Antifungal Drugs

Assistant Prof. Dr. Najlaa Saadi
PhD Pharmacology
Faculty of Pharmacy
University of Philadelphia

Mycoses: Is an Infection disease caused by fungi.

Many common mycotic infections are:

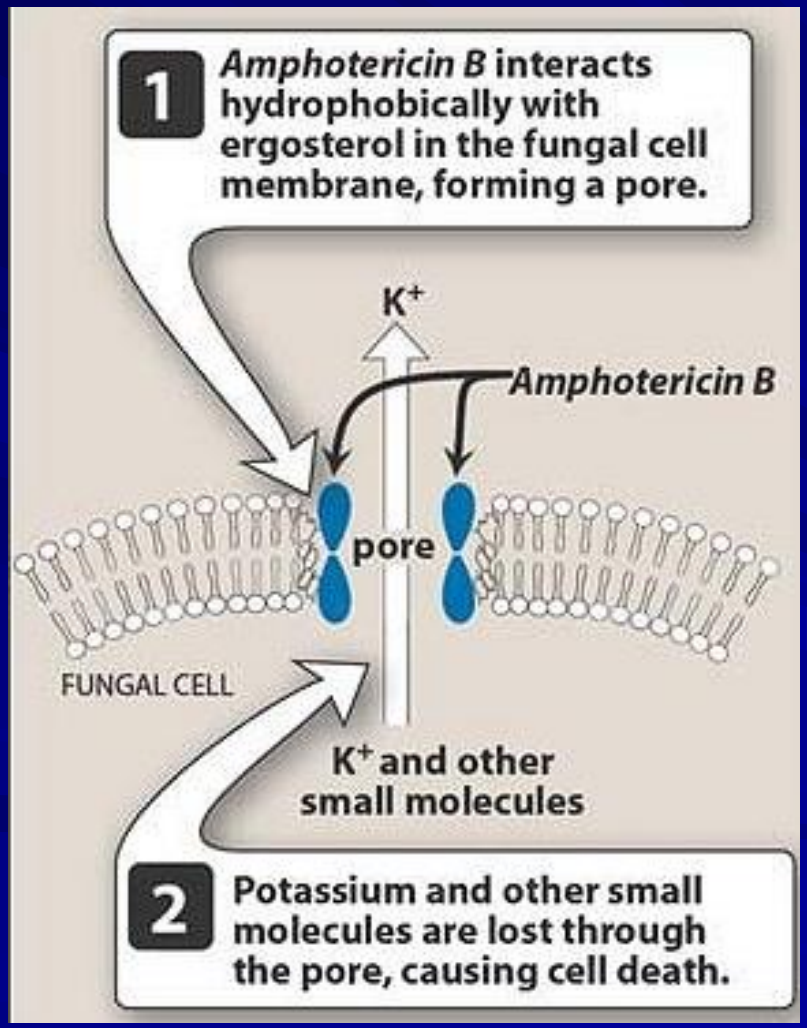
- Cutaneous mycoses (superficial and only involve the skin)
- Subcutaneous infections (fungi may penetrate the skin)
- Systemic mycoses (most difficult to treat)

Drugs for Subcutaneous and Systemic Mycotic

Amphotericin B

- Naturaly polyene macrolide ,antibiotic produce by Strptomyces nodosus
- Bind to ergosterol in plasma membrane of sensitive fungal cell they form pores (channels), disrupt membrane function allowing electrolyte k to leak from the cell resulting in cell death

Model of a pore formed by amphotericin B in the lipid bilayer membrane

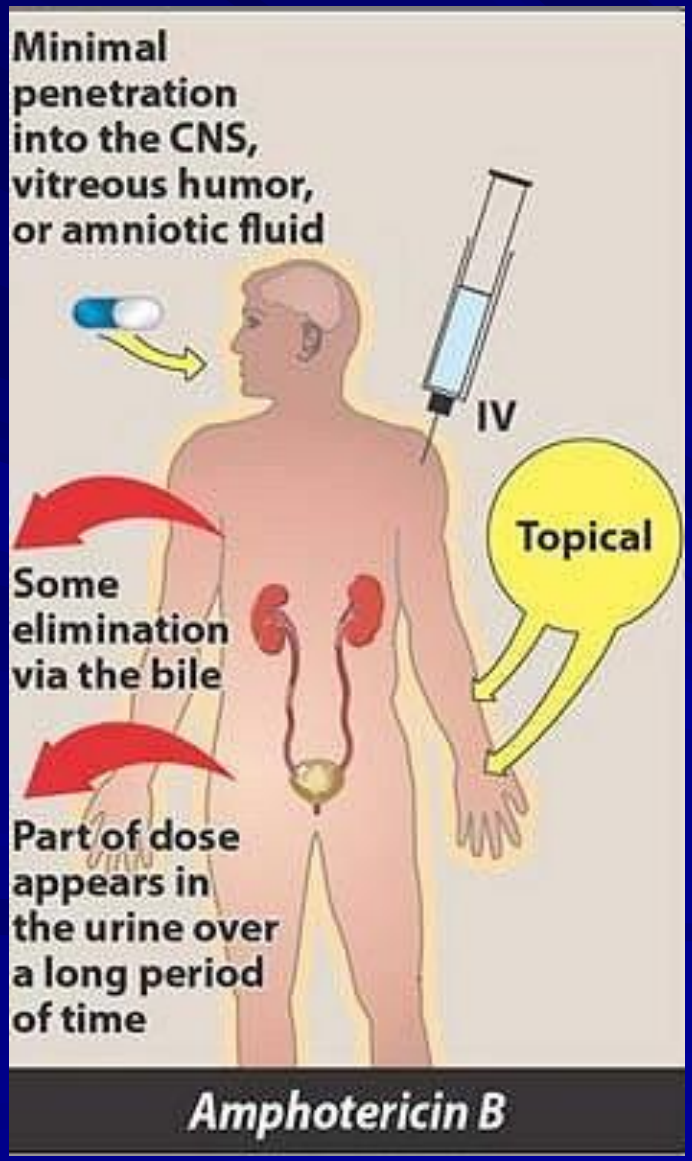


- Either fungicidal or fungistatic depending on organism and concentration of drug.
- Its acts against Candida albicans and histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, and many strains of aspergillus.
- Amphotericin B is also used in the treatment of the protozoal infection, leishmaniasis.

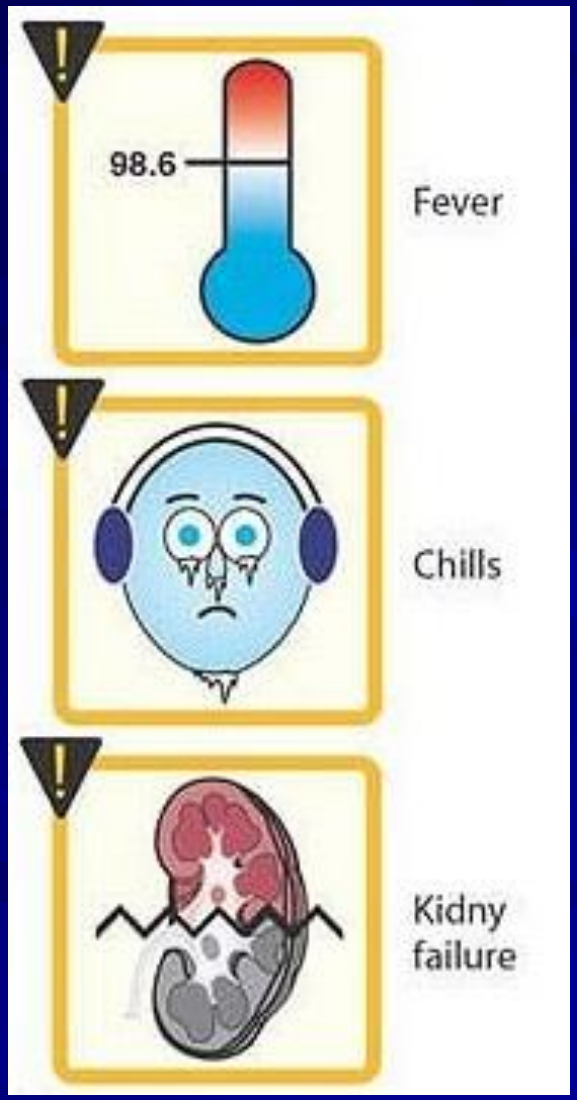
Pharmacokinetic of Amphotericin B

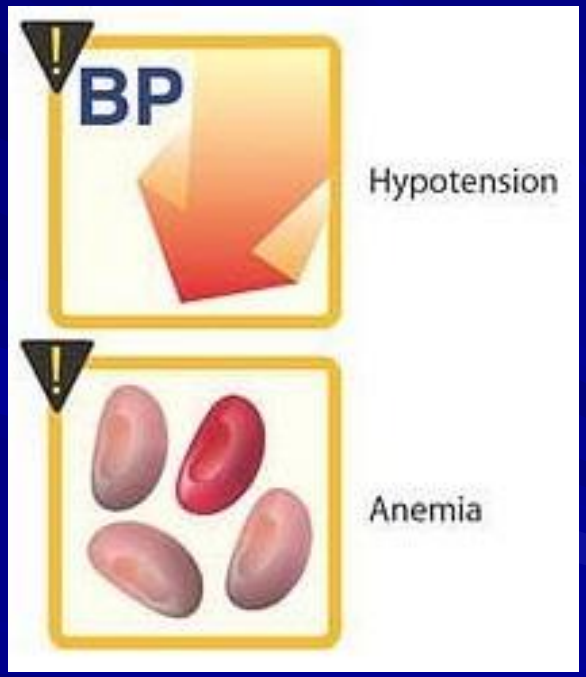
- Intravenous infusion (slow)
- The intrathecal for the treatment of meningitis caused by fungi that are sensitive to the drug (more dangerous).
- Bound to plasma protein .
- Excreated by urine and bile.

Administration and Fate of Amphotericin B



Adverse Effects of Amphotericin B



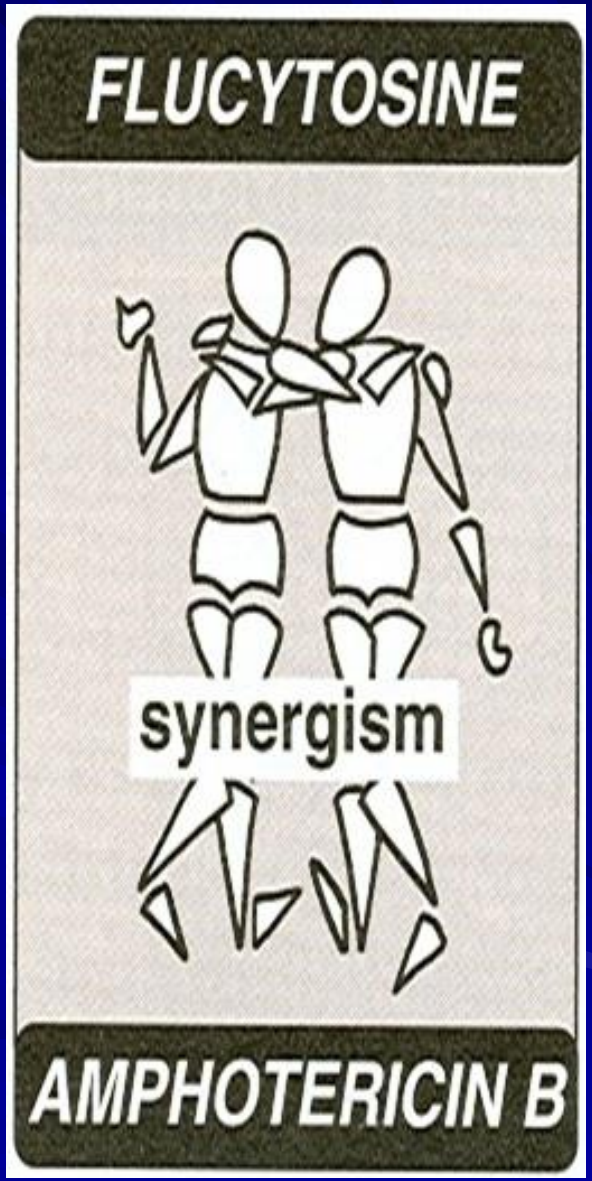


Side Effects of Amphotericin B

- Fever and chills
- Renal impairment
- Hypotension, hypokalemia
- Anemia
- Neurologic effects (by Intrathecal administration)
- Thrombophlebitis

Flucytosine

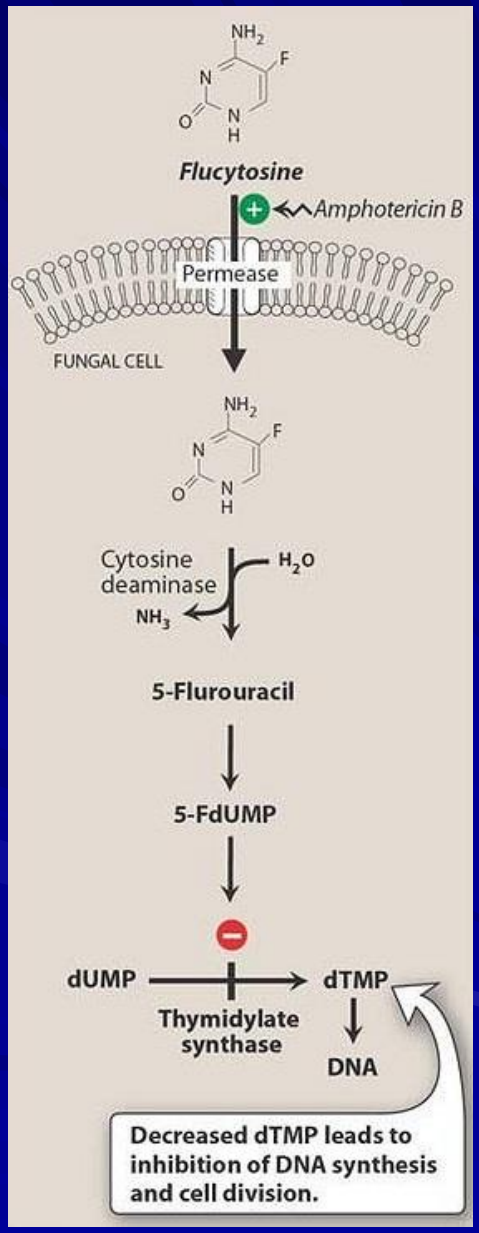
- Used in combination with amphotericin B (for the treatment of systemic mycoses and for meningitis caused by Cryptococcus neoformans and Candida albicans)



- Flucytocin is taken by fungal cell and its converted intracellurally to 5 FluorouraciL
- 5-FU inhibits DNA and RNA synthesis.

Note: Amphotericin B increases cell permeability, allowing more Flucytocin to penetrate the cell.

Mode of action of flucytosine. 5-FdUMP = 5-fluorodeoxyuridine 5'-monophosphate; dTMP = deoxythymidine 5'-monophosphate



Pharmacokinetic of Flucytocin

- Well absorbed by the oral route.
- penetrates well into the CSF
- Excretion of both the parent drug and its metabolites is by urine

Adverse effects of Flucytocin

1. Neutropenia, thrombo-cytopenia, bone marrow depression
2. Reversible hepatic dysfunction
3. Gastrointestinal disturbances and severe enterocolitis

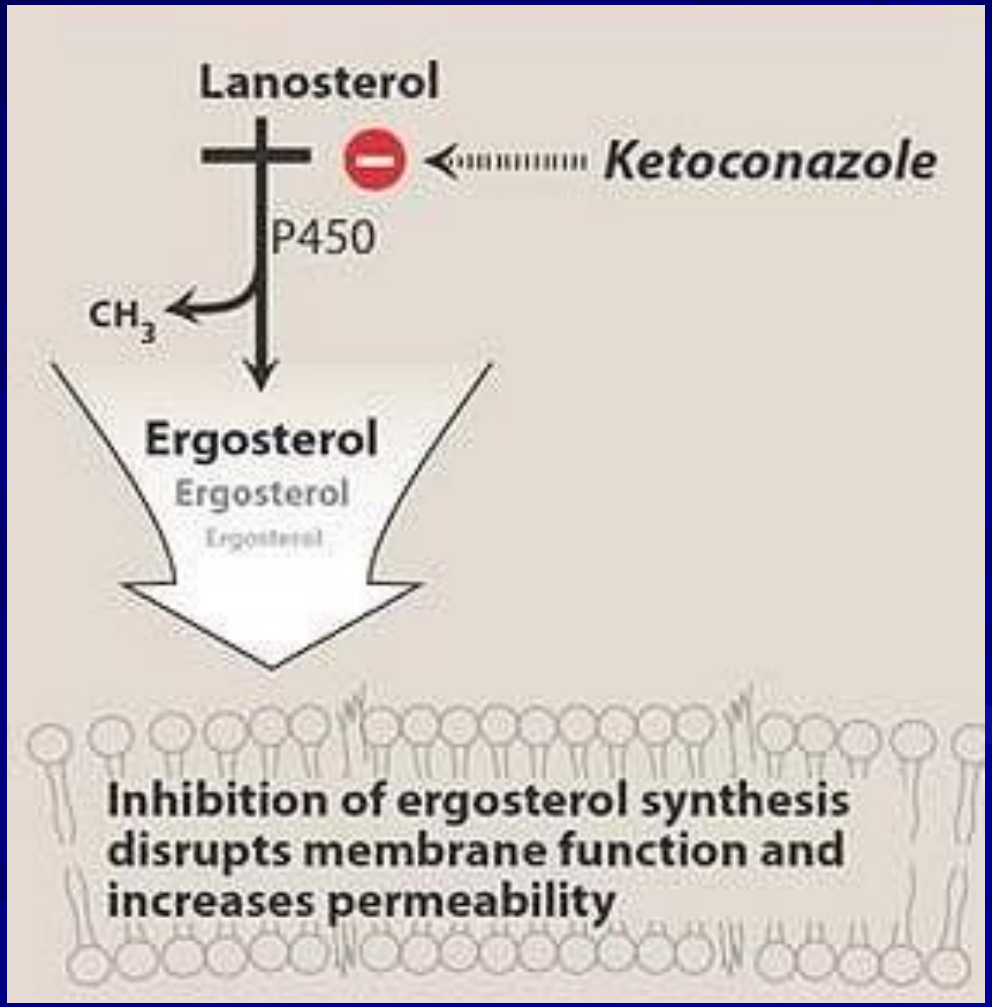
AZOLE

- Ketoconazole
- Itraconazole
- Fluconazole
- Voriconazole

Ketoconazole

- Was the first orally active azole for the treatment of systemic mycoses.
- Block the demethylation of lanosterol to ergosterol which the principle sterol of fungal membrane (inhibit fungal cell growth).

Mode of Action of Ketoconazole



Pharmacokinetics of Ketoconazole

- Orally administion
- It requires gastric acid for dissolution and is absorbed through the gastric mucosa.
- Bound to plasma proteins.
- Although penetration into tissues is limited, it is effective in the treatment of histoplasmosis in lung, bone, skin, and soft tissues.
- Metabolism occurs in the liver, excretion through the bile.
- Levels of parent drug in the urine are too low to be effective against mycotic infections of the urinary tract

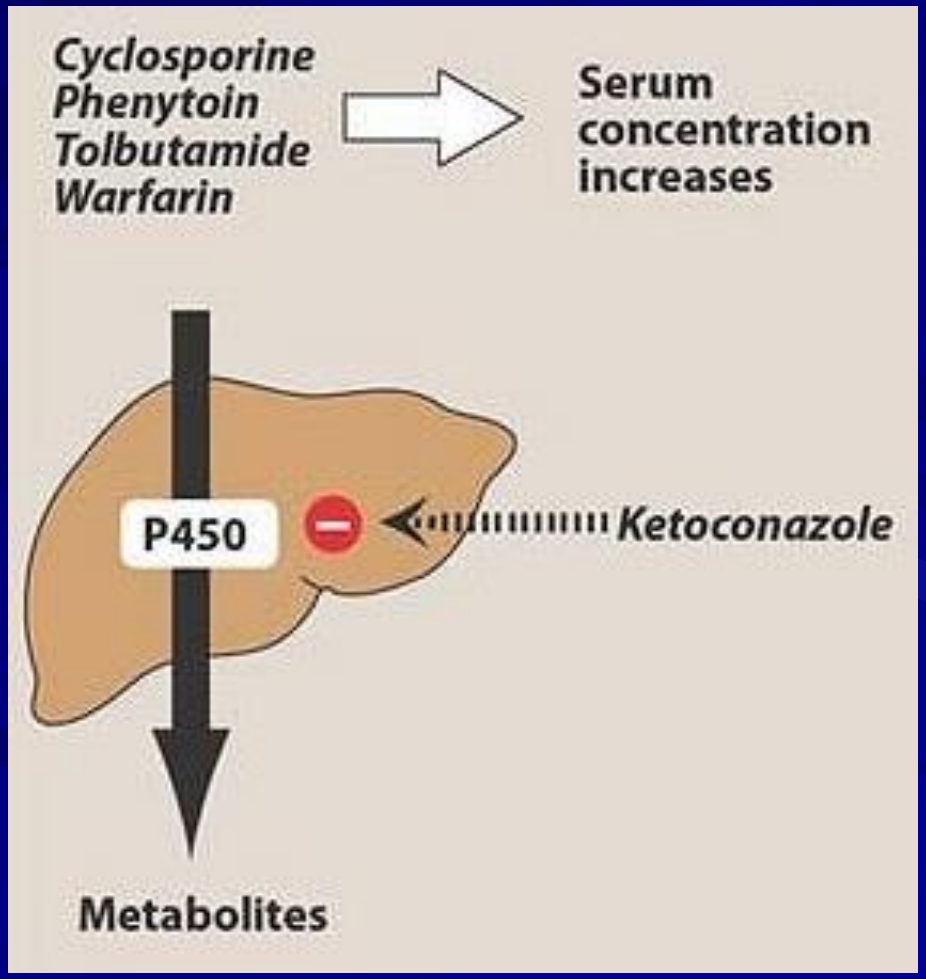
Adverse Effects of Ketoconazole

1. Allergic reaction
2. GIT disturbance
3. Hepatic dysfunction
4. Endocrine effect (blocking androgen and adrenal steroid synthesis) so may cause gynaecomastia,impotence in men and menstrual irregularities in women

Drug Interaction of Ketoconazole

- **Ketoconazole** (enzyme inhibitor) Inhibits Cytochrome P450 ,can potentiate the toxicity of cyclosporin, phenytoin, warfarin.
- Rifampin (enzyme inducer) decrease the action of ketaconazole
- H_2-receptor blockers, antacids, proton-pump inhibitors and sucralfate, can decrease absorption of ketoconazole

By inhibiting cytochrome P450, ketoconazole can potentiate the toxicities of other drugs



Fluconazole

- Its same as ketoconazole.
- Its effective against all form of candidiasis
- Given orally or I.V.
- Indicated for treatment of meningitis (Penetrate CSF)
- Excreted via kidney.
- Lack of endocrine effect of ketoconazole
- Have GIT disturbance.
- Teratogenic effect

Itraconazol

- For treatment of blastomycosis, histoplasmosis, AIDS.
- Given orally require acid for dissolution.
- Metabolize by liver.

Side effects of Itraconazol

Nausea ,vomiting, Rash, Hypertension hypokalemia, edema and headache.

Echinocandins (Caspofungin, Micafungin and Anidulafungin)

Caspofungin

- Echinocandins interfere with the synthesis of the fungal cell wall leading to lyses and cell death

Caspofungin

- It is a second-line antifungal for those who have failed or cannot tolerate amphotericin B or an azole.
- Not active by the oral route.
- Bound to serum proteins
- It is slowly metabolized by hydrolysis and N-acetylation.
- Urinary and fecal elimination.

Adverse Effects of Caspofungin

Fever, rash, nausea, phlebitis and flushing

Drugs for Cutaneous Mycotic Infections

Fungi that cause superficial skin infections are called dermatophytes

Terbinafine

- Fungicidal
- The drug of choice for treating dermatophytoses and, especially, onychomycoses (fungal infections of nails).
- More effective than either itraconazole or griseofulvin.
- Inhibits fungal squalene epoxidase, thereby decreasing the synthesis of ergosterol, accumulation of toxic amounts of squalene result in the death of the fungal cell.

Note: Significantly higher concentrations of terbinafine are needed to inhibit human squalene epoxidase, an enzyme required for the cholesterol synthetic pathway.

Pharmacokinetics of Terbinafine

- Orally active
- Bioavailability is only 40 percent due to first-pass metabolism.
- Terbinafine is greater than 99 percent bound to plasma proteins.
- It is deposited in the skin, nails and fat.
- A prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues.
- Patients with either moderate renal impairment or hepatic cirrhosis have reduced clearance

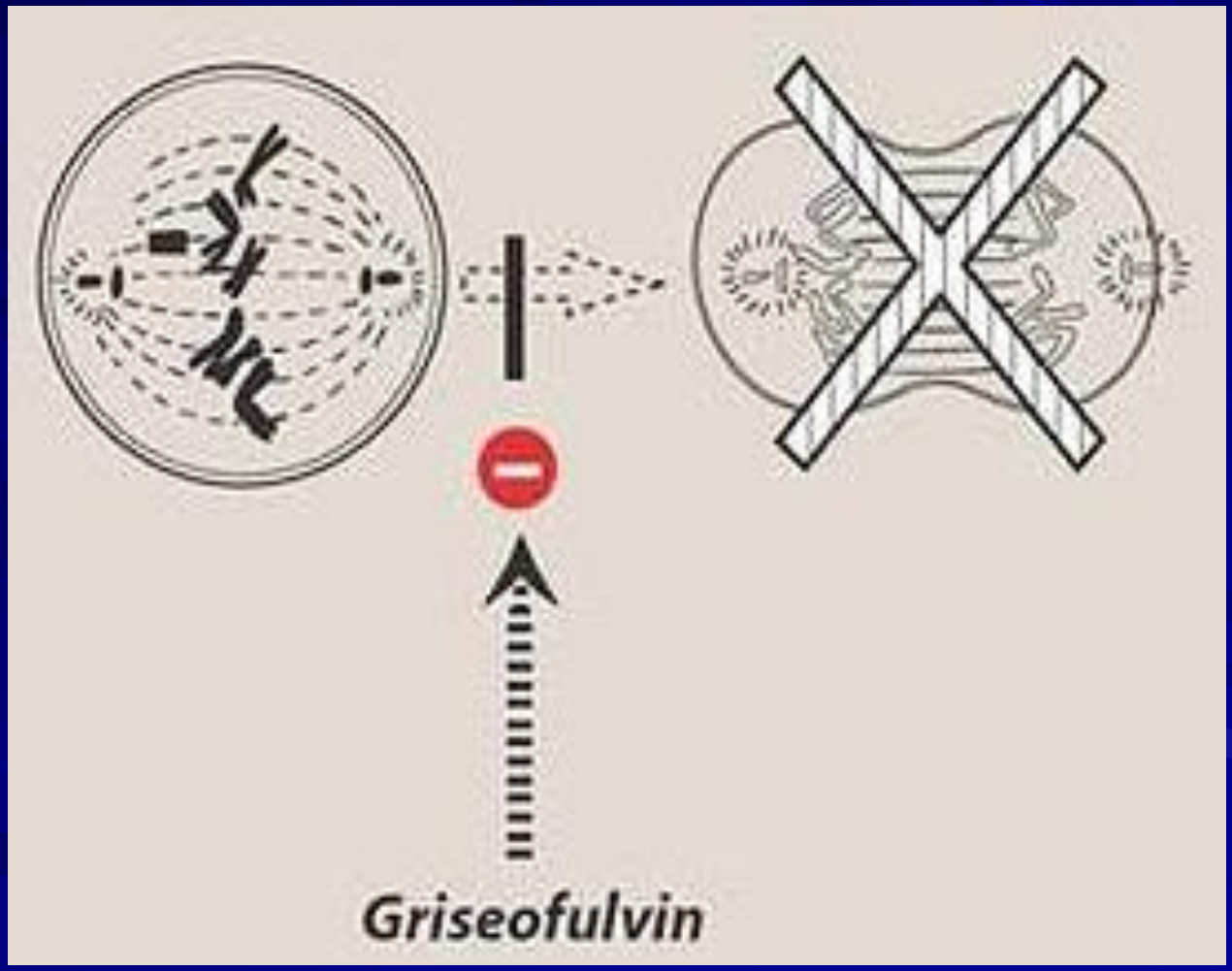
Adverse Effects of Terbinafine

1. Gastrointestinal disturbances
2. Headache and rash
3. Taste and visual disturbances
4. Transient elevations in serum liver enzyme
5. Hepatotoxicity and neutropenia (rarely)

Griseofulvin

- largely replaced by terbinafine for the treatment of dermatophytic infections of the nails.
- Griseofulvin requires treatment of 6 to 12 months in duration.
- It is only fungistatic,
- Griseofulvin accumulates in newly synthesized, keratin-containing tissue, where it causes disruption of the mitotic spindle and inhibition of fungal mitosis
- Duration of therapy is dependent on the rate of replacement of healthy skin or nails.
- The gastrointestinal tract absorption is enhanced by high-fat meals.
- Enzyme inducer, increases metabolism anticoagulants.
- Griseofulvin potentiates the intoxic effects of alcohol.

Inhibition of mitosis by griseofulvin



Nystatin

- Is a polyene antibiotic
- Resemble of amphotericin B in (its structure, chemistry, mechanism of action)
- Have systemic toxicity (Its use is restricted to topical treatment of Candida infections)
- The drug is negligibly absorbed from the gastrointestinal tract and it is never used parenterally.
- It is administered as an oral agent for the treatment of oral candidiasis.
- Excretion in the feces

Topical Agents
Miconazole, clotrimazole, butoconazole and terconazole

- Their mechanism of action and antifungal spectrum are the same as those of ketoconazole.
- Topically active drugs that are only rarely administered parenterally because of their severe toxicity
- Topical use is associated with contact dermatitis, vulvar irritation, and edema.
- Miconazole is a potent inhibitor of warfarin metabolism and has produced bleeding in warfarin-treated patients even when miconazole is applied topically.
- No significant difference in clinical outcomes is associated with any azole or nystatin in the treatment of vulvar candidiasis