DRUG-INDUCED PULMONARY DISEASES

---BRONCHOCONSTRICTION---
Mostly affecting patients with underlying bronchial hyperreactivity, e.g. asthmatic patients

1. Aspirin
   - Unknown pathogenesis
   - Susceptible: ↑ age, women
   - At risk: “classic triad” of 1. severe asthma, 2. nasal polyps, 3. aspirin intolerance
   - Cross-sensitivity with other NSAIDs (except APAP, corticosteroids)
   - Management: avoidance (#1), desensitization by chronic compliant ASA use, leukotriene modifiers

2. β blockers
   - Both nonselective and β₁ selective agents (but less so)
   - Topicals and ophthalmics can also cause systemic adverse effects
   - Management: discontinuation, corticosteroids, bronchodilators

3. Inactive ingredients
   - Sulfites/metabisulfites: preservatives, antioxidants
   - EDTA: stabilizing agent
   - Benzalkonium chloride: bacteriostatic agent in some albuterol nebulizer solutions (ironic)

---APNEA---
Mostly affecting patients with COPD, alveolar hypoventilation, chronic CO₂ retention

1. Benzodiazepines: CNS depressants
   - Synergistic/additive effect with narcotics
   - Lorazepam, alprazolam, clonazepam, etc.

2. Neuromuscular blocking agents
   - Prolonged in patients that are like classical ICU patients:
     - Hepatic or renal dysfunction
     - Concurrently taking high dose corticosteroids or aminoglycoside therapy
   - Pancuronium, vecuronium

---COUGH---
Dry, nonproductive, persistent → annoying

1. ACE inhibitors
   - Susceptible: females, AA, Chinese
   - Can manifest anytime: anywhere between 3 days to 1 year
   - Pathogenesis: ↑ bradykinin + ↑ substance P → inflammation + lung irritation
   - Management: cough suppressants and bronchodilators don’t work, choose alternatives (ARBs) and discontinue ACE inhibitors (resolves in 1-4 or more days)

---PULMONARY FIBROSIS---
Predisposing factors: cumulative dose, ↑ age, radiotherapy, O₂ therapy, cytotoxic drug therapy, pre-existing pulmonary disease

1. Antineoplastics
   - Carmustine (BCNU): highest incidence (20-30%), linear dose-response relationship, high mortality rate
   - Bleomycin: young patients at risk (<7yo), dose limiting SE (vs. the usual bone marrow suppression), manage by discontinuation, corticosteroids may help if used early enough
   - Busulfan: 4 years of therapy until fibrosis shows up, threshold dose response, ↑ risk with radiation

2. Amiodarone
   - Highest risk during 1st year, need to monitor PFTs, manage by ↓dose/discontinuation/alternative

---PULMONARY HYPERTENSION---

1. Fenfluramine-Phentermine (Fen-Phen)
   - Removed from market

2. Maternal SSRI
   - 6x risk of pulmonary hypertension in infants exposed to SSRI from mother
   - Management: wean off prior to delivery, assess risk vs. benefit of discontinuing SSRI

Speaking of which...
PULMONARY HYPERTENSION

---DEFINITION---
- Elevated mean pulmonary arterial pressure
  - At rest ≥25mmHg
  - Exercise ≥30mmHg
  - [Normal is 12-16mmHg]
- Gold standard: diagnosis as per cardiac catheterization
  - Acute vasodilator testing: give NO and see if ↓ pressure
- Causes: usually idiopathic but also many secondary causes
  - Secondary to COPD, scaroidosis, lupus, congenital heart defects, HIV, medications, connective tissue disorders

---PATHOGENESIS---
- ↑bad + ↓good: relative imbalance of mediator substances
  - ↑bad: vasoconstrictors, pro-vasoproliferatives (abnormal growth of vasculature), prothrombotics (↑clots)
  - ↓good: vasodilators, anti-vasoproliferatives
- Bad news: vasoconstriction, pulmonary vascular remodeling, thrombosis

---SIGNS & SYMPTOMS---
- Presentation similar to heart failure
- Signs: leg edema, hepatosplenomegaly, loud 2nd heart sound, murmur, S3 or S4 gallop, jugular venous distention
- Symptoms: exertional dyspnea, fatigue, orthopnea (trouble breathing when sleeping/lying down), weakness, chest pain, syncope (fainting), Raynaud’s phenomenon (fingers/toes turn purple due to poor circulation)

---TREATMENT---
**Drugs that take care of symptoms but not the process:**
- **WARFARIN:** for ≥ class II
- **DIURETICS:** edema
- **DIGOXIN:** right ventricular heart failure
- **CCBs:** for patients with positive response to acute vasodilator testing
  - Dihydropyridines preferable
  - Choose alternative/additional agent if no improvement after 3 months

**Drugs that help modify the disease state:**
- **SILDENAFIL:** phosphodiesterase inhibitor
  - MOA: ↑cGMP by inhibiting its breakdown → vasorelaxation + antiproliferative effects
  - SE: headaches, flushing, vision changes, dyspepsia, nasal congestion (nothing too serious)
  - Interactions: nitrates cause synergistic hypotension
- **EPOPROSTENOL:** synthetic prostacyclin
  - MOA: works on a lot of targets to cause potent vasodilation, antiproliferative activity, and inhibit platelets
  - SE: flushing, headache, diarrhea, abdominal cramping, jaw pain; if given by IV infusion, then risk of infection & catheter malfunction
- **TREPROSTINIL:** prostacyclin analog
  - Route: SQ, IV, inhalation
  - SE: infusion site pain
- **ILOPROST:** prostacyclin analog
  - Route: inhalation, but 6-9 doses/day!
  - SE: cough
- **BOSENTAN:** endothelin antagonist
  - MOA: dual ET\textsubscript{A} (↓vasoconstriction) & ET\textsubscript{B} (↓vasodilation/anti-proliferation) receptor antagonist
  - SE: ↑↑LFTs, ↓hemoglobin, contraindicated in pregnancy
  - Interactions:
    - (+)CYP2C9: warfarin, contraceptives
    - (−)CYP3A4: sildenafil
    - Contraindicated with cyclosporine & glyburide
- **AMBRISENTAN:** endothelin antagonist
  - MOA: selective ET\textsubscript{A} receptor antagonist (↓vasoconstriction)
  - SE: ↑↑LFTs, contraindicated in pregnancy, peripheral edema, flushing, palpitations, nasal congestion