Pharmacology of Antituberculosis Drugs
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Chizoba Anozie, PharmD, has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Objectives

- First-line anti-tuberculosis drugs
- Second-line anti-TB drugs
- Discuss Adverse reactions
- Drug Interactions
- New and Investigational drugs

Anti tuberculosis Drugs
First-Line Drugs

- Rifampin
- Rifabutin
- Isoniazid (INH)
- Pyrazinamide (PZA)
- Ethambutol
Rifampin

- **Class**: Rifamycin
  - **Activity**: Bactericidal
- **Dose Adult**: 10mg/kg/dose (usually 600mg IV or PO)
- **Children**: 10 to 20mg/dose

**Administration**:
- Take without food
- May mix contents of capsule with applesauce or jelly

Rifampin

**Adverse Effects**

**Common**
- Reddish-orange body fluids
- Nausea, vomiting, diarrhea
- Rash, Pruritus
- Flu-like syndrome
- Elevated LFTs
- Vision changes

**Serious**
- Hepatitis
- Renal failure
- Hematological (thrombocytopenia, hemolytic anemia)
Rifabutin

Class: Rifamycin
Activity: Bactericidal
Dose Adult: 5mg/kg/dose (usually 300mg)
Children: Appropriate dose not known. Estimated at 5mg/kg/day
May be taken with or without food

Rifabutin Adverse Effects

Common
- Reddish-orange body fluids
- Rashes, skin discoloration (bronzing or pseudojaundice)
- Arthralgia
- Taste changes

Serious
- Hepatotoxicity
- Leukopenia, Neutropenia, thrombocytopenia
- Anterior uveitis and other eye toxicities
**Isoniazid (INH)**

- **Class:** Isonicotinic acid hydrazide
- **Activity:** Bactericidal
- **Dose (Adult):** 5mg/kg/day (PO or IV) (usual dose 300mg daily)
- **Children:** 10 – 15mg/kg/day
- **Administration:** Best absorbed on empty stomach (about 50% reduction with fatty meal)

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**Isoniazid (INH) Adverse Effects**

<table>
<thead>
<tr>
<th>Common</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Pyridoxine deficiency</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Epigastric discomfort</td>
<td>Drug-induced lupus</td>
</tr>
<tr>
<td>Cramping with oral solution</td>
<td>CNS changes</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
</tr>
</tbody>
</table>
Pyrazinamide (PZA)

- **Class**: Synthetic derivative of nicotinamide
- **Activity**: Bactericidal
- **Dose (Adult)**: 25mg/kg/day (max 2gm)
- **Children**: 20-40mg/kg/day
- May be taken with or without food

Pyrazinamide (PZA) Adverse Effects

**Common**
- Gout (contraindicated in patients with severe gout)
- Elevated LFTs
- Arthralgia
- Rash
- GI symptoms
- Photosensitivity

**Serious**
- Hepatotoxicity
- Anemia
- Drug-induced myopathy
**Ethambutol**

**Class:** Unspecified  
**Activity:** Bacteriostatic  
**Dose (Adult):** 15-25mg/kg/day  
**Children:** 15 – 25mg/kg  
**Administration:**  
- May be taken with or without food  
- Avoid aluminum containing antacid within 4hrs of admin.

**Ethambutol Adverse Effects**

**Common**  
- Nausea, vomiting  
- Abdominal discomfort  
- Blurred vision  
- Rash  
- Psychiatric symptoms (mania, hallucinations, psychosis)

**Serious**  
- Optic neuritis  
- Peripheral neuropathy  
- Blindness (irreversible)
Second-Line Drugs

- Levofloxacin
- Moxifloxacin
- Cycloserine
- Ethionamide
- Para-aminosalicylic acid (Paser)
- Amikacin
- Streptomycin
- Capreomycin
- Linezolid

Levofloxacain (Levaquin)

- **Class**: Fluoroquinolone
- **Activity**: Bactericidal
- **Dose (Adult)**: 500mg – 1000mg daily
- **Children**: Optimal dose is not known, clinical data suggest 15 – 20mg/kg
Levofloxacin

Administration:
Do not administer within 2 hrs after ingestion of milk-based products, antacids or drugs containing divalent cations (iron, magnesium, calcium, zinc, vitamins, sucralfate, didanosine).

How Supplied

Levofloxacin

Adverse Effects

Common
- Nausea and bloating
- Headache
- Dizziness`
- Insomnia
- Arthralgia
- Tendinitis

Serious
- Tendon rupture (rare)
- QT prolongation
- Arthralgia
- Peripheral neuropathy
- Photosensitivity
Moxifloxacin (Avelox)

- **Class:** Fluoroquinolone
- **Activity:** Bactericidal
- **Dose (Adult):** 400mg/day
- **Children:** No established dose

**Administration:**

- Do not administer within 2 hrs after ingestion of milk-based products, antacids or drugs containing divalent cations (iron, magnesium, calcium, zinc, vitamins, sucralfate, didanosine).

Moxifloxacin

Adverse Effects

**Common**

- Nausea, diarrhea
- Headache, dizziness
- Arthralgia
- Tendinitis

**Serious**

- Hepatotoxicity (rare)
- Tendon rupture (rare)
- QTc prolongation
- Peripheral neuropathy
Cycloserine (Seromycin)

- **Class**: Analog of D-alanine
- **Activity**: Bacteriostatic

- **Dose (Adult)**: 15 – 20mg/kg/day (usually 250 – 500mg once or BID)
- **Children**: 15 – 20mg/kg/day in 1 to 2 divided doses

**Administration**:  
- Take on empty stomach  
- Give Vitamin B6 supplement

Cycloserine Adverse Effects

**Common**
- CNS toxicity (behavioral changes, headache, dizziness, lethargy)  
- Peripheral neuropathy  
- Skin changes  
- Skin rash (lichenoid eruptions)

**Serious**
- Seizure  
- Depression  
- Psychosis  
- Suicidal ideation  
- Steven-Johnson syndrome
Ethionamide (Trecator)

- Derivative of Isonicotinic acid
- Bactericidal

**Dose:**
- **Adult:** 15 – 20mg/kg/day (usually 250 – 500mg once or BID)
- **Children:** 15 – 20mg/kg/day in 1 to 2 divided doses

Ethionamide Adverse Effects

**Common**
- GI upset, anorexia
- Metallic taste
- Endocrine effects (Gynecomastia, hair loss, acne, impotence, menstrual irregularity, reversible hypothyroidism)

**Serious**
- Hepatotoxicity
- Neurotoxicity
- Optic neuritis
Para-aminosalicylic acid (Paser)

- **Class**: Salicylic acid – anti-folate
  - **Activity**: Bacteriostatic

**Dose:**
- **Adult**: 8 – 12 grams/day (usually 4 grams 2 – 3 x daily)
- **Children**: 200 – 300 mg/kg/day 2 – 4 times per day

**Administration:**
- Take with food
- Store in refrigerator
- May sprinkle on applesauce or yogurt

Para-aminosalicylic acid (Paser) Adverse Effects

**Common**
- GI symptoms (titrate dose over 2 weeks)
- Hypothyroidism (reversible)

**Serious**
- Hepatoxicity (rare)
- Coagulopathy (rare)
Amikacin/Streptomycin/Capreomycin

Aminoglycoside
- Amikacin, Streptomycin
Cyclic polypeptide
- Capreomycin
Activity: Bactericidal
Dose:
- Adult: 15mg/kg/day
- Children: 15 – 20mg/kg/day
Administration: IM or IV

Amikacin/Capreomycin/Streptomycin
Adverse Effects

Common
- Local pain with IM injections
- Electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia)

Serious
- Nephrotoxicity
- Ototoxicity
- Vestibular toxicity
Linezolid (Zyvox)

- **Class:** Oxazolidinones
- **Activity:** Bactericidal
- **Dose (Adult):** 600mg/day
- **Children:** 10mg/kg/dose every 8 hours

**Administration:**
- Take with or without food
- Take Vitamin B6 supplement
- Avoid tyramine containing food (aged cheese, dried meat, soy sauce, sauerkraut, red wine, tap beer, avoid drug that increase serotonin conc.)

Linezolid Adverse Effects

**Common**
- Diarrhea
- Nausea
- Headache

**Serious**
- Myelosuppression
- Lactic acidosis
- Peripheral neuropathy
- Optic neuritis
- Serotonin syndrome
New and Investigational Drugs

- Clofazimine
  - Bedaquiline

**Clofazimine (Lamprene)**

- Not commercially available in the US.
- Usually as last alternative for cases with very few treatment options

**Adult Dose:**
- 100 – 200mg/day

**Administration:**
- PO only
- Take with food
## Clofazimine
### Adverse Effects

<table>
<thead>
<tr>
<th>Common</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pink or red discoloration of skin, conjunctiva, cornea, and body fluids</td>
<td></td>
</tr>
<tr>
<td>- GI intolerance</td>
<td></td>
</tr>
<tr>
<td>- Photosensitivity</td>
<td></td>
</tr>
<tr>
<td>- Dry skin, rash, pruritus</td>
<td></td>
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<tr>
<td>- GI bleeding</td>
<td></td>
</tr>
<tr>
<td>- Bowel obstruction</td>
<td></td>
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<tr>
<td>- Retinopathy</td>
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## Bedaquiline (Sirturo)

- Not commercially available in the US
- FDA indicated for multi-drug resistant pulmonary TB in adults 18 yrs old and older
- Use only when other treatment options cannot be utilized

### Do not use for
- Latent TB
- Extra-pulmonary TB
- Drug sensitive TB
- Use with at least 3 other susceptible drugs
Bedaquiline

Dosing:
- Weeks 1 – 2: 400mg daily then,
- Weeks 3 – 24: 200mg 3 times per week (at least 48 hrs between doses)

Administration:
- Take with food
- Swallow tablet whole with water
- Avoid alcohol

Bedaquiline
Adverse Effects

Common
- Nausea
- Arthralgia
- Headache
- Elevated AST/ALT

Serious
- QT prolongation
- Hepatotoxicity
- Increase mortality
Drug-drug Interactions

- Most clinically relevant drug-drug interactions involve Rifamycins (Rifampin > Rifabutin)
- Rifamycins are inducers of several metabolic pathways especially involving various isoenzymes of the cytochrome P450 (CYP) system
- Rifamycins can decrease serum concentrations of many drugs (eg., most of HIV – 1 protease inhibitors) to subtherapeutic levels

Drug-drug Interactions
Isoniazid

- Potent inhibitor of several CYP450 isoenzymes
- Increases concentration of some drugs to point of toxicity
  - Phenytain
  - Carbamazepine
  - Diazepam
  - Triazolam
# Drug-drug Interactions

## Rifamycins

<table>
<thead>
<tr>
<th>Substrates (CYP3A)</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam/clonazepam</td>
<td>Amiodarone</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Alorvastatin</td>
<td>Ceritaline</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Clarithromycin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Erythromycin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Fluconazole</td>
<td>Primidone</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Fluoxetine</td>
<td>Peflixin</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Fluoxamine</td>
<td>Peflixin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Grapefruit juice</td>
<td>Peflixin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Indinavir</td>
<td>Peflixin</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Itraconazole</td>
<td>Peflixin</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Ketoconazole</td>
<td>Peflixin</td>
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<tr>
<td>Protease inhibitors</td>
<td>Metronidazole</td>
<td>Peflixin</td>
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<tr>
<td>Losartan</td>
<td>Miconazole</td>
<td>Peflixin</td>
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<tr>
<td>Ondansetron</td>
<td>Nelfinavir</td>
<td>Peflixin</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Nevirapine</td>
<td>Peflixin</td>
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<tr>
<td>Surtraline</td>
<td>Nelfinavir</td>
<td>Peflixin</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Nelfinavir</td>
<td>Peflixin</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Nelfinavir</td>
<td>Peflixin</td>
</tr>
</tbody>
</table>

### Rifampin will decrease levels of these meds in blood

### Decrease levels of rifabutin in blood

### Increase levels of rifabutin in blood

# Food-drug Interactions

## Best on Empty Stomach
- Rifampin
- Isoniazid
- Cycloserine
- Moxifloxacin
- Levofloxacin

## Best with food
- Paser
- Clofazimine
- Ethionamide
- Bedaquiline
Questions

References


2. Micromedex 2.0, Drugdex Evaluations, Greenwood Village, CO: Truven Health Analytics, Inc.
