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 β_1 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 CO_2 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, O_2 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 (<7y/o), 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_A (↓vasoconstriction) & ET_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_A receptor antagonist (↓vasoconstriction)
  - SE: ↑↑LFTs, contraindicated in pregnancy, peripheral edema, flushing, palpitations, nasal congestion