ANTIFUNGAL DRUGS

By

https://elearning.clinicalmedhub.com/department-of-clinical-medicine-surgery/

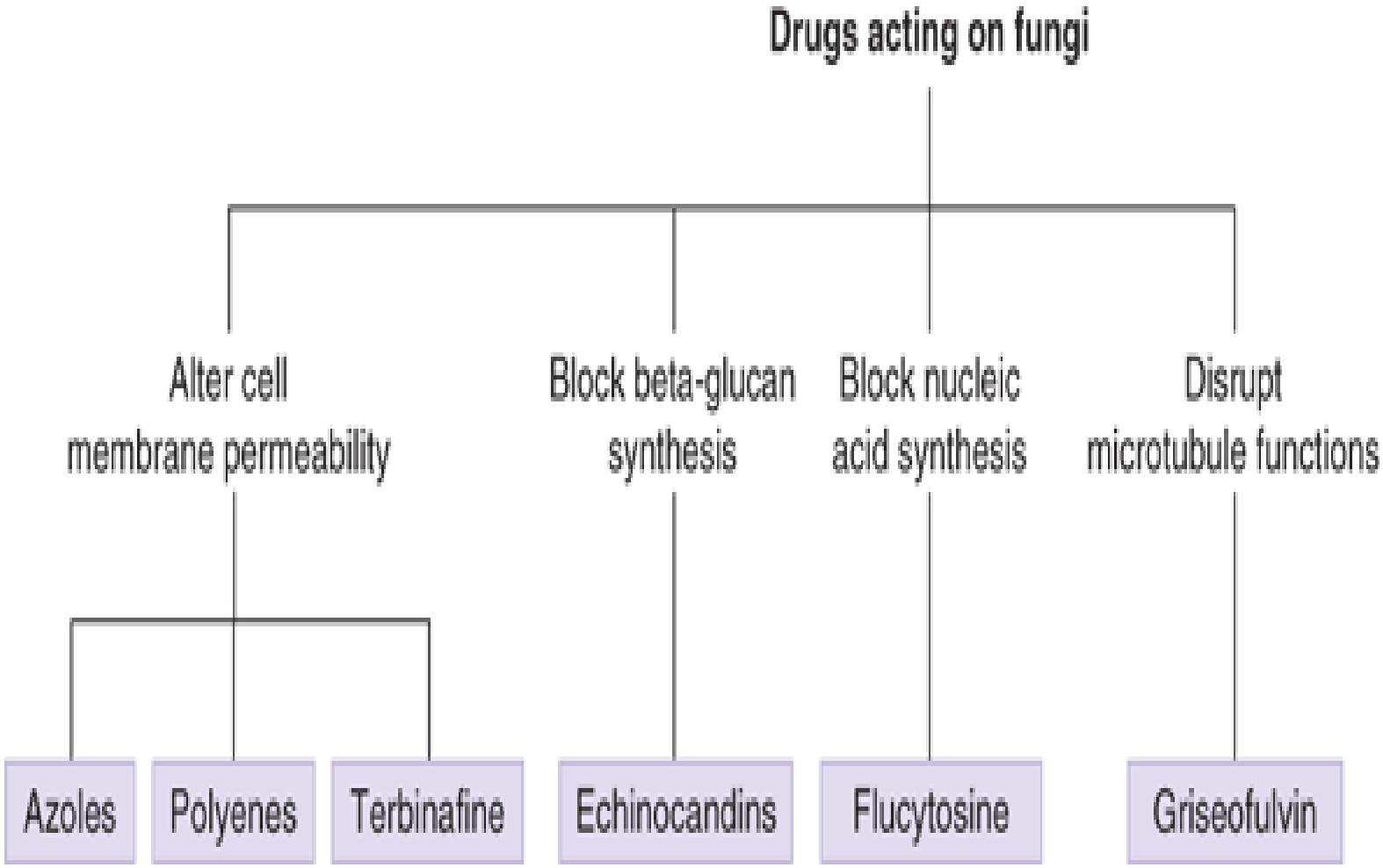
Antifungal drugs

- drugs that selectively eliminates **fungal pathogens** from a host with minimal toxicity to the host
- **Fungi**
  - have rigid cell walls
  - composed largely of **chitin** a polymer of **N-acetyl glucosamine** rather than peptidoglycan
  - cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes
- These chemical characteristics are useful in targeting chemotherapeutic agents against fungal infections

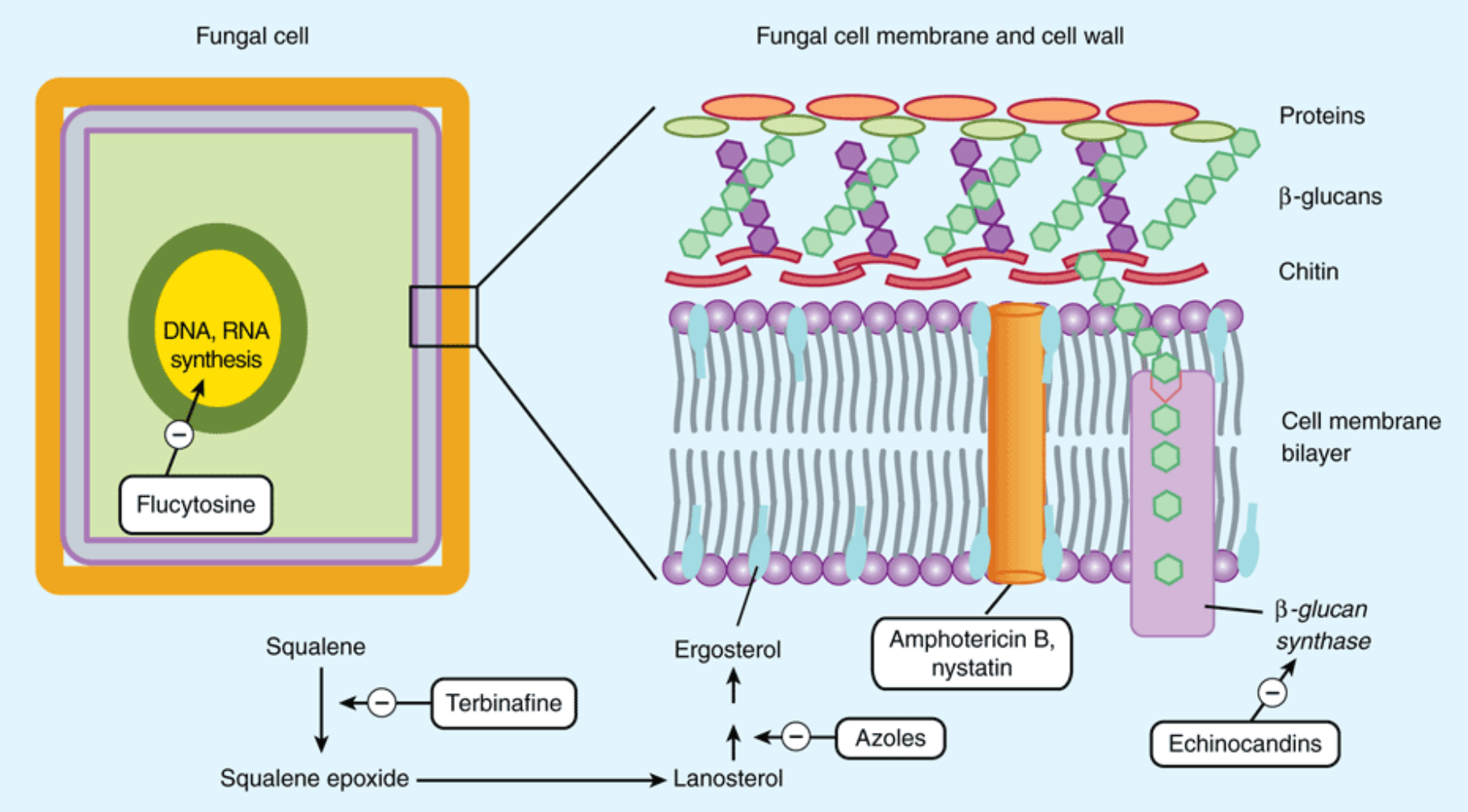
Classification of antifungal agents

- Polyene Antifungal Drugs
- Azole Antifungal Drugs
- Allylamine
- Antimetabolite Antifungal Drugs
- Other antifungal agents
  - Griseofulvin

Classification of antifungal agents



Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Figure: Mechanism of action of antifungal agents

Polyene Antifungal Drugs

- **Amphotericin**
- **Nystatin**
- **Pimaricin**

- **Mechanism of action**

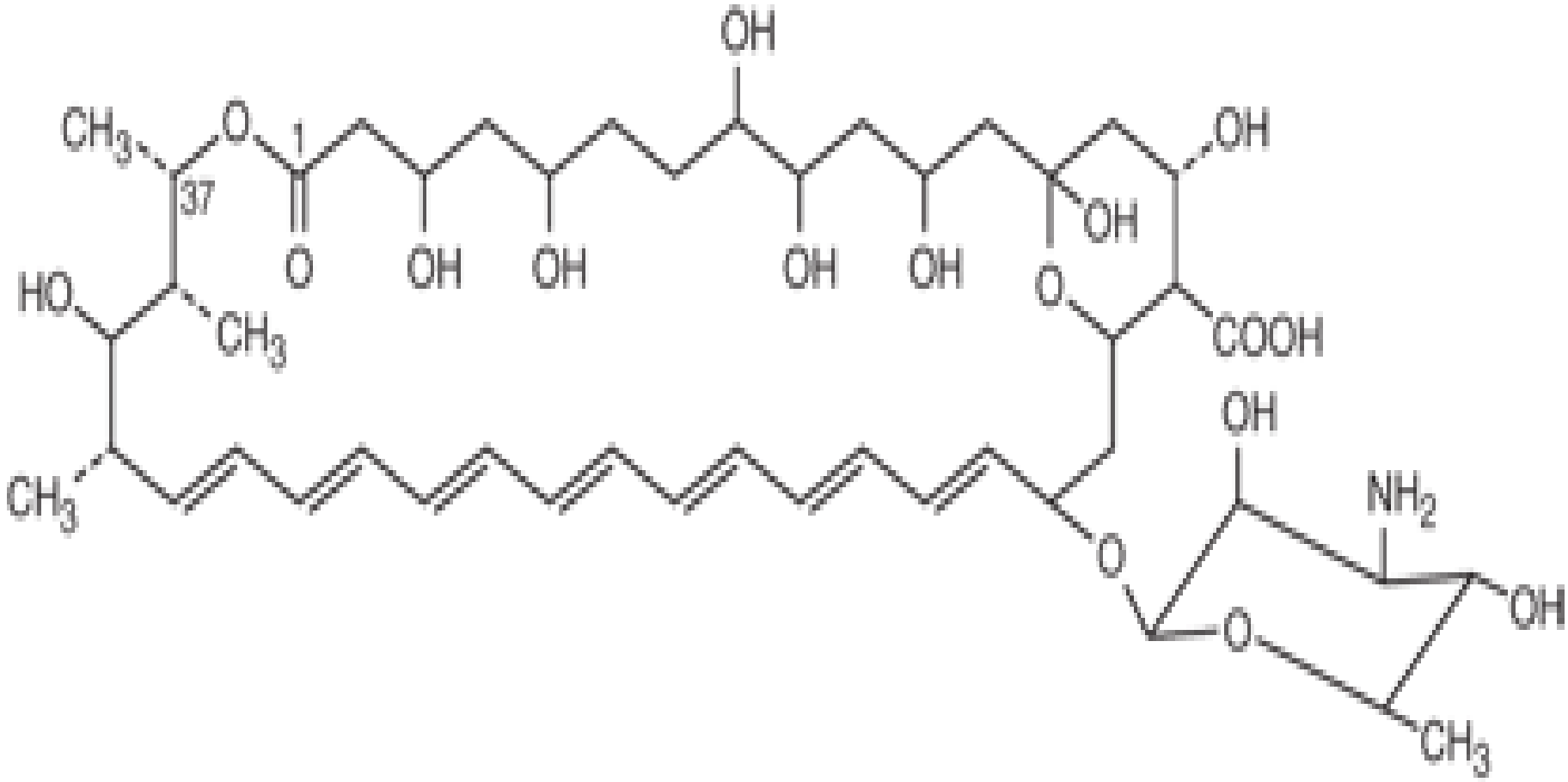
✔interact with sterols in the cell membrane (ergosterol in fungi, cholesterol in humans) to form channels through which small molecules leak from the inside of the fungal cell to the outside

Amphotericin B

- Amphotericin A and B
  - ✔ are antifungal antibiotics produced by Streptomyces nodosus (a filamentous bacterium)
- Amphotericin A is not in clinical use.

Chemistry & Pharmacokinetics of Amphotericin B

- an amphoteric polyene macrolide
  - polyene = containing many double bonds
  - macrolide = containing a large lactone ring of 12 or more atoms
- nearly insoluble in water
  - Hence, prepared as a colloidal suspension of amphotericin B & sodium desoxycholate for IV injection
- Polyenes are molecules with both hydrophilic & lipophilic characteristics (amphipathic)



Amphotericin B

Chemistry & Pharmacokinetics of Amphotericin B

- poorly absorbed from the GIT
  - Oral form is effective only on fungi within the lumen of the tract & cannot be used for treatment of systemic disease
- Placement of the active drug in a lipid delivery system (liposomal Amphotericin B) results in increased efficacy & decreased toxicity

mechanism of actions ----Amphotericin B

- Several *amphotericin B* molecules bind to ergosterol in the plasma membranes of sensitive fungal cells
- they form pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antibiotic and the sterol
- The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death
- Some binding to human membrane sterols does occur, probably accounting for the drug's prominent toxicity

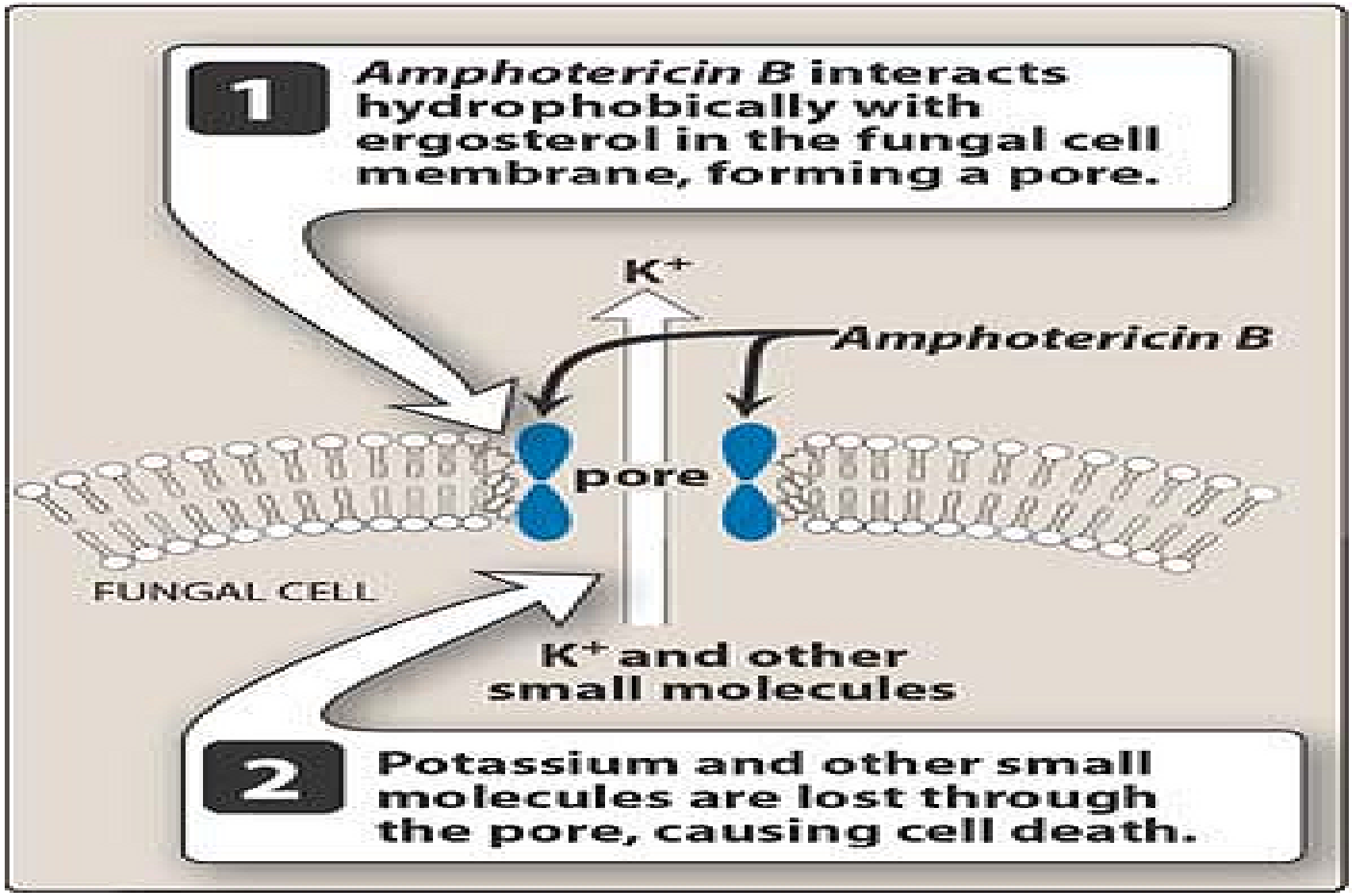


Figure: MOA of Amphotericin B

Resistance to amphotericin B

- occurs if ergosterol binding is impaired
  - ✔ either by decreasing the membrane concentration of ergosterol or
  - ✔by modifying the sterol target molecule to reduce its affinity for the drug.

Lipid Formulation of Amphotericin B

- Therapy with amphotericin B is often limited by toxicity, especially drug-induced renal impairment
- package the active drug in lipid delivery vehicles
- led to the development of lipid drug formulations on the assumption that lipid-packaged drug binds to the mammalian membrane less readily, permitting the use of effective doses of the drug with lower toxicity

Lipid Formulation of Amphotericin B

- The **lipid vehicle** then serves as an amphotericin reservoir, reducing nonspecific binding to human cell membranes
- have reduced nephrotoxic effects, possibly because of decreased binding of the drug to renal cells
- E.g AmBisome (3–5mg/kg/day), Amphotec (5mg/kg/day), Abelcet ((5mg/kg/day)
- **much more expensive**
  - Hence, their use is usually restricted to patients intolerant or not responding to conventional amphotericin treatment

Preparations

- **Amphotericin B** (conventional, 50mg/vial powder for injection)
- **Amphotericin B Desoxycholate** (powder for Injection, 50 mg/vial)
- **Amphotericin B phospholipid Complex**
  - Abelcet- Injectable, 5 mg/mL (dose: 5 mg/kg IV per day)
- **Amphotericin B Liposomal**
  - AmBisome- powder for Injection, 50 mg/vial (Dose: 3-5 mg/kg per day)

Antifungal Activity & Clinical Uses (Amphotericin B)

- broadest spectrum of action
- the drug of choice for the treatment of nearly all life-threatening mycotic infections (Amphotericin B Liposomal 3-5 mg/kg IV qDay)
- often used as the initial induction regimen to rapidly reduce fungal burden
  - Rx of severe cryptococcal meningitis in HIV pts (Amphotericin B Liposomal 6 mg/kg IV qDay)
  - Once a clinical response has been elicited, these patients then often continue maintenance therapy with an azole

Antifungal Activity & Clinical Uses (Amphotericin B)

- effective against a wide range of fungi, including Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans
- used in the treatment of the protozoal infection, visceral leishmaniasis
- For treatment of systemic fungal disease (0.5–1 mg/kg/d slow IV infusion amphotericin B)
- Mycotic corneal ulcers and keratitis (Local or topical administration)

Adverse effects —-Amphotericin B

- **Infusion-related toxicity**
  - Infusion-related reactions are nearly universal & consist of fever, chills, muscle spasms, vomiting, headache, and hypotension
- Can be ameliorated by
  - ➤ slowing the infusion rate
  - ➤decreasing the daily dose
  - ➤Premedication with antipyretics, antihistamines, or corticosteroids can be helpful
- administer a test dose of **1mg** IV to gauge the severity of the reaction

Adverse effects —Amphotericin B

- **Cumulative toxicity**
  - ✔Renal damage is the most significant toxic rxn
    - occurs in nearly all patients treated with clinically significant doses of amphotericin
    - **irreversible form of nephrotoxicity usually occurs in the setting of prolonged administration (> 4 g cumulative dose)**
    - pronounced with concurrent therapy with other nephrotoxins, such as an aminoglycoside
    - **causes renal tubular acidosis with magnesium & potassium wasting**

Adverse effects ---Amphotericin B

- Abnormalities of liver function tests (occasionally)
- Anemia (due to reduced erythropoietin production by damaged renal tubular cells)

ADMINISTRATION

- Reconstitute 50mg vial contents by adding 10ml sterile water for injection to obtain a 5mg/ml solution. Add sterile water for injection rapidly & shake immediately until the colloidal dispersion is clear.
- For IV infusion, dilute further (usually to 0.1mg/ml) with 500ml 5% dextrose. Infuse over 2-6 hrs. protect from light.
- Dry form stored at 2-8 degrees celsius

Nystatin

- a polyene macrolide much like amphotericin B
- too toxic for parenteral administration & is only used topically
- available in suspension, creams, ointments, suppositories, for application to skin & mucous membranes
- not absorbed to a significant degree from skin, mucous membranes, or the GIT
- oral use is often limited by the unpleasant taste

Preparations of Nystatin

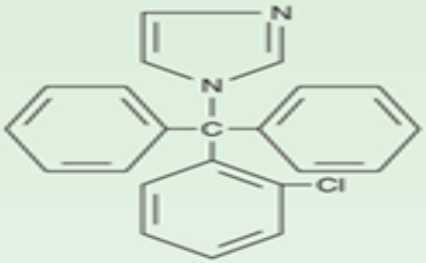
- Oral powder:100,000 units/kg
- Oral suspension : 100,000 units/ml
- Oral tablets: 500,000 units
- Capsules: 500,000 units, 1,000,000 units

Nystatin

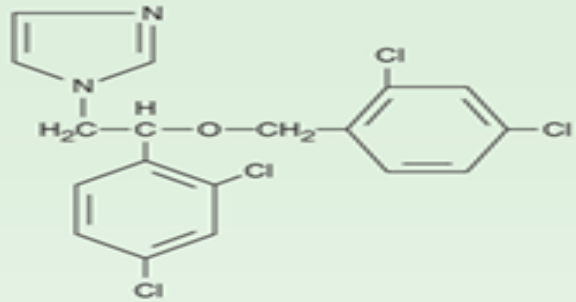
- disrupts fungal membranes by binding to ergosterol
- active against most Candida sp
  - Oropharyngeal candidiasis (oral suspension: 400,000-600,000 units PO q6hr: swish in mouth several minutes and then swallow)
  - Intestinal candidiasis (oral tablets: 500,000 -1,000,000 units PO q8hr
- commonly used for suppression of local candidal infections such as oropharyngeal thrush, vaginal candidiasis
- Administration: retain suspension in mouth as long as possible before swallowing

Azole Antifungal Drugs

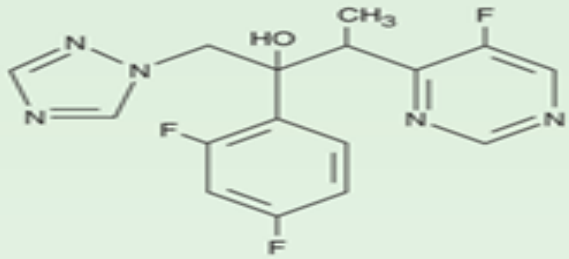
- synthetic compounds that can be classified as either imidazoles or triazoles according to the number of nitrogen atoms in the five-membered azole ring
- **imidazoles**
  - ketoconazole, miconazole, clotrimazole
- **triazoles**
  - itraconazole, fluconazole, voriconazole, and posaconazole



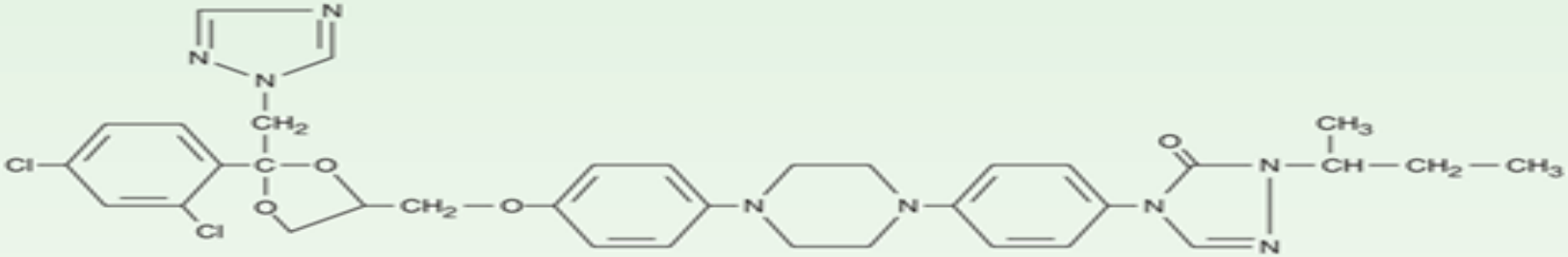
Clotrimazole



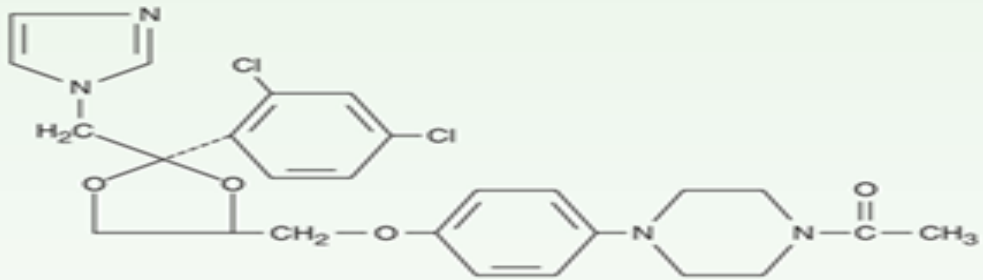
Miconazole



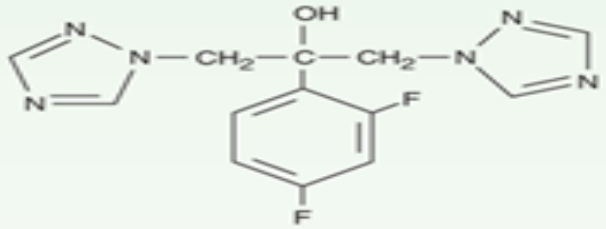
Voriconazole



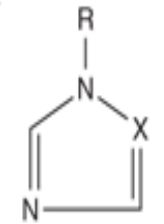
Itraconazole



Ketoconazole



Fluconazole

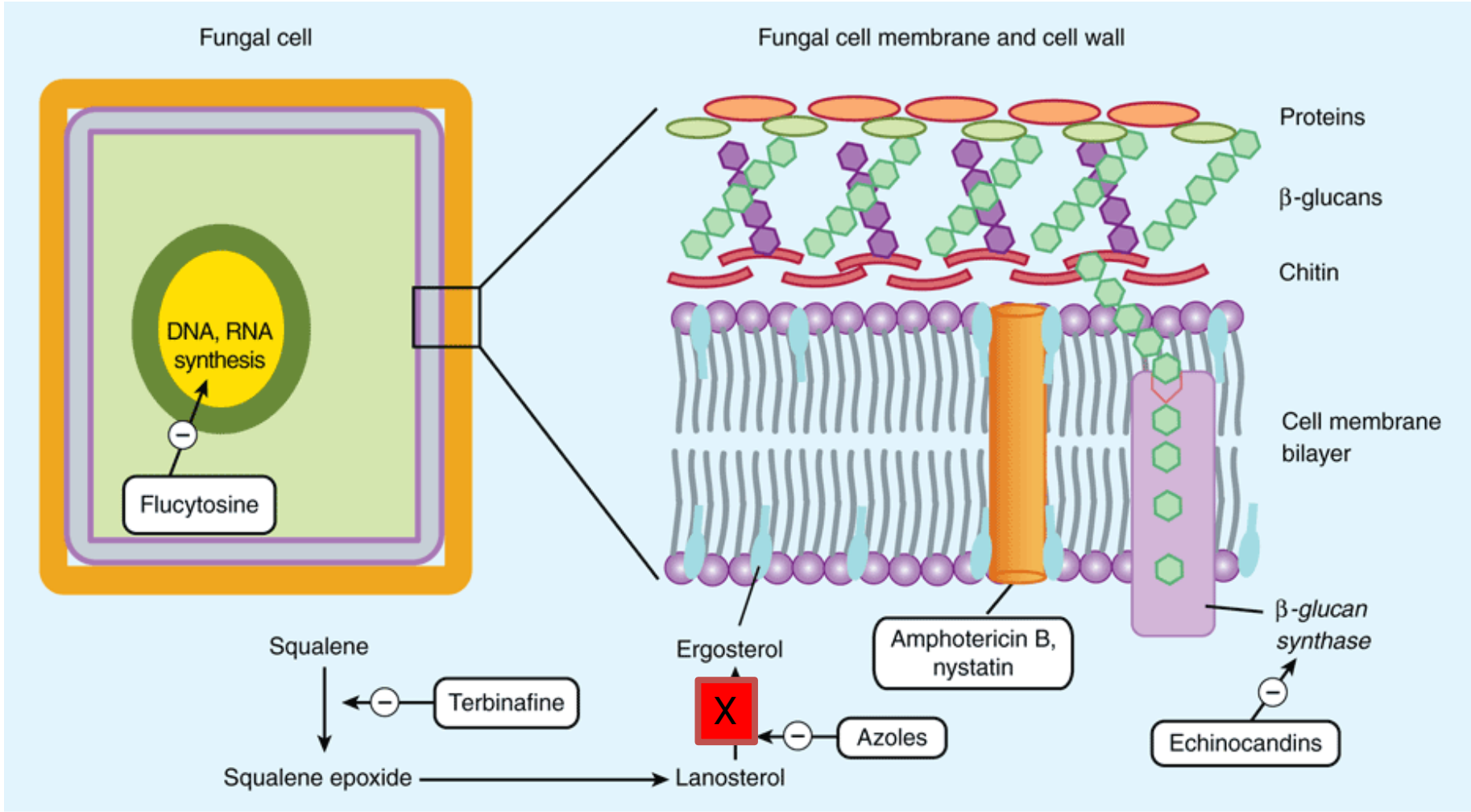


X = C, imidazole
X = N, triazole

Azole nucleus

Azole Antifungal Drugs

- **Mechanism of action**
  - ➤reduction of ergosterol synthesis by inhibition of fungal CYP450 (C14-demethylase)
- selective toxicity results from their greater affinity for fungal than for human CYP450 enzymes
  - Imidazoles exhibit a lesser degree of selectivity than the triazoles, accounting for their higher incidence of drug interactions & adverse effects.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Ketoconazole

- the first oral azole introduced into clinical use.
- greater propensity to inhibit mammalian CYP450 enzymes
- less selective for fungal P450 than the newer azoles
- Dosage form & strength: 200mg tablet, 2% cream

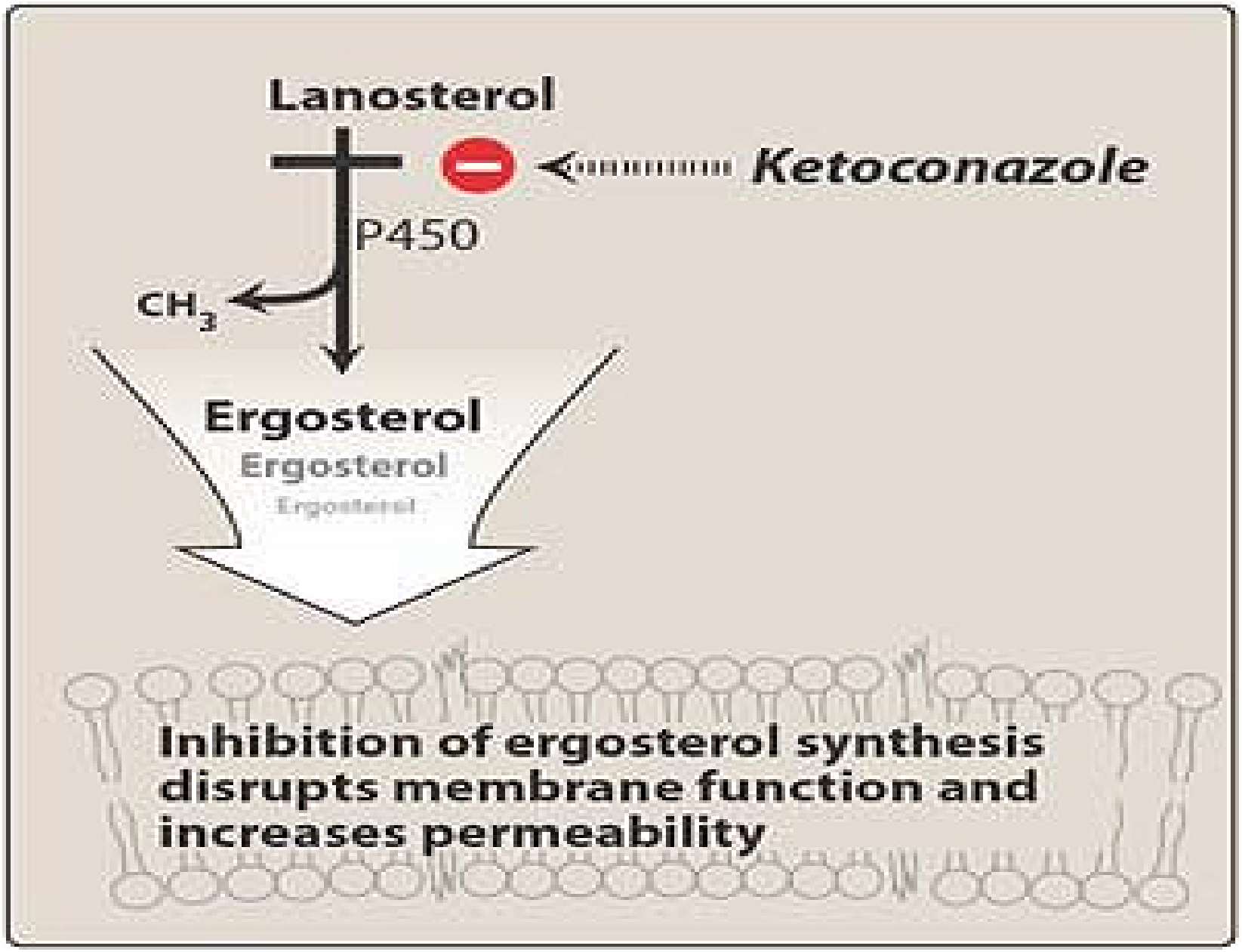


Figure: Mode of action of *ketoconazole*

Mechanisms of resistance– Ketoconazole

- Mutations in the C-14 α demethylase gene, which cause decreased azole binding
- pump the azole out of the cell (some strains of fungi)

Pharmacokinetics: Ketoconazole

- requires gastric acid for dissolution
  - ❖ Drugs that raise gastric pH, such as antacids, or that interfere with gastric acid secretion, such as H2-histamine receptor blockers and proton-pump inhibitors, impair absorption
- penetrates poorly into CSF (should not be used for fungal meningitis)
- Metabolized in the liver
- excretion is primarily through the bile

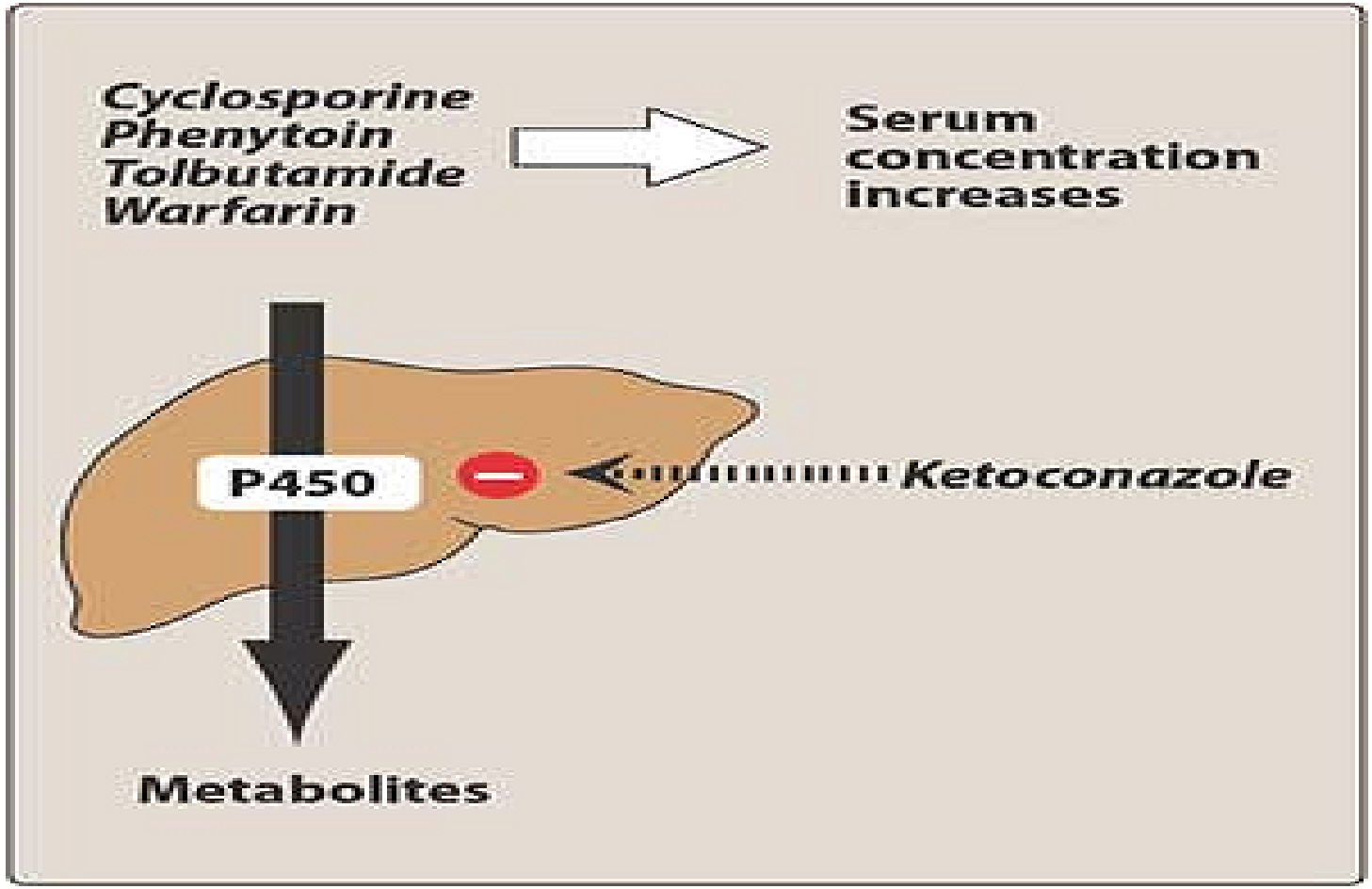
Ketoconazole : clinical uses

- narrow antifungal spectrum and causes more adverse effects than other azoles
- used for chronic mucocutaneous candidiasis and is also effective against dermatophytes (apply q day for two weeks
- effective in the treatment of histoplasmosis in lung, bone, skin, and soft tissues
  - Initial dose: 200 mg orally once a day. If clinical responsiveness insufficient within expected time:
  - Dose may be increased to 400 mg orally once a day.
  - Duration of therapy: 6 months (usual duration for systemic infection)
- Cushing syndrome (off label use)
  - 600-800 mg/day po

Adverse effects: Ketoconazole

- Allergies
- dose-dependent gastrointestinal disturbances
  - such as nausea, anorexia, and vomiting (most common)
- Endocrine effects
  - such as gynecomastia, decreased libido, impotence, and menstrual irregularities

Drug interactions: Ketoconazole



Rifampin can shorten the duration of action of *ketoconazole*

Drug interactions: Ketoconazole

- Drugs that decrease gastric acidity
  - such as H2-receptor blockers, antacids, PPIS & sucralfate, can decrease absorption
- Ketoconazole & amphotericin B should not be used together
  - because the decrease in ergosterol in the fungal membrane reduces the fungicidal action of amphotericin B

Itraconazole

- broad antifungal spectrum
- lacks the endocrinologic side effects of ketoconazole
- well-absorbed orally, but it requires acid for dissolution
- Available formulations
  - 100mg capsule
  - 10 mg/ml oral solution

Itraconazole

- interacts with hepatic microsomal enzymes, though to a lesser degree than ketoconazole
- Poor penetration into the CSF
- used at a dosage of 100–400 mg/d
- extensively used in the treatment of dermatophytoses & onychomycosis

Itraconazole: clinical Indications

- ✔ Blastomycosis
  - 200 mg/ PO TID initially for 3 days, then 200 mg PO /day for 6-12 months
- ✔ Aspergillosis
  - 200-400 mg PO /day
- ✔ Histoplasmosis (200 mg PO/day)
- ✔ Onychomycosis
  - Finger nails-200 mg q 12hr for 1week
  - Toe nails--200 mg PO/day for 12 weeks

Fluconazole

- displays a high degree of water solubility & good CSF penetration
- High oral bioavailability unlike ketoconazole & itraconazole
- less common drug interaction (the least effect of all the azoles on hepatic microsomal enzymes)
- has the widest therapeutic index of the azoles, permitting more aggressive dosing in a variety of fungal infections
- lack endocrine side effects (does not inhibit the CYP450 system responsible for the synthesis of androgens)

Fluconazole

- absorption is not dependent on gastric acidity
- available in oral & IV formulations
  - Oral suspension(10mg/ml, 40mg/ml)
  - injection(2mg/ml)
  - tablet (50,100,150,200 mg)
- used at a dosage of 100–800 mg/d

Fluconazole: clinical Indications

- **esophageal candidiasis**
  - 200 mg/po on day 1, then 100 mg q day for 2 weeks
- **oropharyngeal candidiasis**
  - 200 mg/po on day 1, then 100 mg q day for 3wks & for at least 2wks following resolution of symptoms
  - doses up to 400mg/day may be used based on patient's response
- cryptococcal meningitis
  - 400 mg/po on day 1, then 200 mg q day for 10-12 weeks
- vaginal candidiasis
  - uncomplicated (150 mg PO stat.)
  - Complicated (150 mg PO every 72hr for 3 doses)

Fluconazole: clinical Indications

- equivalent to amphotericin B in candidemia (400 mg/po q day)
- no activity against Aspergillus or other filamentous fungi.

Voriconazole

- available in intravenous & oral formulations
  - 200 mg/5 ml oral suspension, 200 mg injection powder, 50 mg, 200mg tabs
- recommended dosage is 400 mg/d
- well absorbed orally, with a bioavailability exceeding 90%
- Metabolism is predominantly hepatic
- clinically relevant inhibitor of mammalian CYP3A4

Voriconazole

- dose reduction of cyclosporine, tacrolimus, and HMG-CoA reductase inhibitors required when voriconazole is started

Clinical uses: Voriconazole

- similar to itraconazole in its spectrum of action
- excellent activity against Candida sp (including fluconazole-resistant species such as Candida krusei) & the dimorphic fungi
  - 6mg/kg IV q12hr for the 1st 24 hrs, then 4 mg/kg IV q12hr or 200 mg PO q12hr
- treatment of choice for invasive aspergillosis
  - 6mg/kg IV q12hr for the 1st 24 hrs, then 4 mg/kg IV q12hr or 200 mg PO q12hr
- Esophageal candidiasis (200 mg PO q12hr)

Adverse effects: Voriconazole

- rash
- elevated hepatic enzymes
- Visual disturbances (occur in up to 30% of patients receiving IV dose)
- Photosensitivity dermatitis (commonly observed in patients receiving chronic oral therapy)

Posaconazole

- the newest triazole
- Preparations (400mg/ml, 100 mg tab, 18 mg/ml injectable solutions)
- Absorption is improved when taken with meals high in fat

Posaconazole–– clinical uses

- broadest spectrum of activity
- active against most species of Candida & Aspergillus
  - Oral solution: 200 mg(5ml) PO TID
  - **Tablet:** 300mg PO BID on day 1, then 300 mg/day
  - **IV:** 300mg PO BID on day 1, then 300 mg/day
- The only azole with significant activity against the agents of mucormycosis
- Oropharyngeal candidiasis
  - 100mg (2.5 ml) PO BID on day 1, **then 100 mg/day x 13 days**

Topical azoles

- **clotrimazole & miconazole**
  - ✔Both are available OTC & are often used for vulvovaginal candidiasis
  - ✔Oral clotrimazole troches are available for treatment of oral thrush and are a pleasant-tasting alternative to nystatin
  - ✔In cream form, both agents are useful for dermatophytic infections, including tinea corporis (hair), tinea pedis, & tinea cruris (groin)
  - ✔Absorption is negligible

FLUCYTOSINE

MECHANISM OF ACTION

- 5-flucytosine, 5-FC) is an analogue of cytosine that was originally synthesized for possible use as an antineoplastic agent.
- Converted within the fungal cell to **5- fluorouracil**(Not in human cell), by the fungal enzyme **cytosine deaminase** that **inhibits thymidylate synthetase** enzyme that **inhibits DNA synthesis**.
- (Amphotericin B **increases cell permeability ,** allowing more 5-FC to penetrate the cell, they are synergistic).

Flucytosine

- Spectrum of Activity
  - Active against
    - *Candida* species except *C. krusei*
    - *Cryptococcus neoformans*
    - *Aspergillus* species
  - Synergy with amphotericin B has been demonstrated
    - The altered permeability of the fungal cell membrane produced by amphotericin allows enhanced uptake of flucytosine

- Mechanisms of Resistance
  - Loss of cytosine deaminase that permits flucytosine to cross the fungal cell membrane
  - Loss of any of the enzymes required to produce the active forms that interfere with DNA synthesis
  - Resistance occurs frequently and rapidly when flucytosine is given as monotherapy. Combination therapy is necessary

Pharmacokinetics

- Half-life
  - 2 to 5 hours in normal renal function
  - 85 hours in patients with anuria
- Distributes into tissues, CSF, and body fluids
- Toxicities
  - Bone marrow suppression (dose dependent)
  - Hepatotoxicity (dose dependent)
  - Enterocolitis

  Toxicities occur more commonly in patients with renal impairment
- Flucytosine concentrations should be monitored especially in patients with changing renal functions
- **Contraindications**
  - Known hypersensitivity (anaphylaxis has been reported)
  - Pre-existing bone marrow depression **(antiproliferative action)**
  - Pregnancy

Adverse effects

- Moderate hypoplasia of the bone marrow resulting in
  - anaemia, leukopenia, pancytopenia, thrombocytopenia, or rarely agranulocytosis may occur.
- Death from aplastic anaemia has been reported.
- Nausea, vomiting, anorexia, abdominal bloating, diarrhoea, and rarely bowel perforation, and rash have also been reported.
- Confusion, hallucinations, headaches, sedation, vertigo, and liver enlargement have been reported more rarely.

Indications

- Flucytosine is indicated only in the treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus.*
- ***Candida***
- Septicemia, endocarditis and urinary system infections have been effectively treated with Flucytosine..

- ***Cryptococcus***

Meningitis and pulmonary infections have been treated effectively. Studies in septicemias and urinary tract infections are limited, but good responses has been reported.

Indications and Doses

Candidiasis/Cryptococcus Infection

- 50-150 mg/kg/d div q6hr PO
- Adjust dose for renal dysfunction

Candidiasis/Cryptococcus Infection

- Child: same as adult dosing; 50-150 mg/kg/d div q6hr PO
- Neonates (<28 days old): 80-160 mg/kg/d div q6hr PO
- Adjust dose for renal dysfunction

Dosage forms

- Capsule

strength 250mg and 500mg.

- Injection then it is diluted in 250mL saline solution to make it equivalent to 2.5 g (10mg/mL). Amphotericin B is one of the many drugs that are physically incompatible with this solution.

Drug interactions

- Possible additive toxicity with other myelosuppressive drugs e.g. zidovudine, ganciclovir, pyrimethamine, sulphonamides etc.
- The dose of flucytosine needs to reduced in renal failure. Therefore caution with nephrotoxic drugs e.g. amphotericin B, foscarnet and pentamidine..

Overdosage

- In the event of flucytosine overdosage the manufacturer recommends prompt use of **gastric lavage or an emetic.**
- Because flucytosine is eliminated essentially unchanged in urine, **adequate fluid intake** should be maintained and **IV fluids** given if necessary.
- **Haematological parameters** should be assessed frequently and liver and kidney function carefully monitored. Consideration should be given to the use of **haemodialysis**, which readily removes the drug in anuric patients

ECHINOCANDINS

INTRODUCTION

- Echinocandins is the first class of antifungals to target the **fungal cell wall**.
- Echinocandins were discovered as fermentation metabolites with antifungal activity during screening programs for new antibiotics.
- The candidate molecules were subsequently modified to improve solubility, antifungal spectrum of activity, and pharmacokinetic characteristics.
- Three semi-synthetic echinocandin derivatives have been developed for clinical use: **caspofungin, micafungin** and **anidulafungin.**

CONT…

- They **inhibit the synthesis of β-D-glucan** in fungal cell walls. Their strengths **include low toxicity, rapid fungicidal activity against most isolates of *Candida* spp. and predictable favourable kinetics allowing once a day dosing.** In addition to *Candida*spp., their inhibitory spectrum includes *Aspergillus* spp. and *Pneumocystis carinii*, but not *Cryptococcus neoformans*

MECHANISM OF ACTION

- Echinocandins noncompetitively inhibit **beta-1,3-D-glucan synthase enzyme** complex in susceptible fungi to disturb **fungal cell glucan synthesis**.Beta-glucan destruction prevents resistance against osmotic forces, which leads to cell lysis. They have **fungistatic** activity against *Aspergillus* species. and fungicidal activity against most *Candida* spp., including strains that are fluconazole-resistant. .

Echinocandins

	Caspofungin	Micafungin	Anidulafungin
Absorption	Not orally absorbed. IV only		
Distribution	Extensive into the tissues, minimal CNS penetration		
Metabolism	spontaneous degradation, hydrolysis and N-acetylation		Chemical degradated
Elimination	Limited urinary excretion. Not dialyzable		
Half-life	9-23 hours	11-21 hours	26.5 hours
Dose	70 mg IV on day 1, then 50 mg IV daily thereafter	100 mg IV once daily	200 mg IV on day 1, then 100 mg IV daily thereafter
Dose Adjustment	<u>Child-Pugh 7-9</u> 70 mg IV on day 1, then 35 mg IV daily thereafter <u>CYP inducers</u> 70 mg IV daily	None	None

Indications

Casponfungin

- First line treatment of invasive candida infections
- Treatment of invasive aspergillosis in patients who are refractory or intolerant to other therapies
  - 40% efficacy

Micafungin

- Esophageal candidiasis
- Prophylaxis of Candida infection in patients undergoing stem cell transplant
- Candidemia or invasive candidiasis

Anidulafungin

- Esophageal candidiasis
- Candidemia

Adverse effects

- Generally well tolerated
- Phlebitis, GI side effects, Hypokalemia
- Abnormal liver function tests
- Caspofungin
  - Tends to have higher frequency of liver related laboratory abnormalities
  - Higher frequency of infusion related pain and phlebitis

Interactions

- **Caspofungin**
  - Not an inducer or inhibitor of CYP enzymes
  - CYP inducers (i.e. phenytoin, rifampin, carbamazepine)
    - Reduced caspofungin levels
      - Increase caspofungin dose
  - Cyclosporine
    - Increases AUC of caspofungin
    - Hepatotoxicity
      - Avoid or monitor LFTs
  - Tacrolimus
    - Reduced tacrolimus levels by 20%
      - Monitor levels of tacrolimus
- **Micafungin**
  - Minor substrate and weak inhibitor of CYP3A4
  - Nifedipine
    - Increased AUC (18%) and Cmax (42%) of nifedipine
  - Sirolimus
    - Increased concentration of sirolimus
- **Anidulafungin**
  - No clinically significant interactions

ALLYLAMINES

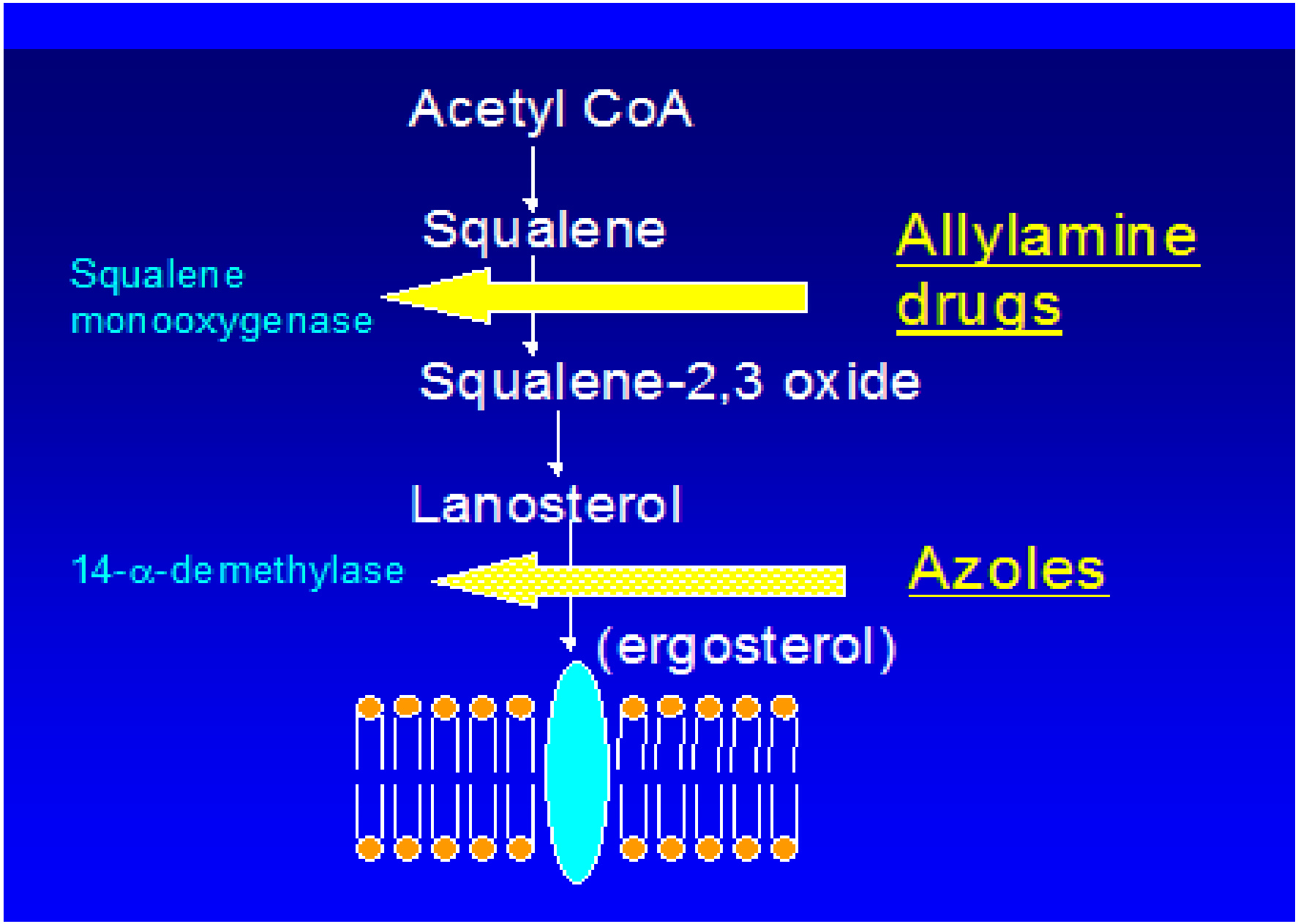
Introduction

Allylamines inhibit the enzyme squalene epoxidase, another enzyme required for ergosterol synthesis:

- **Terbinafine - marketed as Lamisil**
- Amorolfine
- Naftifine
- Butenafine

Mechanism of action

- Non competitive inhibitor **squalene epoxidase**, an earlier step in ergosterol synthesis by fungi accumulation of squalene within fungal cells appears responsible for fungicidal activity


Acetyl CoA
Squalene
Squalene monooxygenase
Allylamine drugs
Squalene-2,3 oxide
Lanosterol
14-α-demethylase
Azoles
(ergosterol)

TERBINAFINE

INTRODUCTION

- Inhibits squalene 2, 3- epoxidase. Squalene is fungicidal to sensitive organisms. CYP450 independent
- Fungicidal AND Fungistatic
- Shorter courses of therapy required
- Low relapse rate
- Metabolized by liver, excreted in urine
- Adverse effects include hepatitis and rashes. Both are rare.

Pharmacokinetics

- Approx 75% absorbed orally but only 5% from unbroken skin
- First pass metabolism further reduces oral bioavailability
- Lipophillic and widely distributed in the body
- Strongly plasma protein bound and concentrated in the sebum, stratum corneum and nail plates

- 80% excreted in urine and 20% in feaces
- Clearance is reduced in moderate and hepatic impairment
- Half life – 11-16 hours prolonged after repeated dosing
- Terbinafine accumulates in breast milk and, therefore, should not be given to nursing mothers
- Not recommended in azotemia or hepatic failure

Side effects

ORAL TERBINAFINE

- Gastric upset
- Taste disturbance
- Hepatic disorder
- Hematological disorder

Interactions

- Enzyme inducers lower and enzyme inhibitors increase its blood concentrations. Eg:
  - Rifampicin decreases its blood concentrations
  - Cimetidine increases its blood concentrations

Indications

- Onychomycosis (fungal infections of nails). 250 mg daily for 6weeks for finger nail infection and for 12 weeks in toe nail infection
- Tinea pedis/corporosis/crurisis/capitis and pityriasis versicolor – applied topicaally as 1% cream or orally 250mg OD 2-6 weeks treatment depending on site of infection

Dosage Forms

- 250mg oral tablet – lamisil, sebiifin
- 1% topical cream - exifine

HETEROCYCLIC ANTIFUNGALS

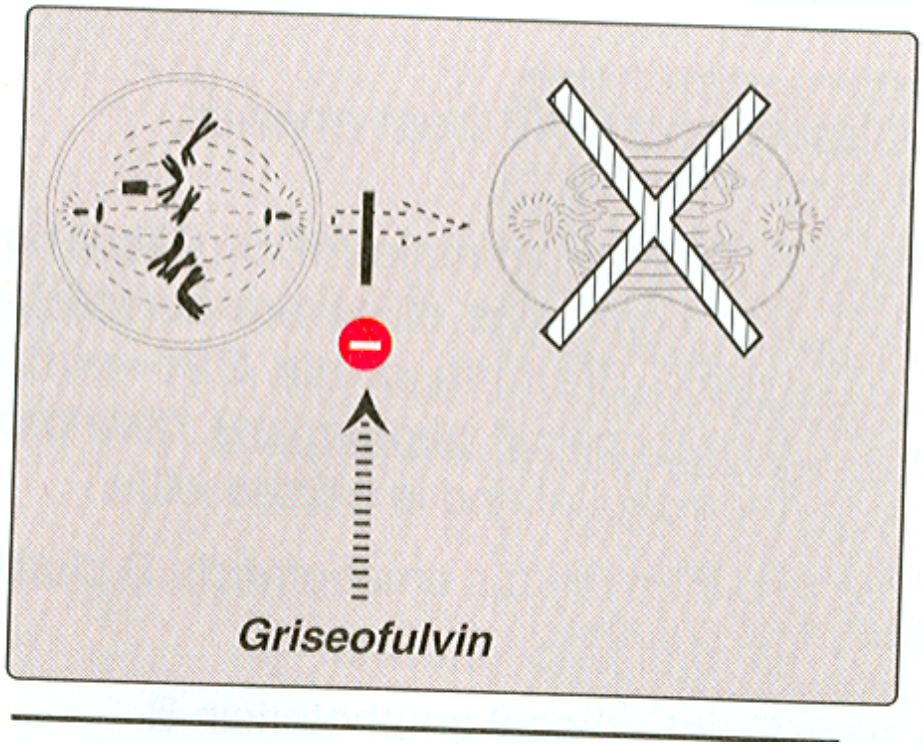
GRISEOFULVIN

Introduction

- A very insoluble fungistatic drug derived from *Penicillium griseofulvum.*
- It is active against most dermatophytes including *Epidermophylon, Tricophyton, Microsporum* etc but not effective against candida and other fungi causing deep mycosis
- Bacteria are also insensitive
- Very insoluble in water
- Dermatophytes actively concentrate it, which probably accounts for its selective toxicity
- Resistance can occur if concentrating ability is lost however emergence of resistance is rare during clinical use

Mechanism of action

- Binds to microtubules and prevents spindle formation and mitosis in fungi. Multi-nucleated and stunted fungal hyphae result from its action.
- It also causes abnormal metaphase configuration, however unlike the typical mitotic inhibitors (colchicine, vinca alkaloids), it does not cause metaphase arrest


Griseofulvin

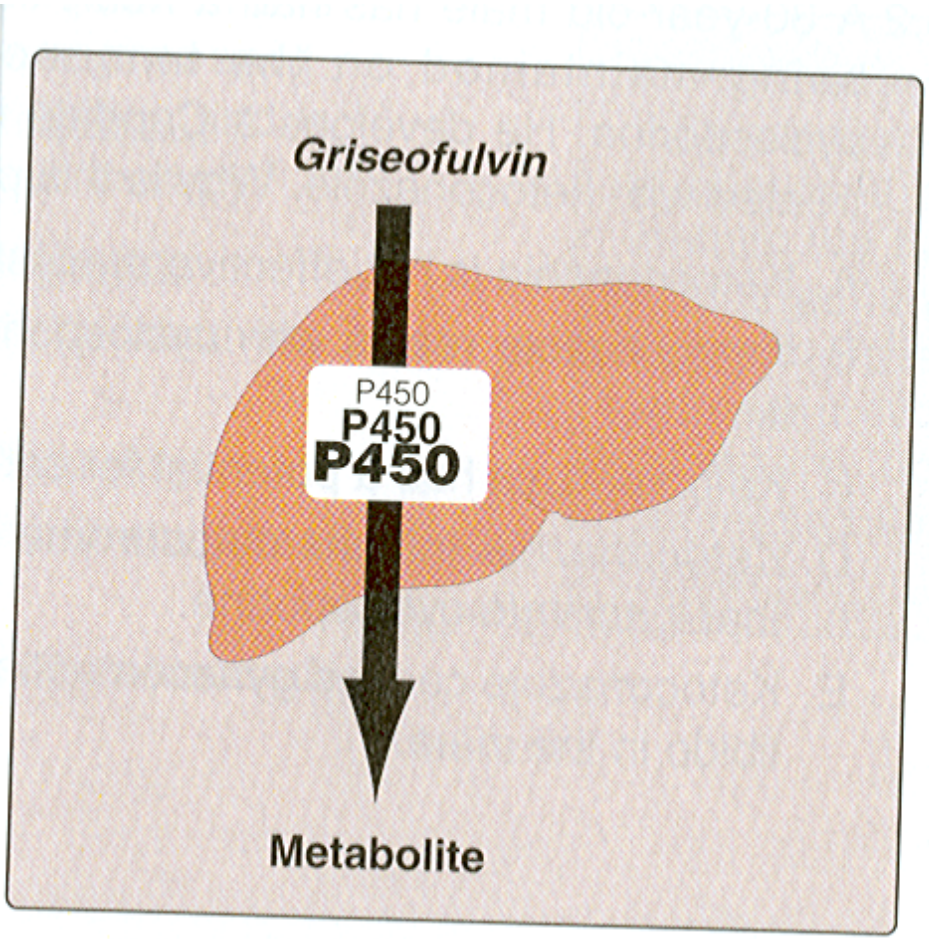
Indications

- Systemic uses for dermatophytoses (eg skin and especially nail infections though for the later terbinafine is preffered.
- Requires extended treatment, usually in combination with triazoles.
- Also highly effective against athletes foot and ring worm

Pharmacokinetics

- Absorption of griseofulvin from GIT is irregular due its low water solubilty
- Griseofulvin absorption increases with fatty meal
- Barbiturates decrease the absorption from GIT
- It is ineffective topically it has to be given orally for Rx of hair and nail dermatophyte infections
- Gets deposited in keratin forming cells of skin, hair and nails.it is specially concentrated in tinea infected cells.
- Newly formed keratin is not invaded by the fungus but the fungus persists in already infected keratin till it is shed off.

- Thus, duration of treatment is dependant on site, thickness of infected keratin and its turnover rate
- Extensively metabolized in liver and induces CYP450
- Largely metabolized by methylation and excreted in urine
- Plasma t ½ is 24 hours but it persists for weeks in skin and keratin


Griseofulvin
P450
P450
P450
Metabolite

Adverse Effects

Generally low toxicity.

- Headache
- GIT disturbances
- Peripheral neuritis , lethargy , mental confusion, impairment in performance of routine task
- Fatigue, vertigo ,syncope, blurred vision

Indications

- Used systemically only for dermatophytosis.
- dose: 125-250 mg QID with meals (duration depends on site of infection)
  - Body skin – 3 weeks
  - Palms, soles – 4-6 weeks
  - Finger nails – 4-6 weeks
  - Toe nails - 8-12 weeks
- Also effective against athletes foot

Drug Interactions

- Griseofulvin induces warfarin metabolism
- Reduces efficacy of oral contraceptives
- Phenobarbitone reduces oral absorption and induces metabolism of griseofulvin – failure of therapy may occur
- Griseofulvin can cause intolerance to alcohol

OTHER TOPICAL AGENTS

TOLNAFTATE

- Tolnaftate is a synthetic over-the-counter anti-fungal agent. It may come as a cream, powder, spray, or liquid aerosol, and is used to treat jock itch, athlete’s foot and ringworm. It is sold under several brand names, most notably Tinactin and Odor Eaters.
- Effective drug for Tinea cruris and tinea corporis

Mechanism of action

- Tolnaftate is a topical fungicide. Though its exact mechanism unknown, it is believed to prevent ergosterol biosynthesis by inhibiting squalene epoxidase. It has also been reported to distort the hyphae and to stunt mycelial growth in susceptible organisms.

Pharmacokinetics

- Poor penetrability
- There is limited information regarding *Pharmacokinetics* of Tolnaftate in the drug label.
  Onset
  24-72 hours.
- Resistance does not occur

Adverse effects

- Well tolerated
- Slight irritation

Indications

- Superficial dermatophyte infections, Pityriasis versicolor
- Adult: Apply a 1% gel/solution/powder/cream bid for 2-6 weeks; repeat if necessary. Continue treatment for 2 wk after disappearance of all symptoms to prevent recurrence of infection.

Drug interactions

- Salicylic acid can help tolnaftate by keratolytic action
- TINAVATE 1% lotion

UNDECYLENIC ACID

- Topical fungistatic
- Used in combination with its zinc salt
- Inferior to drugs described above
- Used for tenia pedis, nappy rash and tenia cruris
- Irritationn and sensitization infrequent
- Eg: zinc undecenoate 8 %

BENZOIC ACID

- Antifungal and antibacterial property in slighlty acidic medium
- Fungistatic – weaker than tolnaftate
- Eradication of fungus needs prolonged application till keratin is shed
- On hyperkeratotic lesions, used with salicylic acid, the infected tissue by its keratolytic action helps to remove the infected tissue and promotes the penetration of benzoic acid into the lesion

- ADRS
  - Irritation and burning sensation
- Whitfields ointment: benzoic acid 5%, salicyclic acid 3%
- Brand name: Ringcutter ointment

QUINIODOCHLOR

- Weak antifungal and antibacterial activity
- Indication:
  - Dermatophtosis
- Brand name
  - Vioform 3% cream
  - Dermoquinol4%, 8% cream

CICLOPIROX OLAMINE

- Newer drug
- Effective in tenia infections and dermal and viginal candidiasis
- High cure rates reported
- It penetrates superficial layers and reaches hair roots but systemic absorption is negligible
- Local tolerance without irritation is good
- Sensitization occurs occasionally

MECHANISM OF ACTION

- Ciclopirox is a hydroxypyridone antifungal agent that acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

PHARMACOKINETICS

- Pharmacokinetic studies in men with tagged Ciclopirox solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically to 750 cm2 on the back followed by occlusion for 6 hours. The biological half-life was 1.7 hours and excretion occurred via the kidney. Two days after application only 0.01% of the dose applied could be found in the urine. Fecal excretion was negligible.

- Ciclopirox olamine cream is indicated for the topical treatment of the following dermal infections:
  - tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum*, and *Microsporum canis*;
  - candidiasis (moniliasis) due to *Candida albicans*; and tinea (pityriasis) versicolor due to *Malassezia furfur.*

- Brand names:
    - Batrafen 1% cream
    - Olamine 1% cream

SODIUM THIOSULPHATE

- Sodium thiosulfate lotion is a topical antifungal and keratolytic agent. It works by killing the fungus that causes tinea versicolor. The keratolytic helps the antifungal reach the deep layers of the skin.
- **Side effects**
  - Mild, temporary burning or stinging at the application site.

- INDICATIONS
  - Treating tinea versicolor, a fungal infection of the skin.
- INTERACTIONS
  - Isotretinoin - skin irritation

THANK YOU FOR
YOUR ATTENTION!!!