

Class III antiarrhythmics

Potassium channel blockers that slow the heart cell's recovery phase after each beat. That longer recovery is what steadies the rhythm - and it is also what stretches the QT interval and brings torsades de pointes into the risk profile of every drug in the class.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/class-iii-antiarrhythmics>

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Quick revision

One Liner: Class III agents block the potassium channels that let the heart cell recover after each beat, so recovery takes longer, the refractory period lengthens and the QT interval on the electrocardiogram stretches - which is simultaneously how the class works and why every member of it can trigger torsades de pointes.

1. Class III drugs block potassium channels, which prolongs recovery of atrial, Purkinje and ventricular muscle cells, increases the effective refractory period and lengthens the QT interval. [1]
2. Repolarisation is phase 3 of the cardiac action potential, the stage in which potassium leaves the cell to reset it; blocking potassium exit slows that phase down and stretches the whole action potential. [1]
3. The named class III agents are amiodarone, dronedarone, dofetilide, sotalol, ibutilide and vernakalant. [1]
4. Prolonging the QT interval is shared by all potassium channel blockers, and it raises the risk of torsades de pointes. [1]
5. Amiodarone is unusual because it also blocks beta-adrenergic receptors, calcium channels and sodium channels, so it touches all four of the classical antiarrhythmic targets rather than only one. [2]
6. Amiodarone has an exceptionally long half-life of several weeks, takes up to six weeks for its full clinical effect and keeps working for one to three months after it is stopped. [2]
7. Amiodarone's examinable toxicity list runs organ by organ: thyroid, lung, liver, eye, skin, nerve and heart. [2]
8. Corneal microdeposits appear in at least 90% of patients taking amiodarone, while optic neuropathy and visual halos affect far fewer. [2]
9. Amiodarone can cause either an underactive or an overactive thyroid, with the underactive form nearly twice as common. [2]
10. Amiodarone lung toxicity usually shows itself within the first year of treatment and the reported mortality is close to 10%. [2]
11. Sotalol is a non-cardioselective beta blocker that also blocks potassium channels, and the potassium effect is what places it in class III. [3]
12. Sotalol shows reverse use-dependence: its potassium blockade is greatest when the heart is beating slowly, so QT prolongation and arrhythmia risk are worst during bradycardia. [3]
13. Sotalol is cleared mainly by the kidneys, so reduced kidney function raises exposure and the risk that comes with it. [3]
14. Dronedarone is a synthetic relative of amiodarone that deliberately leaves out the iodine atoms, and it is contraindicated in permanent atrial fibrillation. [4][1]
15. Low potassium, low magnesium, low calcium, a slow heart rate, female sex and age over 65 all raise the risk of torsades de pointes. [5]
16. Intravenous magnesium is the first-line drug treatment for torsades de pointes. [5]

Overview

1. Class III antiarrhythmics are the potassium channel blockers of the Vaughan Williams system. A heart muscle cell fires by letting sodium and calcium in, then recovers by letting potassium out; that recovery is phase 3 of the cardiac

action potential, and it is the stage these drugs slow down. Blocking the potassium exit prolongs recovery in atrial, Purkinje and ventricular cells, increases the effective refractory period - the interval during which a cell cannot be restimulated - and lengthens the QT interval on the electrocardiogram. [1]

2. That single change is the therapeutic effect and the principal hazard at the same time. A longer refractory period makes it harder for a reentry circuit to sustain itself, which is why these drugs restore and maintain sinus rhythm. But prolonged repolarisation is also the condition in which torsades de pointes arises, a polymorphic ventricular tachycardia whose QRS complexes twist around the isoelectric line. Every potassium channel blocker shares that liability, so the class is never learnt without its safety half. [1][5]

3. The agents themselves are far from interchangeable. Amiodarone is the broadest, adding beta-adrenergic, calcium channel and sodium channel blockade to its potassium action, and it carries an organ-by-organ toxicity list that dominates examinations. Sotalol pairs potassium blockade with non-cardioselective beta blockade and is cleared by the kidneys. Dronedarone is an iodine-free relative of amiodarone with a narrower licence. Dofetilide, ibutilide and vernakalant complete the group named in the reference literature. [1][2][3][4]

4. Because the mechanism is shared, the monitoring is shared too. Serum potassium and magnesium are checked and corrected, the corrected QT interval is measured before and during treatment, other QT-prolonging medicines are avoided where possible, and slow heart rates are treated as an amplifier of risk rather than an incidental finding. Amiodarone adds a second monitoring layer of its own for thyroid, liver, lung and eye. [5][3][2]

Classification and drug examples

Intro: Class III is not formally lettered the way class I is. The practical way to divide it is by what each agent does in addition to blocking potassium channels, because those extra actions decide the licensed use, the elimination route and the safety profile that has to be watched.

1. Name: Multichannel agents - amiodarone and dronedarone

1. Note: Class III agents whose actions extend well beyond potassium channels. Amiodarone blocks beta-adrenergic receptors, calcium channels and sodium channels as well, and dronedarone shares electrophysiological properties affecting potassium, sodium and calcium channels. The breadth of action is matched by breadth of adverse effect.

1. Name: Amiodarone

1. Route: Oral/IV

1. Note: Inhibits the potassium rectifier currents that repolarise the heart during phase 3, and additionally blocks beta-adrenergic receptors, calcium channels and sodium channels, reducing sinoatrial node automaticity and slowing atrioventricular node conduction. Highly fat-soluble with a half-life of several weeks. [2]

2. Name: Dronedarone

2. Route: Oral

2. Note: A synthetic derivative of amiodarone, deliberately made without iodine so as to sidestep amiodarone's end-organ toxicity. Used orally for paroxysmal or persistent atrial fibrillation or flutter, and contraindicated once atrial fibrillation is permanent. [4][1] [2][4]

2. Name: Potassium blockade combined with beta blockade - sotalol

2. Note: A non-cardioselective beta blocker whose potassium channel blocking effect predominates, which is why the Vaughan Williams system places it in class III rather than class II. The two mechanisms generate two separate sets of adverse effects, and the drug is cleared principally by the kidneys.

Name: Sotalol

Route: Oral/IV

Note: Prolongs action potential duration and the effective refractory period in atrium, ventricle, and nodal and extranodal tissue. Shows reverse use-dependence, so potassium blockade and QT prolongation are greatest at slow heart rates. [3] [3]

3. Name: Agents directed mainly at atrial arrhythmias - dofetilide, ibutilide and vernakalant

3. Note: Further class III potassium channel blockers named in the reference literature. Dofetilide is used for atrial

arrhythmias only, and the shared class hazard of QT prolongation and torsades de pointes applies to each of them.

1. Name: Dofetilide

1. Route: Oral

1. Note: A class III potassium channel blocker used for atrial arrhythmias only. It is listed among the QT-prolonging drugs to avoid combining with amiodarone. [1][2]

2. Name: Ibutilide

2. Route: IV

2. Note: An intravenous class III agent named alongside dofetilide and vernakalant in the potassium channel blocking group. [1]

3. Name: Vernakalant

3. Route: IV

3. Note: An intravenous agent listed within the class III group in the antiarrhythmic reference literature. [1] [1]

Mechanism of action

Summary: Class III agents block the potassium channels that carry the outward current of phase 3, so the cell takes longer to reset after each beat. Action potential duration and the effective refractory period both lengthen, reentry circuits become harder to sustain, and the QT interval on the surface electrocardiogram grows longer as the visible sign of all three.

Target: Delayed rectifier potassium channels of cardiac myocytes and conducting tissue

1. Step: 1

1. Title: Potassium efflux normally ends the beat

1. Detail: After depolarisation, potassium ions flow out of the cardiac cell through delayed rectifier channels. This outward current is phase 3 of the action potential, and it returns the cell to its resting state so it can be excited again. [1]

2. Step: 2

2. Title: The drug blocks the channel and slows that exit

2. Detail: When a potassium channel blocker is given, phase 3 is prolonged because potassium leaves the cell more slowly. The whole action potential therefore lasts longer. [1]

3. Step: 3

3. Title: The refractory period lengthens

3. Detail: A longer action potential means a longer effective refractory period in atrial, Purkinje and ventricular muscle, so the tissue spends more of each cycle unable to respond to a new stimulus. Repolarisation reserve - the spare capacity the cell has for recovering on time - is reduced. [1]

4. Step: 4

4. Title: Reentry circuits are harder to sustain

4. Detail: Reentry depends on finding tissue that has already recovered and can be re-excited. Extending refractoriness removes that excitable gap, which is how the class restores and then maintains sinus rhythm. [1]

5. Step: 5

5. Title: The electrocardiogram shows a longer QT interval

5. Detail: Because the QT interval measures ventricular depolarisation plus repolarisation, prolonged recovery lengthens it. The corrected QT interval is therefore the routine bedside measure of how much class III effect a patient is receiving. [1][5]

6. Step: 6

6. Title: Excessive prolongation permits torsades de pointes

6. Detail: Inhibition of the delayed rectifier potassium current prolongs repolarisation and sets up the R-on-T phenomenon, in which a premature ventricular beat lands on the T wave and triggers polymorphic ventricular tachycardia. A corrected QT interval above 500 milliseconds carries a two- to threefold increased risk. [5]

7. Step: 7

7. Title: Individual drugs add mechanisms of their own

7. Detail: Amiodarone layers beta-adrenergic, calcium channel and sodium channel blockade onto the potassium effect, sotalol adds non-cardioselective beta blockade, and dronedarone shares actions on potassium, sodium and calcium channels. Those additions explain why members of one class behave so differently in practice. [2][3][4]

Major clinical uses

1. Drug: Amiodarone

1. Indication: Life-threatening ventricular arrhythmias, ventricular fibrillation, pulseless ventricular tachycardia and wide complex tachycardia in advanced cardiac life support

1. Line: targeted

1. Note: Not a first-line antiarrhythmic. The licensed indication is restricted to documented, life-threatening recurrent ventricular fibrillation and life-threatening recurrent haemodynamically unstable ventricular tachycardia in adults who have not responded to adequate doses of other available antiarrhythmic drugs, or in whom those alternatives cannot be tolerated, because its use carries substantial toxicity. For haemodynamically unstable patients with a heart rate above 150 beats per minute, direct current cardioversion is considered rather than drug treatment alone. [2]

2. Drug: Amiodarone

2. Indication: Maintenance of sinus rhythm in atrial fibrillation, particularly where there is left ventricular systolic dysfunction

2. Line: targeted

2. Note: An off-label use in many settings. Amiodarone is also the antiarrhythmic most commonly used to suppress ventricular arrhythmia, and it is used off-label in supraventricular tachyarrhythmias and atrial flutter. [1][2]

3. Drug: Sotalol

3. Indication: Haemodynamically stable ventricular tachycardia, and maintenance of sinus rhythm in paroxysmal atrial fibrillation

3. Line: targeted

3. Note: Intravenous loading is also licensed as a way of starting oral therapy. Initiation is described as taking place in hospital with continuous rhythm monitoring. [3]

4. Drug: Sotalol

4. Indication: Off-label roles in premature ventricular contractions, pharmacological cardioversion of atrial fibrillation, postoperative atrial fibrillation after cardiac surgery and supraventricular tachycardia

4. Line: alternative

4. Note: Transplacental treatment of fetal supraventricular tachycardia and fetal atrial fibrillation is also described, with complete or partial resolution reported in 85% of cases. [3]

5. Drug: Dronedarone

5. Indication: Oral treatment of paroxysmal or persistent atrial fibrillation or flutter

5. Line: alternative

5. Note: It reduces hospitalisation for atrial fibrillation in patients in sinus rhythm with non-permanent disease, but must not be used where atrial fibrillation cannot be converted back to sinus rhythm. [4]

6. Drug: Dofetilide

6. Indication: Atrial arrhythmias only

6. Line: targeted

6. Note: Unlike amiodarone and sotalol, its role does not extend to ventricular arrhythmias. It appears on the list of QT-prolonging drugs that should not be combined with amiodarone. [1][2]

Pharmacokinetics

1. Drug: Amiodarone

1. Route: Oral/IV

1. Absorption: Notably variable, ranging from 22% to 86%

1. Metabolism: Hepatic via cytochrome P450, primarily CYP2C8 and as a CYP3A4 substrate, generating an active metabolite

1. Elimination: Primarily biliary, with less than 1% excreted unchanged in the urine

1. Half Life: Exceptionally long, of the order of several weeks

1. Dose Adjust: Highly fat-soluble with extensive accumulation in skeletal muscle and fat; full clinical effect may take up to six weeks and effects persist one to three months after stopping [2]

2. Drug: Sotalol

2. Route: Oral/IV

2. Absorption: Oral absorption may be slightly reduced by food or antacids

2. Metabolism: Minimal hepatic metabolism with no active metabolites and no cytochrome P450 involvement

2. Elimination: Eliminated primarily by the kidneys, with up to 20% excreted in the faeces

2. Half Life: 10 to 20 hours where renal function is normal

2. Dose Adjust: Adjustment is required when the estimated glomerular filtration rate falls below 60 mL/min, and a creatinine clearance under 40 mL/min is a contraindication in atrial fibrillation or flutter [3]

3. Drug: Dronedarone

3. Route: Oral

3. Absorption: Given orally; see a current prescribing reference for absorption detail

3. Metabolism: Metabolised by the CYP3A enzyme system

3. Elimination: See a current prescribing reference

3. Half Life: See a current prescribing reference

3. Dose Adjust: Liver injury has been reported, so hepatic monitoring accompanies treatment [4]

1. The two best-known agents in the class are handled by opposite organs, which is the single most useful pharmacokinetic contrast here: amiodarone is a hepatic and biliary drug, sotalol a renal one. [2][3]

2. Because amiodarone accumulates in fat and muscle and has a half-life measured in weeks, both the onset and the offset of its effects are slow, and adverse effects can appear or persist long after a change in treatment. [2]

3. Sotalol has no cytochrome P450 involvement, so its clinically important interactions are pharmacodynamic - additive effects on heart rate, conduction and the QT interval - rather than metabolic. [3]

4. Monitoring described for amiodarone includes baseline and periodic liver function tests, baseline chest radiography and pulmonary function testing with reassessment every three to six months, thyroid function at baseline and every six months, regular electrocardiograms, blood pressure and electrolyte checks, and fundoscopy with slit lamp examination. [2]

5. This page gives no dose regimens by design. Doses depend on indication, formulation, comorbidity, renal and hepatic function and concurrent medicines, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Corneal microdeposits

1. Detail: Seen in at least 90% of patients taking amiodarone. Photophobia and visual halos occur less often, and slit lamp examination is part of the recommended surveillance. [2]

2. Effect: Gastrointestinal upset

2. Detail: Nausea, loss of appetite and constipation are described with amiodarone. [2]

3. Effect: Skin changes

3. Detail: Photosensitivity and a blue-grey skin discolouration, sometimes nicknamed smurf skin, are characteristic of long-term amiodarone. [2]

4. Effect: Bradycardia and fatigue

4. Detail: These follow the non-cardioselective beta blockade of sotalol, along with breathlessness. [3]

5. Effect: Injection site phlebitis

5. Detail: Reported when amiodarone is given through a peripheral intravenous line. [2]

1. Effect: QT prolongation and torsades de pointes

1. Detail: The class effect. Every potassium channel blocker can prolong the corrected QT interval and thereby raise the risk of this polymorphic ventricular tachycardia, and amiodarone may be the most common drug cause of it.

1. Action: Serial electrocardiograms with correction of potassium, magnesium and calcium; intravenous magnesium is first-line if torsades occurs, with synchronised cardioversion or overdrive pacing for refractory cases. [1][2][5]

2. Effect: Amiodarone pulmonary toxicity

2. Detail: Usually manifests within the first year and resembles interstitial lung disease; it can also present as organising pneumonia, pleural effusion or diffuse alveolar haemorrhage. Reported mortality is nearly 10%.

2. Action: Baseline chest radiography and pulmonary function testing including diffusion capacity, reassessed every three to six months. [2]

3. Effect: Amiodarone thyroid dysfunction

3. Detail: Both underactive and overactive thyroid states occur, the underactive form being nearly twice as prevalent, and thyroiditis is also associated.

3. Action: Thyroid function tests at baseline and every six months. [2]

4. Effect: Amiodarone hepatotoxicity

4. Detail: Liver toxicity has an annual incidence of about 1% and is usually reversible on stopping, but rarely progresses to cirrhosis; intravenous administration can cause acute liver injury within 24 hours.

4. Action: Baseline and periodic liver function tests. [2]

5. Effect: Amiodarone neurological and ocular injury

5. Detail: Neurological effects affect as many as 27.5% of patients and range from cognitive impairment to peripheral neuropathy and ataxia; optic neuropathy is the sight-threatening eye complication as distinct from the near-universal corneal deposits.

5. Action: Fundoscopy and slit lamp examination form part of routine surveillance. [2]

6. Effect: Bradycardia and conduction block

6. Detail: Amiodarone can cause bradycardia and atrioventricular or intraventricular conduction abnormalities, and sotalol's beta blockade compounds any tendency to a slow rate.

6. Action: Continuous cardiac monitoring in acute settings and regular electrocardiograms thereafter. [2][3]

7. Effect: Dronedarone liver injury

7. Detail: Serum enzyme elevations occur at a variable rate, and rare instances of clinically apparent, hepatocellular liver injury have been severe enough to cause death or require transplantation; injury typically emerges within two to six months.

7. Action: The FDA has issued warnings about severe liver injury and liver failure, and hepatic monitoring accompanies treatment. [4]

8. Effect: Worsening heart failure with sotalol

8. Detail: American Heart Association and American College of Cardiology 2022 guidance states that sotalol should be avoided in decompensated heart failure because of its proarrhythmic properties and its beta blockade.

8. Action: Assessment of heart failure status before and during treatment by the treating clinician. [3]

1. Drug: Amiodarone

1. Effect: The multi-organ toxicity profile - thyroid, lung, liver, eye, skin and nerve - together with bradycardia and drug-induced torsades de pointes. Rare epididymitis and erectile dysfunction are also described. [2]

2. Drug: Sotalol

2. Effect: Dose-related QT prolongation occurring in 1% to 2% of cases, which can lead to torsades de pointes or new ventricular tachycardia or fibrillation, with the intravenous formulation carrying a higher incidence. [3]

3. Drug: Dronedarone

3. Effect: Hepatocellular liver injury, and an increased risk of cardiovascular events, heart failure, stroke and death

when used in atrial fibrillation that cannot be returned to sinus rhythm. [4]

4. Drug: Dofetilide

4. Effect: Shares the class QT-prolonging liability and is named among the drugs that should not be combined with amiodarone for that reason. [2]

Contraindications, precautions and interactions

1. Amiodarone in second- or third-degree heart block without a pacemaker. [2]

2. Amiodarone in Wolff-Parkinson-White syndrome with concurrent atrial fibrillation, where an accessory pathway pre-excites the ventricle. [2]

3. Amiodarone where the baseline corrected QT interval is already prolonged, or in congenital long QT syndrome, and where hyperkalaemia or other electrolyte abnormalities are uncorrected. [2]

4. Sotalol in bronchial asthma or other bronchospastic disease, sinus bradycardia, second- or third-degree atrioventricular block without a pacemaker, cardiogenic shock, decompensated heart failure, sick sinus syndrome without a pacemaker, and labile diabetes. [3]

5. Sotalol in acquired or congenital long QT syndrome, and where hypokalaemia or hypomagnesaemia has not been corrected. [3]

6. Sotalol for atrial fibrillation or flutter where creatinine clearance is below 40 mL/min. [3]

7. Dronedarone in permanent atrial fibrillation and in pregnancy. [1]

1. Low potassium, low magnesium and low calcium, each of which is a listed risk factor for torsades de pointes and should be corrected before and during class III treatment. [5]

2. A slow heart rate, which both raises torsades risk in its own right and deepens sotalol's potassium blockade through reverse use-dependence. [5][3]

3. Age over 65 years and female sex, both listed among the risk factors for torsades de pointes. [5]

4. Iodine allergy with amiodarone, although retrospective studies suggest this may not be an absolute barrier. [2]

5. Reduced kidney function with sotalol, where clearance falls and exposure rises. [3]

6. Existing liver disease or unexplained fatigue, abdominal discomfort or jaundice during dronedarone treatment, given its hepatocellular injury pattern. [4]

1. With: Warfarin

1. Effect: Amiodarone reduces warfarin clearance, so anticoagulant effect increases and close monitoring of the international normalised ratio is advised. [2]

2. With: Digoxin

2. Effect: Amiodarone can produce a notable rise in digoxin concentrations, potentially doubling them; sotalol and digoxin both slow atrioventricular conduction and lower heart rate, increasing the risk of bradycardia. [2][3]

3. With: Statins, particularly lovastatin and atorvastatin

3. Effect: Amiodarone interferes with their metabolism, raising statin exposure. [2]

4. With: Other QT-prolonging drugs

4. Effect: Combination should be avoided. Named examples include dofetilide, quinidine, sotalol, pimozide, macrolide antibiotics such as erythromycin and clarithromycin, and quinolone antibiotics. [2]

5. With: Cytochrome P450 inhibitors

5. Effect: Azole antifungals, cimetidine, protease inhibitors and grapefruit juice can inhibit amiodarone metabolism and raise its serum level; St John's wort and phenytoin are also named as interacting. [2]

6. With: Calcium channel blockers

6. Effect: With sotalol they may further reduce atrioventricular conduction, adversely affecting ventricular function and blood pressure. [3]

7. With: Insulin and oral hypoglycaemic agents

7. Effect: Sotalol's beta blockade may mask the warning symptoms of a low blood glucose. [3]

8. With: Clonidine and catecholamine-depleting agents

8. Effect: Added to sotalol, clonidine increases bradycardia risk, and catecholamine-depleting drugs may cause a disproportionate fall in sympathetic tone leading to hypotension, marked bradycardia and syncope. [3]

Comparison tables

1. Title: Amiodarone, sotalol and dronedarone side by side
1. Caption: All three block potassium channels; what separates them is everything else. Actual therapy is governed by a current prescribing reference.
1. Key: drug
1. Label: Drug
1. Is Row Header: true
2. Key: extra
2. Label: Actions beyond potassium blockade
3. Key: use
3. Label: Characteristic use
4. Key: elimination
4. Label: Elimination
5. Key: safety
5. Label: Dominant safety concern
1. Drug: Amiodarone
1. Extra: Beta-adrenergic, calcium channel and sodium channel blockade
1. Use: Life-threatening ventricular arrhythmias; sinus rhythm maintenance in atrial fibrillation with left ventricular dysfunction
1. Elimination: Hepatic metabolism, mainly biliary excretion; half-life of several weeks
1. Safety: Multi-organ toxicity - thyroid, lung, liver, eye, nerve, skin - plus drug-induced torsades de pointes [2][1]
2. Drug: Sotalol
2. Extra: Non-cardioselective beta blockade
2. Use: Haemodynamically stable ventricular tachycardia; sinus rhythm maintenance in paroxysmal atrial fibrillation
2. Elimination: Renal, with a half-life of 10 to 20 hours when kidney function is normal
2. Safety: Dose-related QT prolongation and torsades, worst at slow heart rates; beta-blocker contraindications apply [3]
3. Drug: Dronedarone
3. Extra: Shared actions on sodium and calcium channels; no iodine in the molecule
3. Use: Paroxysmal or persistent atrial fibrillation or flutter, taken orally
3. Elimination: CYP3A metabolism
3. Safety: Hepatocellular liver injury, and harm if used once atrial fibrillation is permanent [4][1]
2. Title: Amiodarone organ by organ
2. Caption: The classic examinable profile, paired with the surveillance described for each organ. Recognition prompts review by the treating clinician, not self-directed change.
1. Key: organ
1. Label: Organ
1. Is Row Header: true
2. Key: effect
2. Label: What happens
3. Key: monitoring
3. Label: Described monitoring
1. Organ: Thyroid
1. Effect: Underactive or overactive thyroid, the underactive form nearly twice as common; thyroiditis also associated

1. Monitoring: Thyroid function at baseline and every six months [2]
2. Organ: Lung
2. Effect: Interstitial lung disease pattern within the first year; organising pneumonia, pleural effusion or diffuse alveolar haemorrhage; mortality near 10%
2. Monitoring: Baseline chest radiograph and pulmonary function tests with diffusion capacity, repeated every three to six months [2]
3. Organ: Liver
3. Effect: About 1% annual incidence of liver toxicity, usually reversible; acute injury within 24 hours is possible after intravenous use
3. Monitoring: Baseline and periodic liver function tests [2]
4. Organ: Eye
4. Effect: Corneal microdeposits in at least 90%; photophobia, visual halos and optic neuropathy in fewer patients
4. Monitoring: Fundoscopy and slit lamp examination [2]
5. Organ: Skin
5. Effect: Photosensitivity and blue-grey discolouration
5. Monitoring: Clinical observation; sun protection is commonly advised by the treating clinician [2]
6. Organ: Nervous system
6. Effect: Affects as many as 27.5% of patients, from cognitive impairment through peripheral neuropathy to ataxia
6. Monitoring: Clinical assessment during follow-up [2]
7. Organ: Heart
7. Effect: Bradycardia, atrioventricular and intraventricular conduction abnormality, and torsades de pointes
7. Monitoring: Continuous cardiac monitoring acutely, regular electrocardiograms and electrolyte checks thereafter [2]

High-yield exam pearls

1. Pearl: One mechanism explains both the benefit and the danger.
1. Why: Blocking potassium channels prolongs recovery and the refractory period, which is how the rhythm is stabilised; the same prolonged recovery stretches the QT interval, and a stretched QT interval is the substrate for torsades de pointes. [1]
2. Pearl: Amiodarone is a class III drug that behaves like all four classes at once.
2. Why: Beyond blocking the potassium currents that repolarise the heart in phase 3, it blocks beta-adrenergic receptors, calcium channels and sodium channels, and it reduces automatic firing of the sinoatrial node and slows conduction through the atrioventricular node. [2]
3. Pearl: Amiodarone's pharmacokinetics are the reason its adverse effects outlast the prescription.
3. Why: It is highly fat-soluble and accumulates in skeletal muscle and fat, its half-life runs to several weeks, and its effects persist for one to three months after the drug is stopped - so stopping it does not immediately end the exposure. [2]
4. Pearl: Amiodarone may be the commonest drug cause of torsades de pointes.
4. Why: Despite a reputation for being comparatively rhythm-safe, the StatPearls review states that amiodarone may be the most common cause of drug-induced torsades de pointes, alongside bradycardia and conduction abnormalities. [2]
5. Pearl: Sotalol's risk peaks when the heart rate falls, not when it rises.
5. Why: Reverse use-dependence means the maximum potassium channel blockade occurs at slower heart rates, so QT prolongation and arrhythmia risk increase during bradycardia rather than during tachycardia. [3]
6. Pearl: Amiodarone and sotalol leave the body by opposite routes.
6. Why: Amiodarone is metabolised in the liver and eliminated mainly in bile, with less than 1% appearing unchanged in urine; sotalol undergoes minimal liver metabolism, has no active metabolites and is cleared principally by the kidneys. [2][3]
7. Pearl: Dronedarone was designed to dodge amiodarone's organ toxicity but brought its own problems.

7. Why: Removing the iodine was intended to avoid the thyroid and other end-organ effects, yet dronedarone causes serum enzyme rises and occasional severe liver injury, and it is contraindicated in permanent atrial fibrillation and in pregnancy. [4][1]

8. Pearl: Correcting potassium and magnesium is part of prescribing in this class, not an afterthought.

8. Why: Low potassium, low magnesium and low calcium are listed risk factors for torsades de pointes, uncorrected hypokalaemia and hypomagnesaemia are contraindications to sotalol, and intravenous magnesium is the first-line drug treatment once torsades occurs. [5][3]

Common exam traps

1. Trap: "Amiodarone does not cause torsades de pointes."

1. Correction: It can and it does. The StatPearls review describes amiodarone as possibly the most common cause of drug-induced torsades de pointes, and baseline QT prolongation or congenital long QT syndrome is listed among its contraindications. [2]

2. Trap: "Sotalol is only a beta blocker."

2. Correction: Its potassium channel blocking action predominates, which is why the Vaughan Williams system files it as a class III agent even though it is also a non-cardioselective beta blocker. [3]

3. Trap: "Amiodarone causes hypothyroidism, so an overactive thyroid rules it out."

3. Correction: It causes both. Underactive and overactive thyroid states are described, with the underactive form nearly twice as prevalent, and amiodarone is also associated with thyroiditis. [2]

4. Trap: "Amiodarone lung damage is a problem only after years of treatment."

4. Correction: Pulmonary toxicity typically manifests within the initial year of therapy, resembling interstitial lung disease, and it can also appear as organising pneumonia, pleural effusion or diffuse alveolar haemorrhage. [2]

5. Trap: "Dronedarone is simply a safer amiodarone."

5. Correction: It avoids iodine, but the FDA has warned of severe liver injury and liver failure including cases needing transplantation, and it must not be used where atrial fibrillation is permanent. [4][1]

6. Trap: "Sotalol can simply be started at home like any other beta blocker."

6. Correction: A box warning states it should be started in a facility able to provide continuous electrocardiographic monitoring and cardiac resuscitation, and patients beginning it are described as hospitalised for at least three days with rhythm monitoring. [3]

7. Trap: "A long QT interval on the monitor means torsades is already happening."

7. Correction: A prolonged QT interval is the setting, not the arrhythmia. Torsades de pointes is the polymorphic ventricular tachycardia itself, recognised by QRS complexes that twist around the isoelectric line with changing amplitude. [5]

Self-test questions

1. Question: What is the defining action of a class III antiarrhythmic?

1. Blockade of fast sodium channels, depressing phase 0
2. Blockade of potassium channels, prolonging recovery and the refractory period
3. Blockade of L-type calcium channels in the atrioventricular node
4. Blockade of beta-adrenergic receptors only

1. Explanation: Class III agents block potassium channels. That prolongs action potential recovery in atrial, Purkinje and ventricular muscle cells, increases the effective refractory period, reduces repolarisation reserve and lengthens the QT interval on the electrocardiogram. [1]

2. Question: Which feature makes amiodarone atypical among class III agents?

1. It has no effect on the QT interval
2. It is eliminated entirely unchanged by the kidneys
3. It also blocks beta-adrenergic receptors, calcium channels and sodium channels

4. It acts only on atrial tissue

2. Explanation: Amiodarone inhibits the potassium rectifier currents that repolarise the heart during phase 3, which is the class III action, but it additionally blocks beta-adrenergic receptors, calcium channels and sodium channels. That combined profile also reduces sinoatrial node automaticity and slows atrioventricular node conduction. [2]

3. Question: Which amiodarone adverse effect occurs in at least 90% of patients?

1. Corneal microdeposits
2. Pulmonary fibrosis
3. Optic neuropathy
4. Blue-grey skin discolouration

3. Explanation: Corneal microdeposits are reported in at least 90% of patients on amiodarone. Photophobia, optic neuropathy and visual halos are described in far fewer, and the skin and lung effects are separate parts of the toxicity profile. [2]

4. Question: Why does sotalol carry its greatest arrhythmia risk when the heart rate is slow?

1. Because renal clearance rises during bradycardia
2. Because it shows reverse use-dependence, with maximum potassium blockade at slower rates
3. Because beta blockade is lost at low heart rates
4. Because it is converted to an active metabolite only during bradycardia

4. Explanation: Sotalol exhibits reverse use-dependent effects: the maximum potassium channel blockade occurs at slower heart rates. That increases QT prolongation and arrhythmia risk during bradycardia rather than during fast rhythms. [3]

5. Question: How is amiodarone eliminated?

1. Almost entirely unchanged in the urine
2. Primarily in bile, with less than 1% excreted unchanged in urine
3. By plasma esterases within minutes
4. By exhalation as a volatile metabolite

5. Explanation: Amiodarone is metabolised in the liver by cytochrome P450 enzymes and eliminated primarily by the biliary route, with less than 1% excreted unchanged in the urine. Its half-life is several weeks and its absorption is variable, ranging from 22% to 86%. [2]

6. Question: In which situation is dronedarone contraindicated?

1. Paroxysmal atrial fibrillation
2. Persistent atrial fibrillation that has been cardioverted
3. Permanent atrial fibrillation
4. Atrial flutter of recent onset

6. Explanation: Dronedarone is contraindicated in permanent atrial fibrillation, and also in pregnancy. Its licensed role is oral treatment of paroxysmal or persistent atrial fibrillation or flutter. The PALLAS trial, conducted specifically in patients with permanent atrial fibrillation, was stopped early because of an increased rate of primary outcome events including death - which is exactly why the contraindication is worded around permanent atrial fibrillation. [1][4]

7. Question: What is the first-line drug treatment for torsades de pointes?

1. Intravenous magnesium
2. Intravenous amiodarone
3. Oral potassium alone
4. Intravenous adenosine

7. Explanation: Intravenous magnesium is described as the first-line pharmacological therapy for torsades de pointes. Correction of electrolyte abnormalities, synchronised cardioversion and overdrive pacing for refractory cases are the other elements of management. [5]

8. Question: Which pair of amiodarone interactions is most often examined?

1. Warfarin, whose clearance is reduced, and digoxin, whose concentration can double

2. Paracetamol and ibuprofen
3. Insulin and metformin
4. Levothyroxine and calcium carbonate
8. Explanation: Amiodarone reduces warfarin clearance, so close monitoring of the international normalised ratio is advised. It can also produce a notable increase in digoxin concentrations, potentially doubling them, and it interferes with the metabolism of lovastatin and atorvastatin. [2]

Frequently asked questions

1. Question: What does a class III antiarrhythmic actually do?
1. Answer: It blocks the potassium channels that let a heart cell recover after each beat. Recovery therefore takes longer, the refractory period grows, reentry circuits are harder to sustain, and the QT interval on the electrocardiogram lengthens as the outward sign of all of that. [1]
2. Question: Why does this class prolong the QT interval?
2. Answer: The QT interval measures how long the ventricles take to depolarise and then recover. Because potassium channel blockade slows phase 3 of the action potential, recovery takes longer and the measured interval lengthens. That is an expected pharmacological effect, not an unrelated side effect. [1]
3. Question: What is torsades de pointes and why does it matter here?
3. Answer: It is a polymorphic ventricular tachycardia in which the QRS complexes change amplitude and twist around the isoelectric line. It arises when repolarisation is prolonged, so it is the characteristic hazard of this class. A corrected QT interval above 500 milliseconds carries a two- to threefold increase in risk. [5]
4. Question: Why is amiodarone treated as a special case?
4. Answer: Because it is not only a potassium channel blocker. It also blocks beta-adrenergic receptors, calcium channels and sodium channels, its half-life runs to several weeks, and it has an adverse effect for almost every organ system - which is why its monitoring schedule is longer than that of any other antiarrhythmic. [2]
5. Question: Is sotalol a beta blocker or a class III agent?
5. Answer: Both, but the classification follows the dominant action. Sotalol is a non-cardioselective beta blocker that also blocks potassium channels, and because the potassium effect predominates it is placed in class III. In practice its contraindications include the beta-blocker ones, such as asthma and decompensated heart failure. [3]
6. Question: What does reverse use-dependence mean?
6. Answer: It means the drug's effect is strongest when the heart is beating slowly and weakest when it is beating fast - the reverse of what would be most useful. For sotalol, maximum potassium channel blockade occurs at slower heart rates, so QT prolongation and arrhythmia risk are greatest during bradycardia. [3]
7. Question: How does dronedarone differ from amiodarone?
7. Answer: Dronedarone is a synthetic derivative of amiodarone built without iodine, specifically to avoid amiodarone's end-organ effects. It shares actions on potassium, sodium and calcium channels, is licensed for paroxysmal or persistent atrial fibrillation or flutter, and must not be used once atrial fibrillation is permanent. Liver injury remains a genuine concern with it. [4][1]
8. Question: Why are potassium and magnesium checked so often with these drugs?
8. Answer: Low levels of potassium, magnesium and calcium are recognised risk factors for torsades de pointes, uncorrected hypokalaemia and hypomagnesaemia are contraindications to sotalol, and intravenous magnesium is the first-line treatment if torsades develops. Keeping those electrolytes normal is part of using the class safely. [5][3]

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