To describe the pharmacology of anti-asthma drugs with particular reference to beta-2 agonists, corticosteroids, anticholinergics, leukotriene antagonists and theophylline.

Asthma → recurrent reversible airway disease a/w ↑ resistance to airflow due to:
- (i) ↑ AW mucosal inflammation and oedema
- (ii) ↑ bronchial SM tone (or bronchoconstriction)
- (iii) ↑ bronchiolar secretions
- (iv) ↑ airway hyperresponsiveness

Drugs used to treat asthma are generally administered by the “inhaled route” → b/c this:
- (1) ↑ delivery to site of action → ↑ effect
- (2) allows administration of lowest dose possible
- (3) ↓ adverse effects due to systemic absorption

Classes of drugs used to treat asthma:

1. **β2 agonists**:

<table>
<thead>
<tr>
<th>Types</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Short-acting agents (Eg. salbutamol)</td>
<td>Direct β2 adrenoceptor agonist → GPCR (Gs) → inhibits adenylyl cyclase causing ↓ IC cAMP → causes (i) relaxation of bronchial SM, (ii) ↑ ciliary clearance of mucous, and (iii) ↓ mast cell mediator release</td>
<td>Due to systemic absorption:</td>
</tr>
<tr>
<td>- Used to treat acute asthma (inhaled – aerosolised as MDI/spacer, or nebulised) → effect in 30 mins, lasting 4-6 hrs</td>
<td>- β2 effects – Muscle tremor, ↓ K+, postural hypotension</td>
<td></td>
</tr>
<tr>
<td>- Used to treat status asthmaticus (IV)</td>
<td>- β1 effects – Tachycardia, arrhythmias, hypertension, ↑ BGL, anxiety</td>
<td></td>
</tr>
<tr>
<td>(ii) Long-acting agents (Eg. salmeterol)</td>
<td>Used as prophylaxis to prevent asthma attack (inhaled – aerosolised as MDI/spacer) → effect lasting 12 hrs</td>
<td></td>
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</tbody>
</table>

2. **Anticholinergics**:

<table>
<thead>
<tr>
<th>Types</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used to treat acute asthma (Eg. ipratropium → t ½ ~ 2 hrs) and as prophylaxis to prevent asthma attack (Eg. tiotropium → t ½ 6 hrs) → given via inhaled route (aerosolised as MDI)</td>
<td>Competitive M3 receptor antagonist → GPCR (Gq) → ↓ PLC activation causing ↓ DAG (↓ PKC) and ↓ IP3 (↓ Ca²⁺) → causes (i) relaxation of bronchial SM, (ii) ↑ ciliary clearance of mucous, and (iii) ↓ mucous secretion production</td>
<td>- Minimal side-effects as agents are quaternary N-analogues of atropine → ionised so ↓ systemic absorption from lungs</td>
</tr>
</tbody>
</table>

3. **Corticosteroids**:

<table>
<thead>
<tr>
<th>Types</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Inhaled fluticasone, budesonide via MDI → prophylaxis against asthma attack</td>
<td>- Binds to IC glucocorticoid receptor → alters gene transcription and protein synthesis → causes:</td>
</tr>
<tr>
<td>- IV hydrocortisone → treat severe acute asthma or status asthmaticus</td>
<td>- (i) ↓ synthesis of inflammatory mediators → ↑ lipocortin production inhibits PLA2 → causing ↓ arachidonic acid generation and subsequent conversion to prostaglandins and leukotrienes</td>
</tr>
<tr>
<td>- PO prednisolone → treat chronic or severe acute asthma</td>
<td>- (ii) Suppression of immune response → ↓ cytokine production and ↓ immune cell activation</td>
</tr>
<tr>
<td></td>
<td>- (iii) Upregulation of β2 receptors</td>
</tr>
</tbody>
</table>
- Onset of effects are delayed (6-8 hrs) b/c of this

| Adverse effects | - Inhaled steroids deposit in oropharynx → cause oral candidiasis and dysphonia  
- Chronic use (esp of oral or IV) → ↑ BGL, adrenal suppression, Cushingoid (Eg. central adiposity, moon facies, Etc.), thinned skin, easy bruising, myopathy |
|-----------------|-----------------------------------------------------------------------------------|

(4) **Leukotriene antagonists:**

<table>
<thead>
<tr>
<th>Types</th>
<th>Montelucast and Zafirlukast → given orally</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Competitive inhibition of LT receptors → ↓ effects of LTC4, D4 and E4 → relaxes bronchial SM</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Minimal side-effects (Eg. headaches, GI disturbances)</td>
</tr>
</tbody>
</table>

(5) **Methylxanthines:**

<table>
<thead>
<tr>
<th>Types</th>
<th>Theophylline → given PO (as 2nd line therapy for acute asthma) or IVI (for status asthmaticus)</th>
</tr>
</thead>
</table>
| Mechanism of action     | - Phosphodiesterase inhibitor → ↑ IC cAMP and GMP → ↓ Ca²⁺ → bronchial SM relaxation  
- Inhibitor of endogenous adenosine? |
| Adverse effects         | Narrow therapeutic index:  
- CVS effects – Tachycardia/arrhythmias (+ve chronotropic effect), ↑ C.O. (+ve inotropic effect), hypotension (due to vasodilation)  
- CNS effects – ↑ alertness, tremor, nervousness, seizures and death 2° to respiratory failure  
- GIT effects – Anorexia, N/V  
- Renal effects – Weak diuretic effect (↑ GFR)  
- Metabolism dependent on hepatic CYP450 → ↑ drug levels with liver failure or drug inhibition of CYP450 (Eg. OCP, cimetidine, erythromycin) |
To outline the pharmacology of drugs used to treat pulmonary hypertension.

1. Prostanoids:
   - (a) Epoprostenol
     - **Overview** – Synthetic PGI-2 given continuously by IVI (via CVC)
     - **Mechanism of action** – PGI-2 analogue that causes pulmonary arterial SM relaxation → vasodilation and ↓ PA pressures
     - **Adverse effects** – Effects of PGs (Eg. headache, flushing, N/V, ↓ BP, jaw pain, flu-like symptoms), risk of CVC insertion (Eg. thrombosis, sepsis, Etc.), and need continuous infusion due to short t ½ (pump failure can be fatal!!!)
   - (b) Treprostinil
     - **Overview** – Synthetic PGI-2 given IV, S/C or inhaled route
     - **Mechanism of action** – As epoprostenol
     - **Adverse effects** – Effects of PGs (as epoprostenol) but do not need to give via CVC (can be given via continuous S/C delivery or inhaled route) and longer t ½ means pump failure is not fatal
   - (c) Iloprost
     - **Overview** – Synthetic PGI-2 given inhaled route
     - **Mechanism of action** – As epoprostenol
     - **Adverse effects** – Effects of PGs (as epoprostenol) and needs to be given frequently (6-9x/day)

2. Endothelin receptor antagonists:
   - **Overview** – Bosentan → given orally
   - **Mechanism of action** – Non-selective ET-1 receptor antagonist → inhibit potent vasoconstrictor effects of ET-1 → vasodilation of pulmonary artery → ↓ PA pressures
   - **Adverse effects** – Hepatotoxicity, peripheral oedema, teratogenic

3. PDE5 inhibitors:
   - **Overview** – Sildenafil, Tadalafil → given orally
   - **Mechanism of action** – Inhibit PDE-5 isozyme → ↑ IC cAMP/GMP → vascular SM relaxation causing pulmonary arterial vasodilation → ↓ PA pressures
   - **Adverse effects** – Headaches, flushing, hypotension, epistaxis

4. Calcium channel blocker:
   - **Overview** – Long-acting forms of diltiazem or nifedipine → given orally
   - **Mechanism of action** – Inhibit L-type VG-Ca\(^{2+}\) channels on vascular SM → ↓ Ca\(^{2+}\) influx → vascular SM relaxation causing pulmonary arterial vasodilation → ↓ PA pressures
   - **Adverse effects** – Hypotension, bradycardia, -ve intropy (heart failure), peripheral oedema

5. Other therapy:
   - (i) **Diuretics** (Eg. frusemide) – Used to treat fluid retention (Ie. ↓ APO and hepatic congestion) → issues with ↓ C.O. (2º to ↓ preload), arrhythmias 2º to electrolyte disturbances (esp ↓ K\(^{+}\)), metabolic alkalosis
   - (ii) **Anticoagulation** (Eg. warfarin) – Used to ↓ risk of PE → issues with bleeding
   - (iii) **Digoxin** – Used to control HR in those with SVT and ↑ RVEF
   - (iv) **Supplemental O\(_{2}\) therapy**
(c) **To describe the pharmacology of oxygen including its manufacture and adverse effects.**

**Overview of oxygen (O₂):**
- O₂ is a gaseous inorganic element that plays an essential role in oxidative phosphorylation for ATP production.
- It is administered by inhalation route (up to FiO₂ of 100%) and is used clinically:
  - (1) To manage all forms of hypoxia (except histotoxic)
  - (2) As an adjunct in management of shock and treatment of CO poisoning, anaerobic infections and decompression sickness

**O₂ preparation and storage:**
- Preparation:
  - (1) Fractional distillation of liquid air
    - Used for commercial production
    - Based on different boiling points of O₂ and N₂
  - (2) O₂ concentrator
    - Used for home use/remote locations
    - Zeolite mesh adsorbs N₂ so remaining gas is 97% O₂
  - (3) Hydrolysis of water to O₂ and H₂
- O₂ is then stored either as (i) a compressed gas in a cylinder (at 137 bar at 15 °C), or (ii) a liquid in a vacuum insulated evaporator (at 10 bar and -180 °C) → Nb. 1 volume of liquid O₂ = 840 volume of gaseous O₂

**Physicochemical properties of O₂:**
- Molecular formula: O₂
- Others: Colourless, odourless, tasteless gas
- MWT: 32
- Supports combustion
- Critical temperature: -119 °C
- An oxidant
- Critical pressure: 51 atm
- Non-conductor
- Boiling point: -182 °C
- Paramagnetic
- Cannot be measured by IR analyser
  (i.e. measured by mass spect, Clarke electrode, paramagnetic analysis)

**Potential adverse effects of O₂ administration:**
- (1) Free radical toxicity
  - (i) Pulmonary effects (can occur at pO₂ ≈ 100 kPa or 1 atm) – Lipid peroxidation of alveolar capillary membranes → regional lung collapse
  - (ii) CNS effects (esp at pO₂ > 200 kPa or 2 atm) – Anxiety, N/V, seizures
- (2) Absorption atelectasis
  - FiO₂ 100% eliminates N₂ from lungs → loss of N₂ as an alveolar splint → causes atelectasis and V/Q mismatching
- (3) Respiratory depression
  - In normal patients → ↑FiO₂ causes mild respiratory depression
  - Patients with COPD who are CO₂ retainers are dependent on hypoxia for respiration (as chronic hypercapnoea blunts CO₂-ventilatory drive) → ↑FiO₂ impairs their hypoxic-respiratory drive → ↓stimulation of medullary ventilatory centres → ↓RR and MV
- (4) Retrolental fibrodysplasia in neonates
  - ↑PaO₂ (rather than PAO₂) causes retrolental fibroplasia 2º to vasoconstriction of retinal vessels during development → thus, avoid by keeping PaO₂ < 140 mmHg
- (5) CNS effects
  - FiO₂ 100% causes ↓CBF 2º to cerebrovascular vasoconstriction
- (6) CVS effects
- **FiO₂** 100% causes ↓ coronary perfusion (2º to coronary vasoconstriction), and mild myocardial depression (↓ HR, BP and CO)
  
- (7) Haematological effects
  - **FiO₂** 100% may interfere with RBC formation
To describe the pharmacology of nitric oxide with particular reference to its inhaled use.

Overview of nitric oxide (NO):
- (1) NO is an endogenous molecule (aka. Endothelium-derived relaxing factor (EDRF)) synthesised throughout the body (Eg. endothelium, neurons, macrophages/PMNL, vascular and skeletal muscle, platelets, Etc.)
- (2) Inhaled NO is used to treat pulmonary HT (following cardiopulmonary bypass or in newborns), treat severe RSHF, treat RDS in premature infants, and improve oxygenation with severe ALI/ARDS
- (3) NO is also a potential contaminant in N₂O cylinders

Production of endogenous NO:
- NO is synthesised from one of the terminal guanidine N-atoms of L-arginine in a reaction catalysed by Nitric Oxide Synthase (NOS)
- NOS belongs to a family of Ca²⁺-activated enzymes with 2 forms:
  - (i) Constitutive – Present in endothelium (artery > vein), neurons, skeletal muscle, cardiac tissue and platelets → continuously produce NO
  - (ii) Inducible – Upregulated in endothelium (artery > vein), vascular SM, myocytes, macrophages and PMNLs in response to cytokines/endotoxins → produce large [NO] and related-free radicals → cytotoxicity and ↑ capillary leakage

Mechanism of action of NO:
- NO diffuses from the producing cells (Eg. endothelium, neuron, Etc.) into the target cells (Eg. VSMC, platelet, Etc.) → activates guanylyl cyclase (converts GTP to cGMP) → ↑ IC [cGMP] → activates various protein kinases that cause ↓ IC [Ca²⁺] → various effects (Eg. VSMC relaxation, ↓ platelet aggregation, neurotransmission, Etc.)
- Produces localised effects only due to short t ½ (< 5 secs) → endogenous NO readily binds to Fe²⁺ of haeme-based proteins (esp Hb to form Met-Hb) where it is inactivated

Aside – SNP and organic nitrates (Eg. GTN) exert their pharmacological effects via spontaneous release of NO or metabolism to NO in SM cells

Physiological effects of NO:

<table>
<thead>
<tr>
<th>System</th>
<th>Physiological effects</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>Regulates basal vasodilator tone (and vascular resistance) of systemic and pulmonary arterioles → flow-induced shear stress and pulsatile arterial flow causes continuous local NO production → vasorelaxant effect</td>
<td>NO deficiency → Essential HTN and cerebral vasospasms after SAH (as NO inactivated by Hb in bleed)</td>
</tr>
<tr>
<td></td>
<td>Main autoregulatory factor of regional blood flow (esp cerebral and pulmonary BF) → ↑ local NO production by endothelium 2° to ↓ PaO₂ → ↑ CBF and PBF</td>
<td>NO excess → Septic shock and cirrhosis (hypotension, hyperdynamic state and ↑ capillary leakage)</td>
</tr>
<tr>
<td></td>
<td>Direct –ve ino- and chronotropy</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Regulates basal vasodilator tone (and vascular resistance) of pulmonary arterioles → opposes hypoxic-induced pulmonary vasoconstriction</td>
<td>NO deficiency → Pulmonary HT</td>
</tr>
<tr>
<td></td>
<td>May cause bronchodilation</td>
<td></td>
</tr>
<tr>
<td>CNS and PNS</td>
<td>CNS – NO is a NT in neurons within brain/spinal cord → released in response to glutamate excitation of NMDA receptors → role in arousal, pain and memory</td>
<td>Suppression of NO → ↑ anaesthesia 2° to ↓ CNS excitation (MAC-sparing effect)</td>
</tr>
</tbody>
</table>
PNS – NO is a NT in non-Adr/non-cholinergic neurons → controls GI motility (via ENS) and blood flow within corpus cavernosum (penile erection)

<table>
<thead>
<tr>
<th>Haematological and immunological</th>
<th>- Endothelium-derived NO inhibits platelet aggregation/activation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Cytokines/endotoxins stimulate NO synthesis in macrophages/PMNL → degrade phagocytosed pathogens</td>
</tr>
<tr>
<td></td>
<td>- High avidity for Hb (1500x ↑ cf. CO!)</td>
</tr>
</tbody>
</table>

- NO excess → Epilepsy, morphine-induced constipation

- NO deficiency → ↑ infection risk, ↑ atherosclerosis 2° to platelet aggregation/vasoconstriction
- NO excess → ↑ bleed risk, ↑ inflammation

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**Clinical use of inhaled NO:**

- **Indications:**
  - (i) Treat pulmonary HT (following cardiopulmonary bypass or in newborns)
  - (ii) Improve oxygenation with severe ALI and ARDS
  - (iii) Treat severe RSHF
  - (iv) Treat RDS in premature infants

- **Mechanism:**
  - (i) Selectively relaxes and dilates pulmonary vessels
    - Inhaled NO diffuses from alveoli to pulmonary vasculature → causes pulmonary arteriolar vasodilation in proportion to degree of pulmonary vascular resistance via aforementioned MOA of NO → ONLY has significant effect on ↓ PVR if there is underlying pulmonary vasoconstriction (i.e. a/w hypoxia)
    - Lacks systemic effects (i.e. hypotension, bleeding) due to rapid metabolism
  - (ii) Also induces bronchodilation

- **Clinical effects:**
  - (i) Bronchodilation
  - (ii) Improved V/Q matching and PaO₂ (↑ PBF through well-ventilated lung regions)
  - (iii) ↓ RV pressures, PAP and PVR
  - (iv) ↑ RVEF and C.O.

- **Pharmacokinetics:**
  - Highly lipid soluble → diffuses across membranes readily
  - Rapidly metabolised (t ½ < 5 secs) → inhaled NO is converted nitrates/nitrites in O₂, and in blood it avidly binds to Hb to form met-Hb

- **Delivery:**
  - Dose of 10-40 ppm delivered into inspiratory circuit of ventilatory via a synchronised inspiratory injection system → maintains constant inspired [NO] despite changes in minute ventilation
  - Requires accurate monitoring via chemiluminescence or electrochemical analysis (accurate to 1 ppm!)

- **Side-effects and issues:**
  - (i) Met-Hb → rarely significant unless risk factors present (i.e. children, MetHb reductase deficiency, concurrent oxidising drugs)
  - (ii) Severe rebound hypoxaemia and PHT with abrupt cessation (thus, wean slowly!)
  - (iii) Pulmonary toxicity → NO is oxidised to NO₂ (esp with high FIO₂), which is cytotoxic → thus, close monitoring of NO delivery is essential
  - (iv) Scavenging may be required if unit poorly-ventilated → limit environmental NO levels < 25 ppm for 8 hrs (time-weighted average)

Contraindications – MetHb, ICH, bleeding diathesis, severe LVF