Antifungals

Topical Antifungals

- Polyenes
- Azoles
- Allylamines/Benzylamines
- Hydroxypyridone (Ciclopirox)
- Selenium Sulfide

Polyenes

- Nystatin
- Amphotericin B

- Macrolide ring of carbons with multiple conjugated double bonds and closed by internal ester or lactose (hence the name polyene)

Nystatin

- Produced by Strep. noursei and albidus
- Water insoluble and not absorbed from intact skin, GI tract, or vagina
- Structure and mode similar to Amphotericin but **only** used topically because of systemic toxicity.

Nystatin

- Mechanism of Action (MOA)
  - Irreversibly **binds to sterol** of susceptible candidal species
  - Thereby changing the **membrane permeability**
  - And allowing **leakage of essential intracellular components**

- **Fungistatic** AND **Fungicidal** (in vitro)

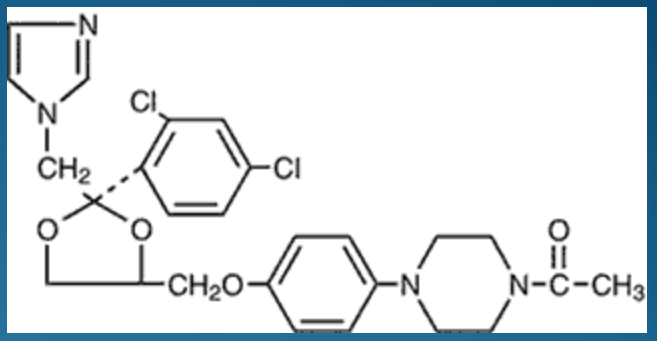
Nystatin

- Clinical Indications (CI)
  - Candida
  - Ineffective for dermatophytes
- Formulations Available (FA)
  - Cream, ointment, and powder (BID application)
  - Suspension or Troche (4-5 times daily)

Nystatin

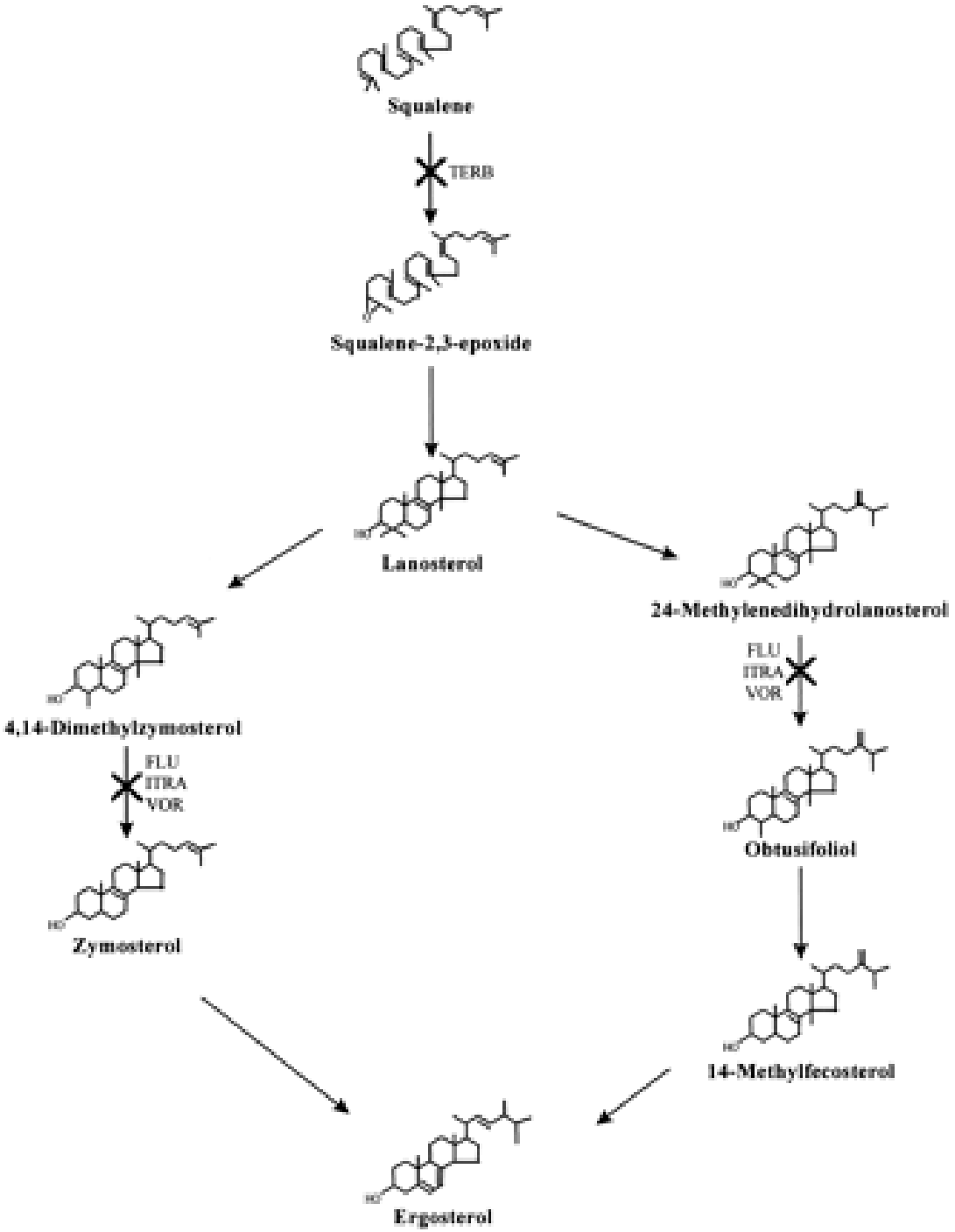
- Adverse Effects (AE's)
  - All uncommon
  - Burning, pruritus, rash, eczema, pain, and Hypersensitivity reaction (v. rare)

Azoles

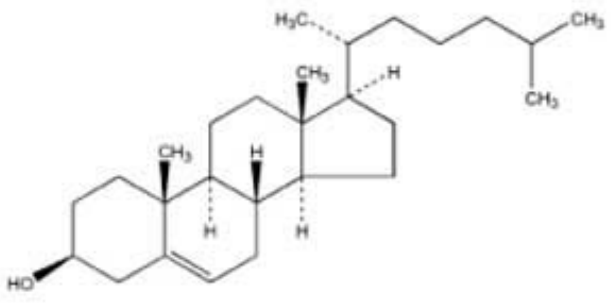


ketoconazole

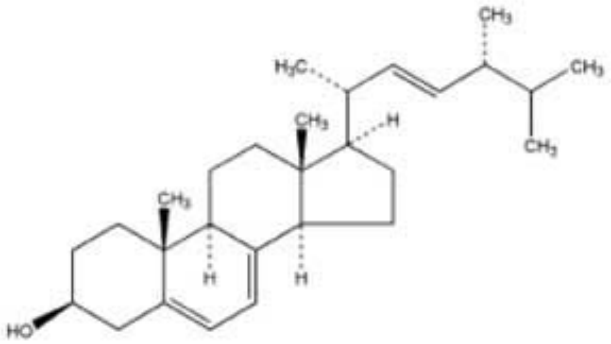
- MOA
  - Inhibits **Lanosterol 14-alpha demethylase** (CYP450 enzyme)
  - The azole nitrogen links to the heme Fe of the cytochrome (the site where oxygen binds)
  - Blocks the CYP450 catalysis of **lanosterol to ergosterol**


Squalene
TERB
Squalene-2,3-epoxide
Lanosterol
24-Methylenedihydrolanosterol
FLU
ITRA
VOR
4,14-Dimethylzymosterol
FLU
ITRA
VOR
Obtusifoliol
Zymosterol
14-Methylfecosterol
Ergosterol

The Target



Cholesterol



Ergosterol

Azoles

- Skin is relatively impermeable to these compounds
- <1% absorption occurs, may increase to 4% on inflamed or damaged skin
- **Fungistatic**

Miconazole (Monistat-Derm, Micatin)

- Action
  - Penetrates S. corneum well, detectable up to 4 d. following single application
- Spectrum
  - T. rubrum, mentagrophytes, and E. floccusum; C. albicans, M. furfur; Gram positive Bacteria

Miconazole (Monistat-Derm, Micatin)

- CI
  - Tinea pedis, corporis, cruris
  - Tinea versicolor
  - Cutaneous candidiasis
- FA
  - Cream; BID dosing

Clotrimazole (Lotrimin, Fungoid, Mycelex Troches)

- Spectrum
  - Trichophyton, Epidermophyton, and Microsporum; Gram pos. Bacteria; Candida
- CI
  - T. pedis, corporis, cruris; TV; Cutaneous Candidiasis
- FA
  - Cream, Lotion, Solution (BID dosing)
  - Intravaginal tab (TID), Troches (4-5 X Qday)

Ketoconazole (Nizoral)

- Action
  - No systemic absorption (hence safe to use in infants)
- Spectrum
  - Broadly covers dermatophytes; C. albicans, and M. furfur
- CI
  - All previous plus Seborrheic Dermatitis
- FA
  - 2% cream; 1%, 2% shampoo

Oxiconazole (Oxistat)

- Action
  - Rapidly absorbed!
  - Systemic Absorption negligible
- CI
  - T. pedis
- FA
  - 1% cream, lotion (choice for large or hairy areas)

Econazole (Spectazole)

- Action
  - Readily found in epidermis down to mid dermis; systemic absorption low
- Spectrum
  - Most strains of Trichophyton, Microsporum, Epidermophyton; C. albicans, and M. furfur; Gram pos. and neg. Bacteria
- CI
  - Same as previous
- FA
  - 1% cream

Sulconazole (Exelderm)

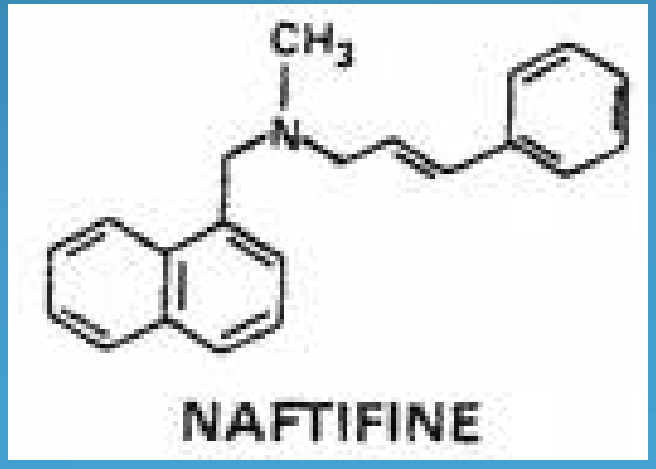
- Action
  - Most systemically absorbed azole (8-11%)
- Spectrum
  - As previous (modest Gram pos. coverage)
- CI
  - Same as previous. Offers little advantage over previous meds
- FA
  - 1% cream, solution; use QD-BID for 2-4 weeks

Sertaconazole (Ertaczo)

- Action
  - Most lipophilic azole leading to greater reservoir effect in S. corneum
  - Second MOA-direct membrane damage of susceptible microbes
- CI
  - T. pedis
- FA
  - 2% cream

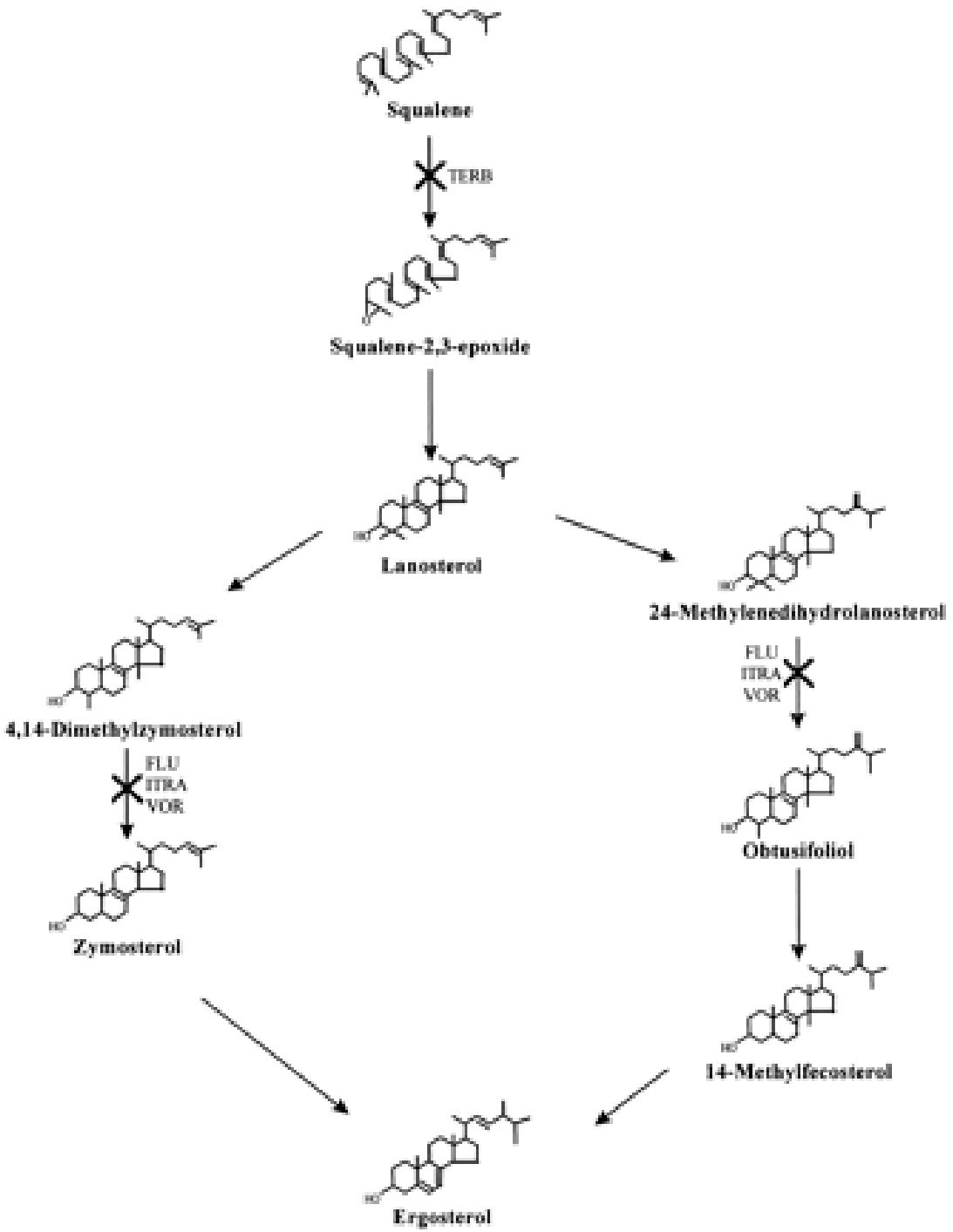
Allylamines/Benzylamines

- Naftifine
- Terbinafine
- Butenafine (Benzylamine)



Allylamines/Benzylamines

- Inhibit Squalene Epoxidase, an earlier step in ergosterol synthesis
- CYP450 independent
- Fungicidal AND Fungistatic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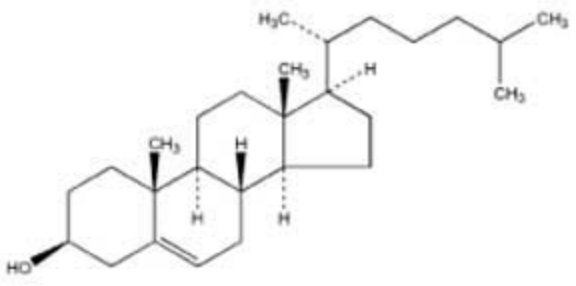

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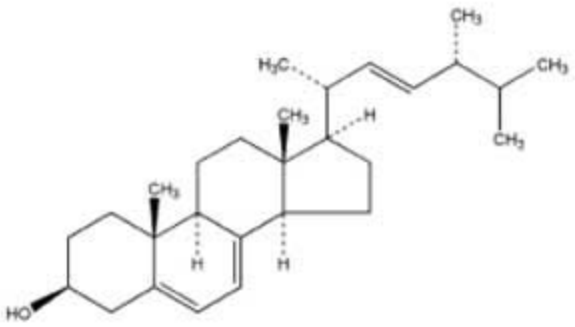

Ergosterol

Naftifine (Naftin)

- Action
  - Highly lipophilic, therefore penetrates S. corneum and hair follicles well
- Spectrum
  - Dermatophytes, yeast, and saprophytes (*T. megntagrophytes)
- FA
  - Cream and gel, QD-BID

Terbinafine (Lamisil)

- Action
  - Highly lipophilic…reducing probability of reinfection
  - 10-100X more potent than naftifine in vitro
  - 3-5% systemically absorbed, peaks at 3-5 days
- Spectrum
  - Dermatophytes, molds, dimorphic fungi, and C. albicans
- FA
  - 1% cream, spray

Butenafine (Mentax)

- Action
  - Allylamine group replaced by a butylbenzene group
  - Interacts and fixes to cutaneous lipids-a great depot effect
  - Also acts by squalene epoxidase inhibition
- Spectrum
  - Dermatophytes, aspergillus, and dimorphic fungi

Ciclopirox Olamine (Loprox, Penlac)

(Hydroxypyridone)

- MOA
  - Does NOT affect sterol synthesis
  - Blocks transport of macromolecular precursors disrupting cell membrane integrity and
  - inhibits enzymes essential for the respiratory process (think of the "OX" in Loprox)
- Spectrum
  - Dermatophytes, M. furfur, C. albicans, Pityrosporum; Gram pos. and neg bacteria
  - **Anti-Inflammatory** by inhibiting PGL's and Leukotriene production by PMN's

Ciclopirox Olamine (Loprox, Penlac)

(Hydroxypyridone)

- FA
  - Cream, gel, shampoo, lotion, and nail lacquer
- Penlac
  - Penetrates nail plate
  - ?40% cure rate
  - Requires prolonged daily use
  - $$$$$

Selenium Sulfide (Selsun, Exsel)

- Cytostatic effect of cells of the epidermis and follicular epithelium.
- Results in decreased corneocyte adhesion and allows shedding of the fungus
- Pregnancy Class C (not studied)

The Big Picture

- Overall, allylamines are more potent that azoles.
- Butenafine=terbinafine>ciclopirox>naftifine>azoles
- Higher efficacy
  - Fungicidal activity
- Lower relapse rates
  - Lipophilicity
    - retained in the epidermis

Candidiasis

- Covered by azoles, allylamines, and hydroxypyridone
- Efficacy is not equal
- Ciclopirox>azoles>>butenafine>naftifine=terbinafine

Anti-Inflammatory Properties

- Azoles
  - Inhibits PMN chemotaxis
  - Inhibits calmodulin, integral in synthesis of PGL's and release of histamine
- Ketoconazole (and bifonazole)
  - Inhibits 5-lipoxygenase…dec. 5-HETE and Leukotriene B_4

Anti-Inflammatory Properties

- Naftifine
  - Interferes with leukocyte pseudopod formation and therefore inhibits PMN chemotaxis
  - Impedes PMN production of Reactive Oxygen Species
  - Inhibits 5-lipoxygenase

Anti-Inflammatory Properties

- Ciclopirox
  - Inhibits 5-lipoxygenase and cyclooxygenase

Antibacterial Properties

- Serve as adjuvant where a dermatophytosis complex is present
- Never agents of choice for primary bacterial infections
- **Ciclopirox for Interdigital T. pedis

Pregnancy

- Topical vulvar and IV multidose treatments with azoles for Vulvovaginal Candida
- Reduces risk of Preterm Labor

Propylene Glycol

- “Two edged sword”
- Enhances percutaneous penetration of medicine but can be an irritant
- With antifungal failure, consider ICD

- Nizoral, Oxistat, Lamisil, Nystatin

Systemic Antifungals

Systemic Antifungals

- Griseofulvin
- Ketoconazole (imidazole)
- Itraconazole (triazole)
- Fluconazole (triazole)
- Terbinafine (allylamine)

Griseofulvin (Gris-PEG…)

- Produced by Penicillium griseofulvum
- MOA: Interferes with microtubule function, causing arrest at metaphase
- Fungistatic for Dermatophytes only

Griseofulvin (Gris-PEG…)

- Ultramicrosized
  - Gris-PEG (125,150 mg tabs; 125 mg/ml susp)
  - Fulvicin P/G (125, 165, 250, 330 mg tabs)
- Microsized
  - Fulvicin U/F (125, 250 mg tabs)
  - Grifulvin V (500 mg tabs;125mg/ml susp)

Griseofulvin (Gris-PEG…)

- Bioavailability: 24%
- Increase in drug bioavailability occurs with:
  - food-induced increase in drug solubility
  - secretion of bile in response to food intake
- So, give with fatty foods!

Griseofulvin (Gris-PEG…)

- AE's
  - GI irritation, photosensitivity, granulocytopenia, hepatotoxicity, teratogenic
- CI
  - Porphyria or Hepatocellular Failure
- Pregnancy Class C

Griseofulvin (Gris-PEG…)

- Drug Interactions
  - A CYP3A4 inducer (you can see loss of efficacy in other drugs)
    - Statins, immunosuppressants, hormonal contraceptives, oral hypoglycemics, chemo, coumadin, anticonvulsants, antiarrhythmics, HIV meds (Protease Inhibitors)
  - May augment photosensitivity potential of other drugs
  - With EtOH, may give a disulfuram-like reaction

Ketoconazole (Nizoral)

- Fungistatic against:
  - Dermatophytes, Candida species, tinea versicolor, many dimorphic fungi
- AE's
  - Fulminant hepatitis
  - Gynecomastia and Impotence
  - Dysregulation of the HPA axis

Ketoconazole (Nizoral)

- Drug Interactions
  - Potent inhibitor of CYP3A4
  - Antacids, H2 Blockers, Long acting H1 Blockers (terfenadine/astemizole), Systemic Steroids, Rifampin, Phenytoin, Warfarin, Sulfonylureas

Itraconazole (Sporanox)

- Triazole: Azole ring containing 3 nitrogen atoms (fluc, itra, and vori)
- Bioavailabilty increased
  - Postprandially
  - Acidic environment
- Clinical Uses:
  - Blastomycosis, histo, aspergillosis, candidiasis, cryptococcosis, coccidioidomycosis, sporotrichosis, dermatophyte infections, onychomycosis

Itraconazole (Sporanox)

- Potent Inhibitor of CYP3A4 also
- Adverse Effects (more common with pulse therapy
  - Headache, GI upset, Cutaneous (angioedema, EM, SJS)
- Drug Interactions
  - Cisapride, pimozide, quinidine, dofetilide, levomethadyl, digoxin, cyclosporine
- Contraindications
  - Any ventricular dysfunction-CHF, proarrythmic condition as itraconazole prolongs the QT interval

Fluconazole (Diflucan)

- Also a triazole
- Clinical Uses: Candidiasis, crypto meningitis, candidal prophylaxis, dermatophyte infections, histo, sporo, tinea versicolor
- Similar AE's as itraconazole, but less frequent
  - N/V/elev. LFT's
  - Alopecia (prolonged use)

Fluconazole (Diflucan)

- Potent inhibitor of CYP2C9
- Drug Interactions (elevates levels)
  - *Coumadin, nortryptiline, midazolam, triazolam, FK506

Terbinafine (Lamisil)

- MOA
  - Inhibits Squalene Epoxidase
- AE's
  - Hepatocellular injury, delayed gastric emptying, dysgeusia, reversible agranulocytosis, *lupus erythematosus, GI disturbance, other rashes
- Contraindications
  - Chronic/acute Liver disease; CrCl <50ml/min

Terbinafine (Lamisil)

- Drug Interactions
  - Inhibits CYP2D6 (doxepin and amitryptiline)
- Pregnancy Category B

Terbinafine (Lamisil)

- Available in 250 mg tabs
  - 6 weeks therapy for fingernails, 12 week therapy for toenails
- No generic
- Bioavailablity 80% to 40% (due to 1st pass hepatic metabolism)

Monitoring

- Terbinafine
  - Baseline AST, ALT
  - If symptoms of liver dysfunction, discontinue and do hepatic profile
  - CBC if patient is immunocompromised and is on med > 6 weeks
- Intraconazole
  - LFT monitoring for all patients

Monitoring

- Griseofulvin
  - With prolonged therapy, check renal, hepatic and CBC
- Ketoconazole
  - Never use over 7-10 days
  - No monitoring needed for short therapy

Special Considerations

- Check CsA levels with *Itraconazole* or *Fluconazole*
- Blood Glucose with concomitant use of *oral hypoglycemics* and *fluconazole*
- Check INR frequently with *coumadin* and *fluconazole* combo therapy

FDA Approved Uses

- Griseofulvin
  - Tinea of skin, hair, and nails
- Itraconazole
  - Onychomycosis
  - Systemic mycoses (Blasto, Histo, Aspergillus)
- Fluconazole
  - Candidiasis (Oral, esophageal, vaginal)
- Terbinafine
  - Onychomycosis

Other Systemics

- Caspofungin (echinocandin)
  - Inhibits glucan synthesis (essential polysaccharide of fungal cell wall)
  - Covers Candida, Aspergillus
- Voriconazole
  - Covers Aspergillus, resistant fusarium and scedosporium

Other Systemics

- Posaconazole
  - Oropharyngeal Candidiasis assoc. with HIV; resistant systemic fungi
- Ravuconazole
  - Similar to fluconazole
  - Oropharyngeal and esophageal candidiasis
  - ? Future treatment of Onychomycosis