

Azole antifungals

A family of drugs that all block the same fungal enzyme, lanosterol 14-alpha-demethylase, but differ sharply from one another in how far their spectrum reaches beyond *Candida* into moulds like *Aspergillus* - a difference that tracks closely with which drug carries which distinctive toxicity, from voriconazole's visual disturbances to isavuconazole's unusual QT-shortening effect.

Online guide: <https://www.medguideglobal.com/pharmacology/antivirals-antifungals-antiparasitics/azole-antifungals>

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Quick revision

One Liner: Every azole blocks the same fungal enzyme, CYP51 (lanosterol 14-alpha-demethylase), but fluconazole's spectrum stays largely confined to *Candida* and *Cryptococcus* while voriconazole, posaconazole and isavuconazole extend into *Aspergillus* and other moulds - and each drug's distinguishing toxicity (visual change, QT prolongation or, uniquely, QT shortening) tracks with its own chemistry, not a single shared class warning.

1. All azoles are non-competitive inhibitors of fungal lanosterol 14-alpha-demethylase (CYP51), the rate-limiting enzyme that converts lanosterol to ergosterol; blocking it destabilises the fungal cell membrane. [6][1]
2. Fluconazole is highly selective for *Candida* species and *Cryptococcus neoformans* with weak mould coverage, and *Candida krusei* is intrinsically considered resistant to it. [1]
3. Voriconazole, posaconazole and isavuconazole extend coverage to *Aspergillus* species and, for posaconazole and isavuconazole, to some Mucorales, which fluconazole does not reach at all. [2][3][4]
4. Voriconazole carries a labelled visual-disturbance rate of about 21% of patients (abnormal vision, colour vision change and/or photophobia) and a specific long-term photosensitivity-linked skin cancer risk (squamous cell carcinoma, melanoma). [2]
5. Fluconazole, voriconazole and posaconazole are all associated with QT prolongation and reported torsades de pointes, and each is contraindicated with other QT-prolonging CYP3A4 substrates such as pimozide and quinidine. [1][2][3]
6. Isavuconazole is the outlier: instead of QT prolongation, its label describes concentration-related QT interval SHORTENING, which is why it is specifically contraindicated in familial short QT syndrome rather than joining the QT-prolongation contraindication list. [4]
7. All the triazoles carry real hepatotoxicity risk, ranging from asymptomatic transaminase elevation to reported hepatic failure, and all interact heavily with the CYP450 system - fluconazole is a moderate CYP2C9/3A4 and strong CYP2C19 inhibitor, while voriconazole, posaconazole and isavuconazole are substrates and/or inhibitors of CYP3A4 with a long list of contraindicated co-medications. [1][2][3][4]
8. Posaconazole raises sirolimus concentrations roughly nine-fold and is contraindicated with ergot alkaloids because of the risk of ergotism. [3]

Overview

1. The azole antifungals are unusual among drug classes taught together in that every member shares one precise molecular target, yet the members differ enormously in practical use. All azoles are non-competitive inhibitors of lanosterol 14-alpha-demethylase, the fungal cytochrome P450 enzyme (also called CYP51) that performs the rate-limiting step converting lanosterol to ergosterol in the fungal cell membrane biosynthetic pathway. With that conversion blocked, the fungal membrane loses structural integrity, becomes abnormally permeable, and the cell eventually lyses. [6][1]
2. The class is generationally organised. Imidazoles such as ketoconazole and miconazole came first and had real safety-profile limitations that later drove development of the triazoles: fluconazole, itraconazole, voriconazole,

posaconazole and isavuconazole. Each newer triazole was designed to address a shortcoming of an earlier one, generally trading a narrower, more predictable spectrum for a broader one, or a simpler interaction profile for a more potent mould-active one, rather than any later drug simply superseding an earlier one across the board. [6]

3. Spectrum is where the real clinical differentiation between these drugs is made. Fluconazole's own label describes it as a highly selective inhibitor whose real-world reach is largely confined to *Candida* species (with *Candida krusei* specifically called out as intrinsically resistant) and to *Cryptococcus neoformans*, which is why it is a mainstay for vaginal, oropharyngeal and oesophageal candidiasis and for cryptococcal meningitis, but it is not a mould-active drug. Voriconazole, by contrast, is labelled for invasive aspergillosis as well as candidaemia, oesophageal candidiasis, and serious infections due to *Scedosporium apiospermum* and *Fusarium* species - a materially broader reach into filamentous fungi. Posaconazole and isavuconazole extend further still, with posaconazole indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in severely immunocompromised patients (such as haematopoietic stem cell transplant recipients with graft-versus-host disease) and isavuconazole indicated specifically for invasive aspergillosis and invasive mucormycosis. [1][2][3][4]

4. Toxicity in this class does not read as one shared warning bolted onto every drug; it reads as a set of drug-specific findings that happen to cluster around two themes, hepatotoxicity and cardiac conduction. Voriconazole's defining adverse effect is visual disturbance, reported in roughly a fifth of patients, alongside a long-term photosensitivity-associated risk of squamous cell carcinoma and melanoma unique to this drug in the group discussed here. Fluconazole, voriconazole and posaconazole are all linked to QT interval prolongation and reported torsades de pointes. Isavuconazole breaks that pattern entirely: its label describes concentration-related QT interval shortening rather than prolongation, which is the reason it carries a contraindication in familial short QT syndrome instead of the QT-prolongation contraindication list the other three share. [2][1][3][4]

Classification and drug examples

Intro: Azoles split first by chemical generation (imidazole versus triazole) and then, more usefully for clinical purposes, by how far their spectrum extends beyond *Candida* into filamentous moulds.

1. Name: Narrow-spectrum triazole (*Candida*/*Cryptococcus*-focused)

1. Note: Highly selective for yeasts, with weak or absent activity against moulds.

Name: Fluconazole

Diflucan

Route: Oral or intravenous

Note: *Candida krusei* is intrinsically resistant, and *Candida glabrata* shows reduced susceptibility; not effective against *Aspergillus*. [1] [1]

2. Name: Broad-spectrum, mould-active triazole

2. Note: Extends coverage into *Aspergillus* and, for some members, other moulds and Mucorales, at the cost of a heavier interaction and monitoring burden.

1. Name: Itraconazole

Sporanox

1. Route: Oral

1. Note: An earlier mould-active triazole with well-documented hepatotoxicity, including rare cases of liver failure and death reported within the first week of treatment. [5]

2. Name: Voriconazole

Vfend

2. Route: Oral or intravenous

2. Note: First-line for invasive aspergillosis; also covers candidaemia, oesophageal candidiasis, and serious *Scedosporium* and *Fusarium* infections. [2]

3. Name: Posaconazole

Noxafil

3. Route: Oral (tablet, suspension) or intravenous

3. Note: Labelled for prophylaxis of invasive *Aspergillus* and *Candida* infections in severely immunocompromised patients, and for treatment of invasive aspergillosis and oropharyngeal candidiasis. [3]

4. Name: Isavuconazole (as isavuconazonium sulfate)

Cresemba

4. Route: Oral capsule or intravenous

4. Note: Indicated for invasive aspergillosis and invasive mucormycosis; the class's outlier for cardiac effect, causing QT shortening rather than prolongation. [4] [2][3][4]

Mechanism of action

Summary: Ergosterol is the fungal membrane's structural analogue of cholesterol in a mammalian membrane, and fungi cannot substitute cholesterol for it. Azoles interrupt ergosterol biosynthesis at a single, shared step: non-competitive inhibition of lanosterol 14-alpha-demethylase (CYP51), the cytochrome P450 enzyme that demethylates lanosterol so the pathway can continue toward ergosterol. Because human cells rely on a related but distinct cytochrome P450 enzyme for cholesterol synthesis, azoles have selective, though incomplete, toxicity toward fungal over human cells - the residual affinity for human CYP450 enzymes is exactly what produces this class's extensive drug-interaction profile.

Target: Fungal lanosterol 14-alpha-demethylase (CYP51)

Cidal Static: Generally fungistatic against *Candida* and fungicidal against some moulds depending on the specific drug and organism; not a uniform cidal/static profile across the class

Kill Kinetics: Effect depends on sustained ergosterol depletion over the fungal cell's growth cycle rather than an immediate lethal hit, which is part of why azole treatment courses run for weeks rather than days in invasive disease

1. Step: 1

1. Title: Lanosterol is produced early in the fungal sterol synthesis pathway

1. Detail: Fungal cells synthesise ergosterol from squalene through a multi-step pathway that passes through lanosterol as an intermediate. [6]

2. Step: 2

2. Title: Lanosterol 14-alpha-demethylase (CYP51) normally converts lanosterol toward ergosterol

2. Detail: This cytochrome P450 enzyme performs the demethylation step that the pathway needs to continue from lanosterol toward ergosterol. [6]

3. Step: 3

3. Title: The azole binds and non-competitively inhibits this enzyme

3. Detail: Fluconazole's own label describes it as 'a highly selective inhibitor of fungal cytochrome P450 dependent enzyme lanosterol 14-alpha-demethylase,' the mechanism shared across the whole class. [1]

4. Step: 4

4. Title: Ergosterol synthesis falls and lanosterol (and other methylated sterol precursors) accumulates

4. Detail: With the pathway blocked, the fungal membrane cannot maintain its normal ergosterol content and instead incorporates abnormal sterol intermediates. [6]

5. Step: 5

5. Title: The abnormal membrane loses integrity and normal function

5. Detail: A membrane with depleted ergosterol and abnormal sterol content becomes structurally compromised, which impairs membrane-bound enzyme function and increases permeability, ultimately arresting fungal growth or causing cell death depending on the organism and drug. [6]

Spectrum of activity

Intro: Spectrum is the single most clinically important axis on which this class divides, because every azole shares the same mechanism but each reaches a different set of organisms.

1. Subclass: Fluconazole

1. Covers: Most *Candida* species (vaginal, oropharyngeal, oesophageal candidiasis) and *Cryptococcus neoformans* (including cryptococcal meningitis in AIDS patients); used prophylactically in bone marrow transplant recipients to reduce candidiasis incidence.

1. Gaps: *Candida krusei* is considered intrinsically resistant; *Candida glabrata* shows reduced and dose-dependent susceptibility; no meaningful activity against *Aspergillus* or other moulds. [1]

2. Subclass: Voriconazole

2. Covers: Invasive aspergillosis (first-line per IDSA guidance), candidaemia in non-neutropenic patients and deep-tissue *Candida* infections, oesophageal candidiasis, and serious infections caused by *Scedosporium apiospermum* and *Fusarium* species.

2. Gaps: Not labelled for prophylaxis in the way posaconazole is, and its own extensive CYP450 interaction and monitoring burden narrows practical first-line use to situations where mould coverage is specifically needed. [2][7]

3. Subclass: Posaconazole

3. Covers: Prophylaxis of invasive *Aspergillus* and *Candida* infections in severely immunocompromised patients (HSCT recipients with GVHD, or haematologic malignancy with prolonged chemotherapy-induced neutropenia); treatment of invasive aspergillosis and oropharyngeal candidiasis.

3. Gaps: Its prophylactic indication is specifically for a defined high-risk population, not general antifungal prophylaxis. [3]

4. Subclass: Isavuconazole

4. Covers: Invasive aspergillosis and invasive mucormycosis, giving it *Mucorales* coverage that fluconazole and voriconazole do not have.

4. Gaps: Narrower labelled indication set than posaconazole (treatment of two specific invasive mould diseases rather than a broader prophylaxis label). [4]

Major clinical uses

1. Drug: Fluconazole

1. Organism: *Candida* species (not *C. krusei*), *Cryptococcus neoformans*

1. Indication: Vaginal, oropharyngeal and oesophageal candidiasis; cryptococcal meningitis; prophylaxis of candidiasis in bone marrow transplant recipients

1. Line: first-line for uncomplicated candidiasis and a mainstay for cryptococcal disease consolidation/maintenance

1. Note: Requires dose reduction in renal impairment. [1]

2. Drug: Itraconazole

2. Organism: Dermatophytes, *Candida*, *Blastomyces*, *Histoplasma*, some *Aspergillus*

2. Indication: Blastomycosis, histoplasmosis, and other indications set out in its own label

2. Line: an alternative mould-active option, tempered by hepatotoxicity concerns

2. Note: Rare hepatotoxicity reported within the first week of treatment in some cases. [5]

3. Drug: Voriconazole

3. Organism: *Aspergillus* species, *Candida* species, *Scedosporium apiospermum*, *Fusarium* species

3. Indication: Invasive aspergillosis, candidaemia, oesophageal candidiasis, serious *Scedosporium*/*Fusarium* infections

3. Line: first-line for invasive aspergillosis per IDSA guidance

3. Note: Requires monitoring for visual disturbance and hepatotoxicity; heavy CYP450 interaction burden. [2][7]

4. Drug: Posaconazole

4. Organism: *Aspergillus* species, *Candida* species

4. Indication: Prophylaxis of invasive *Aspergillus*/*Candida* infection in severely immunocompromised patients; treatment of invasive aspergillosis and oropharyngeal candidiasis

4. Line: prophylactic mainstay in defined high-risk haematology/transplant populations

4. Note: Substantially raises sirolimus levels; contraindicated with ergot alkaloids. [3]

- 5. Drug: Isavuconazole
- 5. Organism: Aspergillus species, Mucorales
- 5. Indication: Invasive aspergillosis, invasive mucormycosis
- 5. Line: option when mucormycosis coverage or a non-QT-prolonging azole is specifically needed
- 5. Note: Causes QT shortening; contraindicated in familial short QT syndrome. [4]

Pharmacokinetics

- 1. Drug: Fluconazole
 - 1. Route: Oral or IV
 - 1. Absorption: High oral bioavailability, largely unaffected by gastric pH
 - 1. Csf Penetration: See prescribing reference
 - 1. Metabolism: Minimal hepatic metabolism
 - 1. Elimination: Primarily renal, largely unchanged
 - 1. Dose Adjust: Dose reduced in renal impairment [1]
 - 2. Drug: Voriconazole
 - 2. Route: Oral or IV
 - 2. Absorption: Well absorbed orally
 - 2. Csf Penetration: See prescribing reference
 - 2. Metabolism: Hepatic, via CYP2C19, CYP2C9 and CYP3A4, with nonlinear (saturable) pharmacokinetics
 - 2. Elimination: Hepatic
 - 2. Dose Adjust: Hepatic impairment; concomitant CYP450 inhibitors/inducers; the IV vehicle accumulates in significant renal impairment [2]
 - 3. Drug: Posaconazole
 - 3. Route: Oral (tablet, suspension) or IV
 - 3. Absorption: Delayed-release tablet and IV forms are not interchangeable with the oral suspension because of different absorption characteristics
 - 3. Csf Penetration: See prescribing reference
 - 3. Metabolism: Hepatic glucuronidation; a CYP3A4 inhibitor rather than primarily a CYP3A4 substrate
 - 3. Elimination: Primarily faecal
 - 3. Dose Adjust: Formulation-specific dosing; hepatic impairment [3]
 - 4. Drug: Isavuconazole
 - 4. Route: Oral (as isavuconazonium sulfate) or IV
 - 4. Absorption: High oral bioavailability
 - 4. Csf Penetration: See prescribing reference
 - 4. Metabolism: Hepatic, via CYP3A4
 - 4. Elimination: Hepatic
 - 4. Dose Adjust: Hepatic impairment; concomitant strong CYP3A4 inhibitors or inducers [4]
1. This page gives no dose regimens by design. Loading doses, formulation-specific dosing (particularly for posaconazole's non-interchangeable formulations), and hepatic or renal dose adjustment belong in a current prescribing reference used by the treating clinician.
2. CYP450 involvement differs enough within this class to change which interactions matter for which drug: fluconazole is mainly an inhibitor (moderate CYP2C9/3A4, strong CYP2C19) rather than substrate, voriconazole is both a substrate and inhibitor of multiple CYP450 isoenzymes with nonlinear kinetics, and posaconazole acts mainly as a potent CYP3A4 inhibitor. [1][2][3]

Adverse effects

- 1. Effect: Gastrointestinal upset

1. Detail: Nausea, diarrhoea and abdominal pain are reported across the class. [6]
2. Effect: Mild to moderate transaminase elevation
2. Detail: Reported in clinical trials of posaconazole and across the class generally as the mildest end of the hepatotoxicity spectrum. [3]
3. Effect: Rash and pruritus
3. Detail: Allergic-type skin reactions are reported across the class. [6]
1. Effect: Visual disturbance
1. Detail: Approximately 21% of voriconazole-treated patients experienced abnormal vision, colour vision change and/or photophobia in trials, typically transient.
1. Action: Patients are counselled about the effect, particularly around driving or operating machinery at night, and it is monitored clinically. [2]
2. Effect: Hepatotoxicity, including hepatic failure
2. Detail: Uncommon but serious hepatic reactions - clinical hepatitis, cholestasis, and fulminant hepatic failure including fatalities - have occurred with voriconazole; itraconazole has caused hepatotoxicity including liver failure and death, in some cases within the first week of treatment; posaconazole causes hepatic transaminase elevation in trials; isavuconazole's label also warns of serious hepatic reactions requiring liver-function monitoring.
2. Action: The treating clinician checks liver function at baseline and during treatment. Marked abnormalities or symptoms of liver injury require prompt clinical assessment and a clinician-led decision about stopping or changing the azole. [2][5][3][4]
3. Effect: QT interval prolongation and torsades de pointes
3. Detail: Fluconazole, voriconazole and posaconazole are each associated with QT prolongation, with torsades de pointes specifically reported for posaconazole and voriconazole in their labels.
3. Action: The treating clinician assesses QT risk, corrects relevant electrolyte abnormalities and considers ECG monitoring where indicated. Suspected arrhythmia needs urgent medical assessment; any change to antifungal treatment is clinician-led. Several specific co-medications are contraindicated outright. [1][2][3]
4. Effect: QT interval shortening (isavuconazole only)
4. Detail: Isavuconazole shortens the QTc interval in a concentration-related manner, with mean differences from placebo of about -13.1 msec at standard dosing and -24.6 msec at higher doses in the trial data described in its label.
4. Action: Isavuconazole is contraindicated in patients with familial short QT syndrome because of this effect. [4]
5. Effect: Photosensitivity-associated skin malignancy
5. Detail: Squamous cell carcinoma of the skin and melanoma have been reported during long-term voriconazole therapy in patients with photosensitivity reactions.
5. Action: Sun exposure is minimised and skin is monitored during prolonged voriconazole therapy. [2]
1. Drug: Voriconazole
1. Effect: The class's most drug-specific adverse-effect signature: visual disturbance at high frequency and a long-term photosensitivity-linked skin cancer risk not described for the other azoles here. [2]
2. Drug: Isavuconazole
2. Effect: The class's cardiac outlier - QT shortening rather than prolongation, and a contraindication (familial short QT syndrome) that is the mirror image of the other azoles' QT-prolongation cautions. [4]
3. Drug: Posaconazole
3. Effect: The approximately nine-fold rise in sirolimus concentration and the ergot-alkaloid contraindication are specific, high-magnitude interactions not paralleled at the same scale by the other azoles discussed here. [3]
4. Drug: Itraconazole
4. Effect: Hepatotoxicity has occurred within the first week of treatment in some reported cases, a rapid-onset pattern specifically called out in its own label. [5]

Contraindications, precautions and interactions

1. Fluconazole: coadministration with drugs that prolong the QT interval and are metabolised via CYP3A4, specifically erythromycin, pimozide and quinidine. [1]
2. Voriconazole: coadministration with CYP3A4-dependent drugs including sirolimus, pimozide and quinidine, and with strong CYP450 inducers including rifampin and carbamazepine. [2]
3. Posaconazole: coadministration with sirolimus, ergot alkaloids, and CYP3A4 substrates such as pimozide and quinidine because of QTc prolongation and torsades de pointes risk. [3]
4. Isavuconazole: familial short QT syndrome, and coadministration with strong CYP3A4 inhibitors (e.g. ketoconazole, high-dose ritonavir) or strong CYP3A4 inducers (e.g. rifampin, carbamazepine, St. John's wort). [4]
1. Baseline and periodic liver function monitoring is standard with any mould-active azole given the hepatotoxicity signal across the class. [2][5][3][4]
2. Pre-existing QT prolongation, electrolyte disturbance, or concomitant QT-prolonging drugs are cautions for fluconazole, voriconazole and posaconazole specifically. [1][2][3]
3. Photosensitivity and long-term sun exposure are specific cautions during prolonged voriconazole therapy because of the reported skin-malignancy association. [2]
1. With: Sirolimus
 1. Effect: Voriconazole and posaconazole both raise sirolimus concentrations substantially (posaconazole by approximately nine-fold), and coadministration is contraindicated for both. [2][3]
2. With: Ergot alkaloids
 2. Effect: Posaconazole coadministration may cause ergotism and is contraindicated. [3]
3. With: Rifampin, carbamazepine and other strong CYP450 inducers
 3. Effect: Reduce voriconazole and isavuconazole exposure substantially; coadministration is contraindicated for both. [2][4]
4. With: Strong CYP3A4 inhibitors (e.g. ketoconazole, high-dose ritonavir)
 4. Effect: Raise isavuconazole exposure; coadministration is contraindicated. [4]

Resistance mechanisms

Intro: Azole resistance is a real and clinically relevant phenomenon rather than a theoretical one, and it clusters around two mechanisms recognised across medical mycology teaching: altered or overexpressed target enzyme, and drug efflux.

1. Mechanism: Intrinsic reduced susceptibility of specific Candida species
 1. Organism: Candida krusei (intrinsically resistant to fluconazole); Candida glabrata (reduced, dose-dependent susceptibility to fluconazole)
 1. Impact: Fluconazole's own label identifies C. krusei as a species that should be considered resistant, which is why identification to species level matters before choosing an azole for candidiasis. [1]
2. Mechanism: Alteration or overexpression of the CYP51 target enzyme, and efflux pump upregulation
 2. Organism: Various Candida and Aspergillus species, described generally in antifungal-mechanism literature
 2. Impact: Mutations in the CYP51 gene can reduce azole binding, and increased expression of fungal efflux pumps can lower intracellular azole concentration; both mechanisms reduce susceptibility across one or more azoles depending on the specific mutation or pump involved. [6]

Comparison tables

Title: Same target, different reach, different signature toxicity

Caption: Every azole here blocks the same enzyme, but spectrum and the drug-specific toxicity that matters most for monitoring differ sharply across the group.

1. Key: drug
1. Label: Drug
2. Key: mould_coverage
2. Label: Mould coverage
3. Key: signature_toxicity
3. Label: Signature toxicity
4. Key: cyp_role
4. Label: Main CYP450 role
1. Drug: Fluconazole
1. Mould Coverage: None (Candida/Cryptococcus-focused)
1. Signature Toxicity: QT prolongation
1. Cyp Role: Moderate CYP2C9/3A4, strong CYP2C19 inhibitor [1]
2. Drug: Voriconazole
2. Mould Coverage: Aspergillus, Scedosporium, Fusarium
2. Signature Toxicity: Visual disturbance; photosensitivity-linked skin cancer risk
2. Cyp Role: CYP2C19/2C9/3A4 substrate and inhibitor, nonlinear kinetics [2]
3. Drug: Posaconazole
3. Mould Coverage: Aspergillus (treatment and prophylaxis)
3. Signature Toxicity: QT prolongation; marked sirolimus interaction
3. Cyp Role: Potent CYP3A4 inhibitor [3]
4. Drug: Isavuconazole
4. Mould Coverage: Aspergillus and Mucorales
4. Signature Toxicity: QT shortening (not prolongation)
4. Cyp Role: CYP3A4 substrate [4]

High-yield exam pearls

1. Pearl: One mechanism, five different clinical personalities - every azole blocks CYP51, but that fact alone predicts nothing about which organism a given azole actually reaches.
1. Why: It is the single fact that makes spectrum, not mechanism, the right axis to organise this class around for clinical decision-making. [6]
2. Pearl: Candida krusei is intrinsically fluconazole-resistant - this is stated directly in fluconazole's own label, not just a general mycology footnote.
2. Why: It is a classic exam trap: species identification changes azole choice even before any acquired resistance testing is considered. [1]
3. Pearl: Isavuconazole shortens the QT interval; every other azole discussed here prolongs it.
3. Why: This single reversal is one of the most testable, counter-intuitive facts in the whole antifungal curriculum, and it is why isavuconazole's contraindication is short QT syndrome, not the QT-prolonging drug list the other azoles share. [4]
4. Pearl: Voriconazole's roughly 21% visual-disturbance rate is one of the highest-frequency labelled adverse effects in this entire page.
4. Why: It is common enough that patients should be counselled about it proactively, not treated as a rare idiosyncratic reaction. [2]
5. Pearl: Posaconazole raising sirolimus levels roughly nine-fold is a magnitude worth memorising as a number, not just as 'increases levels.'
5. Why: Numbers like this are what distinguish a clinically dangerous interaction from a theoretical one, and this one is large enough to be an outright contraindication. [3]

Common exam traps

1. Trap: Assuming fluconazole covers Aspergillus because it is 'a broad-spectrum antifungal.'
1. Correction: Fluconazole's own label describes it as highly selective and largely confined to Candida species and Cryptococcus neoformans; it has no meaningful role against Aspergillus, unlike voriconazole, posaconazole or isavuconazole. [1]
2. Trap: Treating the class-wide QT warning as uniform across every azole.
2. Correction: Isavuconazole is the specific exception: its label describes QT shortening, not prolongation, which is why its contraindication list (familial short QT syndrome) is the mirror image of fluconazole's, voriconazole's and posaconazole's QT-prolongation contraindications. [4][1]
3. Trap: Assuming voriconazole's visual disturbance means permanent vision loss.
3. Correction: The labelled effect (abnormal vision, colour vision change, photophobia) is typically transient and dose-related; the more serious, separate long-term risk with this drug is a photosensitivity-associated skin malignancy with prolonged therapy, not permanent visual impairment from the acute visual effect itself. [2]
4. Trap: Believing all azole hepatotoxicity looks the same across the class.
4. Correction: It spans a real range - from mild, asymptomatic transaminase elevation reported with posaconazole to reported hepatic failure and death with voriconazole and itraconazole - and itraconazole specifically has caused hepatotoxicity within the first week of treatment in some cases, an unusually rapid onset worth knowing as a drug-specific detail. [3][2][5]

Self-test questions

1. Question: What enzyme do all azole antifungals inhibit?
1. Squalene epoxidase
2. 1,3-beta-D-glucan synthase
3. Lanosterol 14-alpha-demethylase (CYP51)
4. Dihydrofolate reductase
1. Explanation: Every azole is a non-competitive inhibitor of fungal lanosterol 14-alpha-demethylase, the enzyme that converts lanosterol toward ergosterol in the fungal membrane synthesis pathway. [6][1]
2. Question: Which Candida species is intrinsically considered resistant to fluconazole?
1. Candida albicans
2. Candida krusei
3. Candida parapsilosis
4. Candida tropicalis
2. Explanation: Fluconazole's own prescribing information states that Candida krusei should be considered resistant to fluconazole. [1]
3. Question: Which azole is distinguished from the others by causing QT interval SHORTENING rather than prolongation?
1. Fluconazole
2. Voriconazole
3. Posaconazole
4. Isavuconazole
3. Explanation: Isavuconazole's label describes concentration-related QT interval shortening, the opposite cardiac effect from fluconazole, voriconazole and posaconazole, and it is contraindicated in familial short QT syndrome for this reason. [4]
4. Question: Approximately what proportion of voriconazole-treated patients experienced visual disturbance in labelled trial data?
1. About 1%

2. About 21%
3. About 50%
4. Visual disturbance was not reported
4. Explanation: Voriconazole's label states approximately 21% of patients experienced abnormal vision, colour vision change and/or photophobia. [2]
5. Question: Which drug interaction is specifically contraindicated with posaconazole because of an approximately nine-fold rise in the other drug's concentration?
 1. Warfarin
 2. Sirolimus
 3. Metformin
 4. Amoxicillin
5. Explanation: Posaconazole increases sirolimus concentrations by approximately nine-fold, and coadministration is contraindicated. [3]
6. Question: Which two organisms does voriconazole cover that fluconazole does not, according to its own labelled indications?
 1. Cryptococcus neoformans and Candida albicans
 2. Scedosporium apiospermum and Fusarium species
 3. Trichophyton and Microsporum
 4. Malassezia and Pityrosporum
6. Explanation: Voriconazole is labelled for serious infections caused by Scedosporium apiospermum and Fusarium species, in addition to invasive aspergillosis and candidiasis, none of which fluconazole reliably covers. [2]

Frequently asked questions

1. Question: Why don't all azoles just replace fluconazole if they cover more organisms?
 1. Answer: Broader mould coverage in voriconazole, posaconazole and isavuconazole comes with a heavier interaction and monitoring burden - CYP450 drug interactions, hepatotoxicity monitoring, and (for voriconazole) visual and long-term skin-cancer surveillance - that fluconazole's narrower, more predictable profile does not carry. For infections fluconazole's spectrum actually covers, its simpler profile is often preferred rather than automatically escalating to a broader-spectrum azole. [1][2][3]
 2. Question: Is isavuconazole safer for the heart than the other azoles?
 2. Answer: It avoids the QT-prolongation risk the other three azoles here carry, which is genuinely useful in a patient where that risk is a specific concern, but it introduces its own cardiac contraindication (familial short QT syndrome) because it shortens rather than prolongs the QT interval. It is a different cardiac risk profile, not simply a safer one in every patient. [4]
 3. Question: Does voriconazole's visual disturbance mean treatment should stop?
 3. Answer: Visual effects were common in trials (about 21% of patients) and are often transient, but new or concerning symptoms should be discussed with the treating clinician. That clinician assesses severity, other possible adverse effects and whether treatment should continue or change; patients should not make that decision from this guide. [2]
 4. Question: Why is posaconazole specifically used for prophylaxis rather than fluconazole in some high-risk patients?
 4. Answer: Posaconazole's label covers prophylaxis of invasive Aspergillus and Candida infections specifically in severely immunocompromised patients such as haematopoietic stem cell transplant recipients with graft-versus-host disease, a population where mould risk, not just Candida risk, is a real concern - a gap fluconazole's narrower spectrum does not close. [3]

References

[1] DIFLUCAN (fluconazole) - prescribing information. DailyMed, U.S. National Library of Medicine .
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f694c617-3383-416c-91b6-b94fda371204>

- [2] VFEND (voriconazole) - prescribing information. DailyMed, U.S. National Library of Medicine .
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ce3ef5cf-3087-4d92-9d94-9eb8287228db>
- [3] NOXAFIL (posaconazole) - prescribing information. DailyMed, U.S. National Library of Medicine .
<https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=b073b082-7b57-4423-8c06-4fd4263d6f84>
- [4] CRESEMBA (isavuconazonium sulfate) - prescribing information. DailyMed, U.S. National Library of Medicine .
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8f7f73b8-586a-4df0-935f-fecd4696c16c>
- [5] SPORANOX (itraconazole) capsule - prescribing information. DailyMed, U.S. National Library of Medicine .
<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a4d555fa-787c-40fb-bb7d-b0d4f7318fd0>
- [6] Antifungal Ergosterol Synthesis Inhibitors. StatPearls Publishing / NCBI Bookshelf .
<https://www.ncbi.nlm.nih.gov/books/NBK551581/>
- [7] Executive Summary: Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases / Infectious Diseases Society of America, via PubMed Central . <https://pmc.ncbi.nlm.nih.gov/articles/PMC4967611/>

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