monoamine oxidase inhibitors, including linezolid and intravenous methylene blue
1. Effect: Impaired metabolism of serotonin on top of blocked reuptake, giving a high risk of serotonin syndrome. The bar applies for 14 days in either direction for most members of the class, and for at least five weeks after fluoxetine. [3][2]

2. With: Other serotonergic drugs

2. Effect: Risk of serotonin syndrome is increased with concomitant use of other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, meperidine, methadone, tryptophan, buspirone, amphetamines and St. John's Wort. [1]

3. With: Antiplatelet drugs and anticoagulants

3. Effect: Concomitant aspirin, NSAIDs, other antiplatelet agents, warfarin and other anticoagulants may add to the bleeding risk that serotonin reuptake inhibition already carries. [5]

4. With: Tamoxifen

4. Effect: Some studies have shown that the efficacy of tamoxifen, measured by the risk of breast cancer relapse and mortality, may be reduced with concomitant paroxetine; the label suggests considering an alternative antidepressant with little or no CYP2D6 inhibition. [3]

5. With: Tizanidine

5. Effect: With fluvoxamine, tizanidine peak concentration rose approximately twelve-fold and its area under the curve thirty-three-fold, with a mean maximal fall of 35 mmHg in systolic blood pressure. The combination is contraindicated. [6]

6. With: Other QT-prolonging medicines

6. Effect: Citalopram and escitalopram may add to the effect of other QT-prolonging drugs, and coadministration is therefore contraindicated in UK regulatory advice. [7]

7. With: CYP2D6 substrates

7. Effect: Paroxetine inhibits CYP2D6 and has been shown clinically to inhibit the metabolism of desipramine, risperidone and atomoxetine, while fluoxetine may make a normal metaboliser resemble a poor metaboliser. [3][2]

Comparison tables

Title: One mechanism, six different problems

Caption: The shared warnings are identical; these are the properties that actually decide which agent suits which patient. Selection remains a clinician's decision.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: cyp

2. Label: Cytochrome effect

3. Key: kinetics

3. Label: Elimination character

4. Key: signature

4. Label: Signature liability

1. Drug: Fluoxetine

1. Cyp: Inhibits CYP2D6

1. Kinetics: Long; active metabolite norfluoxetine persists four to sixteen days

1. Signature: Weeks-long washout, a five-week gap before an MAOI, and contraindication with pimozide and thioridazine [2]

2. Drug: Paroxetine

2. Cyp: Irreversible CYP2D6 inhibition

2. Kinetics: Comparatively short

2. Signature: Greater frequency of withdrawal reactions, reduced tamoxifen efficacy, first-trimester cardiovascular signal [3][8]

3. Drug: Fluvoxamine

3. Cyp: Inhibits CYP1A2, CYP2C9, CYP3A4 and CYP2C19; weak at CYP2D6

- 3. Kinetics: Comparatively short; metabolism 25% faster in smokers
- 3. Signature: Four contraindicated co-prescriptions, tizanidine the most dramatic [6]
- 4. Drug: Citalopram
- 4. Cyp: CYP2C19 contributes to its own clearance
- 4. Kinetics: Intermediate
- 4. Signature: Dose-dependent QTc prolongation, with a labelled dosage ceiling and lower ceilings in poor metabolisers and older patients [4]
- 5. Drug: Escitalopram
- 5. Cyp: CYP2C19 relevant to exposure
- 5. Kinetics: Intermediate
- 5. Signature: Same QT liability in milder form, with reduced ceilings beyond 65 years and in hepatic impairment [5][7]
- 6. Drug: Sertraline
- 6. Cyp: A CYP2D6 inhibitor, but with a less prominent effect at lower doses than some others in the class
- 6. Kinetics: Intermediate
- 6. Signature: Breadth of licensed use, from paediatric obsessive-compulsive disorder to premenstrual dysphoric disorder; the oral solution bars disulfiram [1]

High-yield exam pearls

- 1. Pearl: The boxed warning names pediatric and young adult patients, and the pooled analysis showed fewer suicidal events than placebo in patients aged 25 to 64 and in those 65 and older.
- 1. Why: It is the single most misquoted item on this class, and getting the direction of effect right by age band is what the question is testing. [1]
- 2. Pearl: Fourteen days separates an MAOI from an SSRI in either direction, except that at least five weeks should elapse after stopping fluoxetine before an MAOI is begun.
- 2. Why: The asymmetry is entirely explained by fluoxetine's kinetics, so one fact tests both the interaction and the pharmacokinetics. [1][2]
- 3. Pearl: Linezolid and intravenous methylene blue count as MAOIs for this purpose and appear by name in the contraindication.
- 3. Why: An antibiotic and a dye are the two agents students forget are monoamine oxidase inhibitors, and both appear in real prescribing. [3]
- 4. Pearl: Citalopram causes dose-dependent QTc prolongation and its label directs discontinuation where QTc measurements are persistently above 500 ms.
- 4. Why: It is one of very few psychotropic labels with an explicit numerical stopping rule on the ECG, which makes it easy to examine. [4]
- 5. Pearl: The prominent enzyme inhibitors are fluoxetine and paroxetine at CYP2D6 and fluvoxamine at CYP1A2 among others, and paroxetine's inhibition is described as irreversible.
- 5. Why: It explains the tamoxifen warning, the tizanidine contraindication, and why an SSRI can raise the level of an unrelated drug. [2][3][6]
- 6. Pearl: Hyponatraemia in this class is frequently an SIADH picture, and the labels record cases with serum sodium lower than 110 mmol/L.
- 6. Why: Confusion and unsteadiness in an older person a few weeks after starting an antidepressant is a stock clinical vignette. [5][4]
- 7. Pearl: Fluoxetine's slow fall in plasma concentration at the end of therapy may itself minimise discontinuation symptoms, while paroxetine sits at the opposite end of that spectrum.
- 7. Why: It shows that half-life predicts withdrawal severity, which is the reasoning an examiner wants rather than a memorised list. [2][8]

Common exam traps

1. Trap: Reading the boxed warning as a general statement that SSRIs cause suicide.
1. Correction: The warning is about an increase in suicidal thoughts and behaviours observed in paediatric and young adult patients in short-term studies, and the same pooled analysis found fewer such events than placebo in patients aged 25 and above. [1][8]
2. Trap: Applying the QT warning to the whole class.
2. Correction: The dose-dependent QTc effect is a labelled property of citalopram and, in milder form, escitalopram; it is not a warning carried by every SSRI. [4][5]
3. Trap: Assuming every SSRI needs the same washout before an MAOI is started.
3. Correction: Most require fourteen days, but fluoxetine requires at least five weeks in that direction because the parent drug and norfluoxetine clear so slowly. [2]
4. Trap: Assuming that only fluoxetine, paroxetine and fluvoxamine touch the cytochromes at all.
4. Correction: They are the prominent inhibitors, but the sertraline label also identifies sertraline as a CYP2D6 inhibitor and warns that concomitant use with a CYP2D6 substrate may increase the exposure of that substrate. [1]
5. Trap: Treating SSRIs as free of interactions because they are selective.
5. Correction: Selectivity describes the transporter, not the liver. Fluvoxamine inhibits CYP1A2, CYP2C9, CYP3A4 and CYP2C19, and its interaction with tizanidine raised that drug's exposure thirty-three-fold. [6]
6. Trap: Calling withdrawal symptoms a sign of addiction to the antidepressant.
6. Correction: Regulators describe them as withdrawal reactions common to all SSRIs and SNRIs on stopping or reducing treatment, more frequent with paroxetine and venlafaxine, and less severe when the dose is tapered over several weeks. [8]
7. Trap: Overlooking bleeding risk because an SSRI is not an antiplatelet drug.
7. Correction: Interference with serotonin reuptake itself increases bleeding events, and the labels warn that aspirin, NSAIDs, other antiplatelet drugs, warfarin and other anticoagulants may add to that risk. [5]

Self-test questions

1. Question: Which statement most accurately reflects the boxed warning carried by SSRI antidepressants?
1. Antidepressants increased the risk of suicidal thoughts and behaviour in paediatric and young adult patients in short-term studies
2. Antidepressants increase the risk of completed suicide in patients of every age
3. Antidepressants increase suicidal behaviour only in patients over 65
4. Antidepressants carry no warning about suicidal thoughts once the depression improves
1. Explanation: The boxed warning is restricted by age. It states that antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies, and the supporting pooled analysis found fewer events than placebo in patients aged 25 to 64 and in those 65 and older. [1]
2. Question: A patient is being switched from fluoxetine to a monoamine oxidase inhibitor. What interval does the label require?
1. At least 5 weeks after stopping fluoxetine
2. At least 24 hours after stopping fluoxetine
3. At least 7 days after stopping fluoxetine
4. No interval is required in this direction
2. Explanation: The fluoxetine label states that at least 14 days should elapse between stopping an MAOI and starting fluoxetine, and conversely that at least 5 weeks should be allowed after stopping fluoxetine before starting an MAOI, because of the long half-lives of fluoxetine and norfluoxetine. [2]
3. Question: Which SSRI is described in its label as causing dose-dependent QTc prolongation, with discontinuation directed at persistent QTc above 500 ms?

1. Citalopram

2. Sertraline

3. Fluvoxamine

4. Paroxetine

3. Explanation: The citalopram label states that the drug causes dose-dependent QTc prolongation, an ECG abnormality associated with Torsade de Pointes, and directs discontinuation in patients found to have persistent QTc measurements above 500 ms. [4]

4. Question: A woman taking tamoxifen after breast cancer needs an antidepressant. Which agent does its own label flag as a problem in this setting?

1. Paroxetine

2. Sertraline

3. Escitalopram

4. Fluvoxamine

4. Explanation: The paroxetine label warns that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse and mortality, may be reduced with concomitant paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 and lower blood levels of tamoxifen, and suggests considering an antidepressant with little or no CYP2D6 inhibition. [3]

5. Question: An 82-year-old started on an SSRI four weeks ago presents with confusion, weakness and unsteadiness. Which investigation is most likely to explain the picture?

1. Serum sodium

2. Serum creatine kinase

3. Thyroid stimulating hormone

4. Serum calcium

5. Explanation: SSRI-associated hyponatraemia commonly reflects the syndrome of inappropriate antidiuretic hormone secretion, and the labels list headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness as its signs, with elderly patients at greater risk. [5]

6. Question: Which combination is explicitly contraindicated because of fluvoxamine's potency at CYP1A2?

1. Fluvoxamine with tizanidine

2. Fluvoxamine with paracetamol

3. Fluvoxamine with amoxicillin

4. Fluvoxamine with levothyroxine

6. Explanation: Coadministration of tizanidine with fluvoxamine is contraindicated. In a study of healthy subjects, tizanidine peak concentration rose approximately twelve-fold and its area under the curve thirty-three-fold, with a mean maximal decrease of 35 mmHg in systolic blood pressure. [6]

7. Question: According to UK regulators, which antidepressants seem to be associated with a greater frequency of withdrawal reactions than other SSRIs?

1. Paroxetine and venlafaxine

2. Fluoxetine and sertraline

3. Citalopram and escitalopram

4. Fluvoxamine and mirtazapine

7. Explanation: The MHRA states that all SSRIs and SNRIs may be associated with withdrawal reactions on stopping or reducing treatment, and that paroxetine and venlafaxine seem to be associated with a greater frequency of withdrawal reactions than other SSRIs. [8]

8. Question: Which pair of drugs must be treated as monoamine oxidase inhibitors when an SSRI is prescribed?

1. Linezolid and intravenous methylene blue

2. Metronidazole and gentamicin

3. Rifampicin and isoniazid

4. Ciprofloxacin and clarithromycin

8. Explanation: The sertraline and paroxetine labels contraindicate use in patients taking, or within 14 days of stopping, MAOIs, and both name linezolid and intravenous methylene blue among them because of the increased risk of serotonin syndrome. [1][3]

Frequently asked questions

1. Question: Do SSRIs cause suicidal behaviour?

1. Answer: The evidence in the labels is narrower than that. Short-term placebo-controlled trials showed more suicidal thoughts and behaviours in paediatric patients and in adults up to about 24 years, with roughly 14 additional patients per 1,000 under 18 and 5 additional per 1,000 aged 18 to 24. In the same analysis patients aged 25 to 64 and those 65 and older had fewer such events than on placebo. UK regulators summarise the finding as an increased risk in young people aged up to 25 years, and the labelled response is close monitoring rather than avoidance. [1][8]

2. Question: What actually causes serotonin syndrome on an SSRI?

2. Answer: Adding a second serotonergic influence to blocked reuptake. The labels name triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, meperidine, methadone, tryptophan, buspirone, amphetamines and St John's wort as raising the risk, and separately identify drugs that impair the metabolism of serotonin, meaning the monoamine oxidase inhibitors. Linezolid and intravenous methylene blue belong in that second category even though neither is thought of as a psychiatric drug. [5][3]

3. Question: Why does fluoxetine need a longer gap before an MAOI than the other SSRIs?

3. Answer: Because of how slowly it leaves the body. Fluoxetine has an elimination half-life of one to three days after a single dose and four to six days on chronic dosing, and its active metabolite norfluoxetine persists for four to sixteen days, so active drug substance will persist in the body for weeks after dosing stops. That is why at least five weeks is required in that direction, against fourteen days for the others. [2]

4. Question: Is QT prolongation a problem with all SSRIs?

4. Answer: No. The explicit labelled effect belongs to citalopram, whose label states it causes dose-dependent QTc prolongation, and to escitalopram in milder form. UK regulators lowered the permitted maximum daily doses of both, set lower limits again for people over 65 and those with hepatic impairment, contraindicated their use with other QT-prolonging medicines and in congenital long QT syndrome, and advised correcting hypokalaemia and hypomagnesaemia first. [4][7]

5. Question: Why do some people feel unwell when an SSRI is stopped?

5. Answer: Regulators describe withdrawal reactions after stopping or reducing any SSRI or SNRI, with dizziness, numbness and tingling, gastrointestinal upset particularly nausea and vomiting, headache, sweating, anxiety and disturbed sleep as the commonest. Paroxetine and venlafaxine seem to be associated with a greater frequency of them, and the reactions are less severe when the dose is gradually decreased over several weeks. Any tapering plan is a matter for the treating clinician. [8]

6. Question: Why does an SSRI matter to a patient already taking an anti-inflammatory?

6. Answer: Because the two risks add. Drugs that interfere with serotonin reuptake increase the risk of bleeding events on their own, and the labels state that concomitant aspirin, nonsteroidal anti-inflammatory drugs, other antiplatelet drugs, warfarin and other anticoagulants may add to that risk. The combination is a standard prompt to review whether both medicines are still required, which is a decision for the treating clinician. [5]

References

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[2] PROZAC (fluoxetine hydrochloride) capsule - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4b8fcce1-abfc-4631-9975-9d66e178dab6>

[3] PAXIL (paroxetine hydrochloride) tablet, film coated - prescribing information. DailyMed, U.S. National Library of Medicine .

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[4] CELEXA (citalopram) tablet, film coated - prescribing information. DailyMed, U.S. National Library of Medicine .

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[5] LEXAPRO (escitalopram) tablet, film coated and oral solution - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=13bb8267-1cab-43e5-acae-55a4d957630a>

[6] FLUVOXAMINE MALEATE tablet - prescribing information. DailyMed, U.S. National Library of Medicine .

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[7] Citalopram and escitalopram: QT interval prolongation. Medicines and Healthcare products Regulatory Agency (GOV.UK Drug Safety Update) 2014. <https://www.gov.uk/drug-safety-update/citalopram-and-escitalopram-qt-interval-prolongation>

[8] Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs): use and safety. Medicines and Healthcare products Regulatory Agency (GOV.UK) 2014.

<https://www.gov.uk/government/publications/ssris-and-snr-is-use-and-safety/selective-serotonin-reuptake-inhibitors-ssris-and-serotonin-an>

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