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Systemic antifungal agents

By Sujitha Yadlapati, MD, and Leah Shama-Brown, DO

Name	Mechanism of action	Characteristics
	TRIAZOLES	
Itraconazole (Sporanox)	Blocks ergosterol synthesis by inhibiting **14 alpha-demethylase.** Fungistatic, lipophilic, needs an acidic milieu for absorption. Metabolized mainly in the liver **(CYP3A4).**	Side effects: ↑ LFTs, ↓ WBC, ↑ triglycerides, nephrotoxicity, **CHF worsening, caution with concurrent use of drugs metabolized via CYP3A4 (pimozide, quinidine, and cisapride).** Indications: dimorphic fungi, aspergillosis, candidiasis, superficial dermatophytosis, onychomycosis, sporotrichosis.
Voriconazole	Blocks ergosterol synthesis by inhibiting **14 alpha-demethylase.** **Inhibits cytochrome p450** (↑ levels of digoxin, cyclosporine)	Side effects: **Visual disturbances, severe phototoxicity (pseudoporphyria and xeroderma pigmentosum-like changes), increased risk of SCC,** QT prolongation, hepatotoxicity, periostitis with prolonged use. FDA recommends discontinuation of treatment in patients with skeletal pain or radiologic signs compatible with periostitis. Indications: **First line for invasive aspergillosis**, candida infections, fusarium infections
Fluconazole	Blocks ergosterol synthesis by inhibiting **14 alpha-demethylase.** **Inhibits cytochrome p450** (↑ levels of digoxin, cyclosporine). Potent **CYP2C9 inhibitor.**	Fungistatic, crosses blood–brain barrier. Indications: candidiasis (oral, esophageal, vaginal), tinea versicolor, cryptococcosis, histoplasmosis, superficial dermatophytosis, coccidioidomycosis.
Posaconazole	Blocks ergosterol synthesis by inhibiting **14 alpha-demethylase.**	FDA-approved for invasive aspergillus and candida prophylaxis.

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Name	Mechanism of action	Characteristics
	IMIDAZOLES	
Ketoconazole	Inhibits **14 alpha-demethylase** Fungistatic, lipophilic, needs acidic milieu for absorption, ↑absorption with food, **inhibits cytochrome p450.** Oral ketoconazole is discontinued in the United States due to hepatotoxicity and adrenal insufficiency.	Side effects: fulminant hepatitis (rare), ↑ LFTs, gynecomastia. Topical form indications: dermatophytosis, candidiasis, tinea versicolor, dimorphi fungi.
	ALLYLAMINES	
Terbinafine (Lamisil)	Inhibits **squalene epoxidase** (first step of ergosterol synthesis). Fungicidal**, inhibits CYP2D6** (exercise caution when giving with CYP2D6 substrates like doxepin or amitriptyline).	Side effects: nausea, metallic taste, idiosyncratic liver injury, **drug-induced subacute cutaneous lupus erythematosus, exacerbation of systemic lupus erythematosus.** Indications: onychomycosis, tinea corporis, tinea pedis.
	POLYENES	
Amphotericin B	Inhibits fungal cell wall synthesis through ergosterol binding and pore formation. Induces **cytochrome P-450**	Side effects: acute reaction after infusion (fever, chills, nausea, tachypnea), nephrotoxicity, agranulocytosis, seizures, arrhythmias, hypokalemia, hypomagnesemia. Indication: Drug of choice for treatment of mucormycosis. Ineffective against candidiasis, systemic mycosis, and pityrosporum.
	OTHERS	
Capsofungin	Inhibits **beta-(1,3)-D-glucan synthase** in the fungal cell wall.	IV administration Side effects: facial swelling, increase in alkaline phosphatase, hypokalemia, hematuria/ proteinuria. Indication: candidiasis and aspergillosis.
Griseofulvin	**Disrupts microtubule function**, causes metaphase arrest. Induces cytochrome p450 (may ↓ warfarin level). Fungistatic, ↑ absorption w/ fatty meal.	Side effects: GI disturbances, headaches are most common. Indication: dermatophytosis (more effective in **Microscoporum canis**, resistance noted to Trichophyton).

References:

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2. Bolognia J, Jorizzo J, Schaffer I. *Dermatology*. Philadelphia: Elsevier; 2017.