

Drugs used in Asthma and COPD

Dr Andrew Smith



Outline

- Modes of Delivery
- Overview of the drugs used in Asthma and COPD
 - β -Agonists
 - Anti-Muscarinics
 - Xanthines
 - Corticosteroids
 - Leukotriene Receptor Antagonists
 - Monoclonal Antibodies
 - Others inc. LTOT
 - Pregnancy and Breastfeeding
- Summary
- *Treatment Regimens:*
 - *Long-term management of Asthma*
 - *Acute Exacerbation of Asthma*
 - *Long-term Management of COPD*
 - *Acute Exacerbation of COPD*



Modes of Delivery

- Oral
- Inhalers:
 - **Metered dose** – the standard inhaler. Fixed amount of aerosol drug is administered.
 - **Breath-activated** (may still be pressurised, or dry powder). Easier to use. Examples are the Accuhaler or Turbohaler.
 - **Spacers** can be used to help increase drug delivery.
 - *Inhaler Technique:* www.asthma.org.uk/Sites/healthcare-professionals/pages/inhaler-demos
- **Nebulisers** – air or oxygen is driven through liquid drug via face mask.
- **Intravenous.**



β 2-Agonists – e.g. Salbutamol

- Act directly on smooth muscle causing bronchodilation.
 - *Beta-adrenergic receptors are coupled to stimulatory G proteins which activate adenylyl cyclase, which catalyzes the production of cAMP. In the lung, cAMP causes a decrease in the intracellular calcium concentration and, via activation of protein kinase A, both inactivates myosin light chain kinase and activates myosin light chain phosphatase. In addition, beta-2 agonists open large conductance calcium-activated potassium channels. The combination of decreased intracellular calcium, increased membrane potassium conductance, and decreased myosin light chain kinase activity leads to smooth muscle relaxation and bronchodilation.*
- Have a rapid onset of action so can be used symptomatically or before exercise.
- Long acting versions are used when preventative therapy is required.
- Used in both asthma and COPD.



β2-Agonists

Short acting (3-5 hours) – *INH, NEB, PO, SC, IM and/or IV*

- Salbutamol – Inh 100-200µg qds, Neb 2.5-5mg, IV from 5µg/min
- Terbutaline – Inh 500µg qds, Neb 5-10mg, IV from 90µg/min

Long Acting (12 hours) – *Inhaled only*

- Salmeterol – 50-100µg bd
- Formoterol – 12µg bd



Side-effects

Fine tremor, muscle cramps, nervous tension, palpitations, tachycardia, sleep disturbance, hypokalaemia (*a therapeutic aim in some situations!*)
Paroxysmal bronchospasm can occur.



Anti-Muscarinics – e.g. Ipratropium

- Cause bronchodilation and reduce mucus secretion by blocking muscarinic acetylcholine receptors in the lung which promotes the degradation of cGMP.
- They have longer action and greater bronchodilator effect than the β_2 agonists.
- Used in both asthma and COPD.

Short Acting – *Inhalation and nebulised*

- Ipratropium Bromide

Long Acting - *Inhaled only*

- Tiotropium

Side Effects

- Dry mouth, nausea, constipation. Caution in those with bladder outlet obstruction and glaucoma



Methylxanthines – e.g. Theophylline

- Act as a:
 - **Phosphodiesterase inhibitor** – raising cAMP and therefore bronchodilation
 - **Adenosine receptor blocker** – causing bronchodilation
 - **Histone deacetylase activator** – suppressing genes involved in inflammation.
- Related to caffeine.
- Primarily used in acute/chronic asthma. There is still debate for its use in COPD.

Types:

- Theophylline – given PO
- Aminophylline (more soluble) – given PO or IV
- A loading dose is required for the xanthine-naive



Methylxanthines

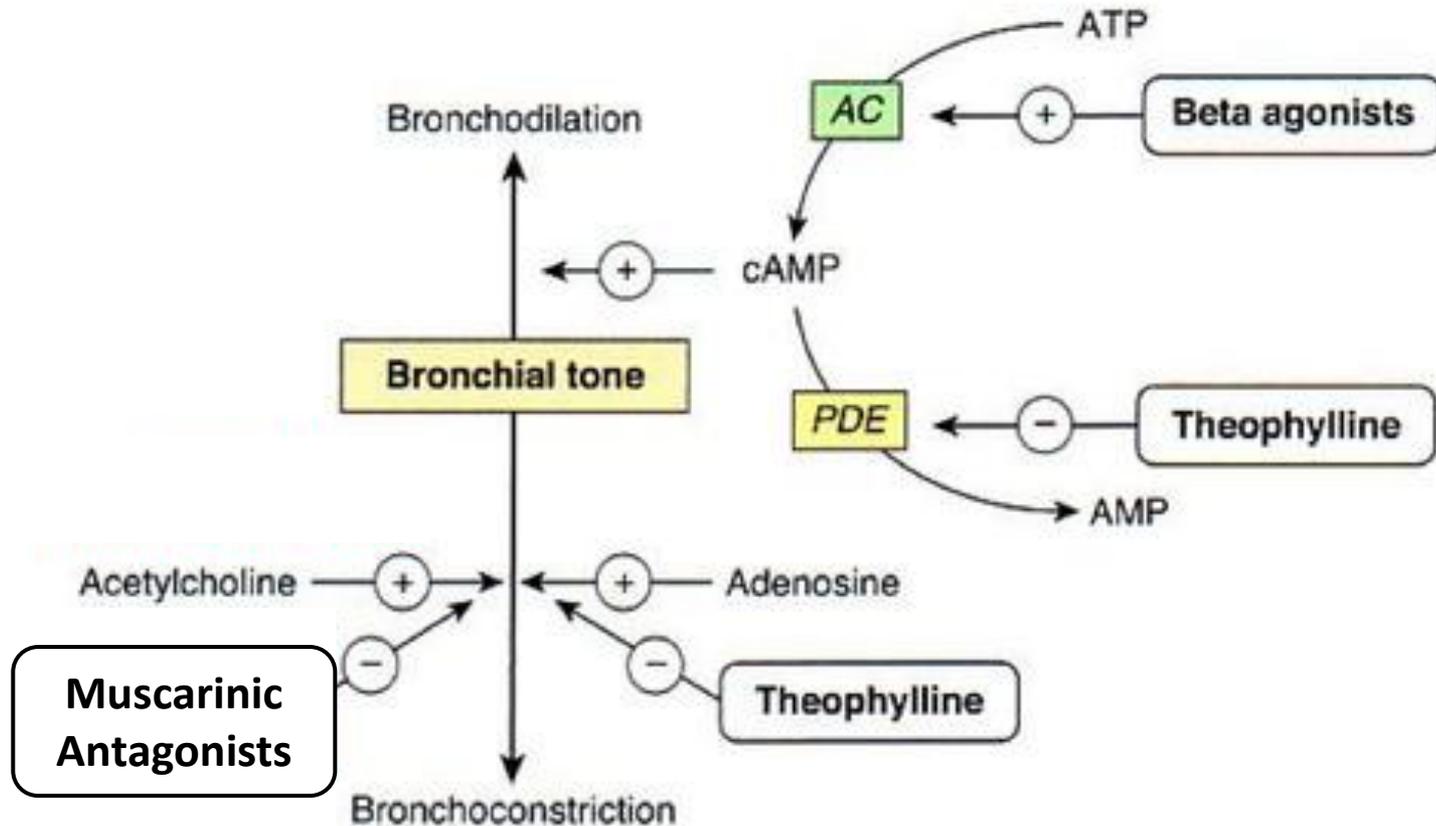
- The therapeutic range is narrow (10-20mg/L). Plasma level monitoring is therefore required.
- It is metabolised in the liver by cytochrome P450 so its concentration is affected by liver disease and enzyme inhibitors/inducers.

Side effects

- Gastro – Nausea, vomiting, gastric irritation, diarrhoea
- Cardiac – palpitations, tachycardia, arrhythmias (mainly due to its effect on adenosine)
- CNS – headache, insomnia, convulsions



Summary of β -agonists, Anti-Muscarinics and Theophylline



AC: Adenylate Cyclase

PDE: Phosphodiesterase

(c)AMP: (cyclic) Adenosine Monophosphate

Corticosteroids

- Used in the prevention and acute management of both asthma and COPD. In COPD, their preventative use should be assessed by a steroid trial.
- *The anti-inflammatory effects are mediated either by direct binding of the glucocorticoid/glucocorticoid receptor complex to glucocorticoid responsive elements in the promoter region of genes, or by an interaction of this complex with other transcription factors, altering gene transcription.*
- *Glucocorticoids inhibit many inflammation-associated molecules such as cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules. And up-regulate anti-inflammatory molecules*
- **All in all they reduce inflammation, oedema and secretions.**



Corticosteroids

Can be given by numerous routes:

Inhaled

- Beclometasone 200-400 μg bd, up to 800 μg bd
- Budesonide- 100-800 μg bd

Oral

- Prednisolone – 30-60mg od

IV

- Hydrocortisone – 100-200mg

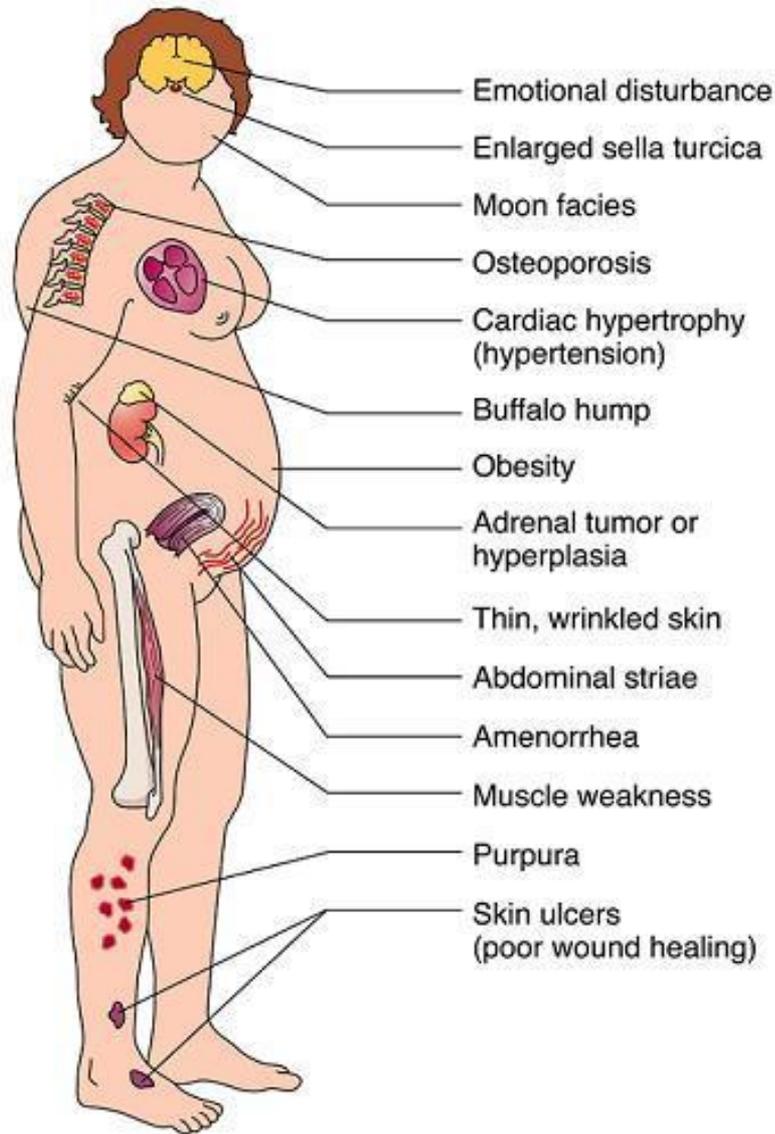
Note, oral and IV steroids have the same benefit in the acute setting (presuming the patient can swallow and isn't vomiting!)

Inhaled Side-effects

- Inhaled steroids have lowered systemic absorption but systemic effects can occur; especially with long use and high doses.
- Furthermore, inhaled steroids can increase oral thrush and lower respiratory tract infections (advise the patient to wash mouth out after use)



Corticosteroids – Systemic Side Effects!



Endocrine: HPA suppression, hyperglycemia

Musculoskeletal: growth retardation, skeletal-muscle myopathy, osteoporosis/fractures, aseptic necrosis of bone, subcutaneous tissue atrophy

Central nervous system: psychiatric disturbances, pseudotumor cerebri

Immune system: impaired wound healing, leukocyte and monocyte inhibition

Fluid/electrolyte balance: sodium and water retention, hypokalemia

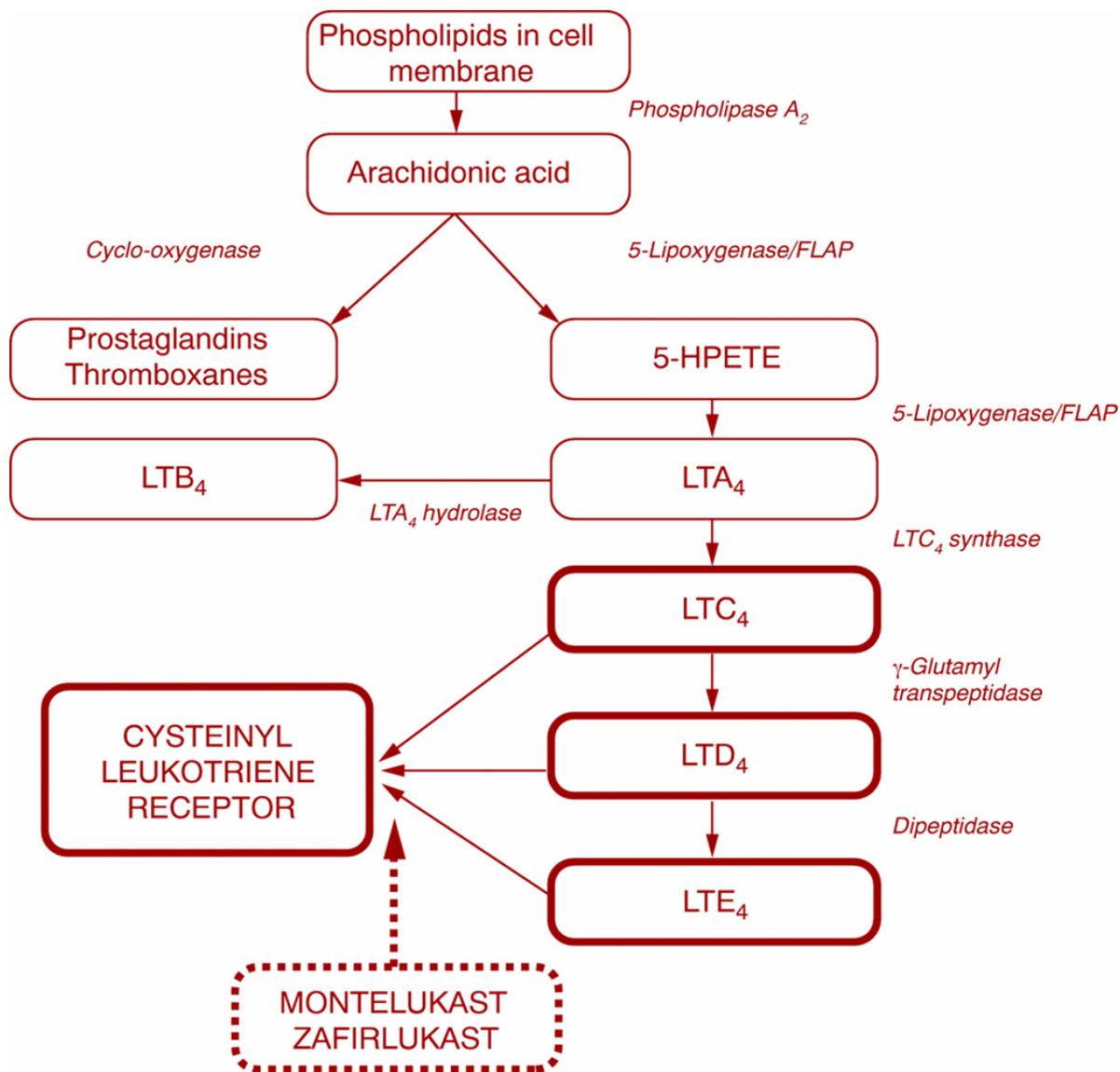
Cardiovascular: hypertension

Ophthalmologic: glaucoma, posterior subcapsular cataracts

Other: pancreatitis, skin striae, moon facies, central redistribution of fat



Leukotriene Receptor Antagonists — e.g. Montelukast



- Block the effects of cysteinyl leukotrienes.
- Used in asthma and have an additive benefit with corticosteroids.
- Of benefit in aspirin and exercise induced asthma.

Leukotriene Receptor Antagonists

Types

- Montelukast – 10mg in the evening PO
- Zafirlukast – 20mg bd PO

Side-effects

- Gastrointestinal disturbances, headache, insomnia, arthralgia, myalgia, bleeding disorders.
- Rare reports of Churg-Strauss syndrome, especially when corticosteroids are reduced. Be aware of eosinophilia, vasculitic rash and worsening pulmonary symptoms.

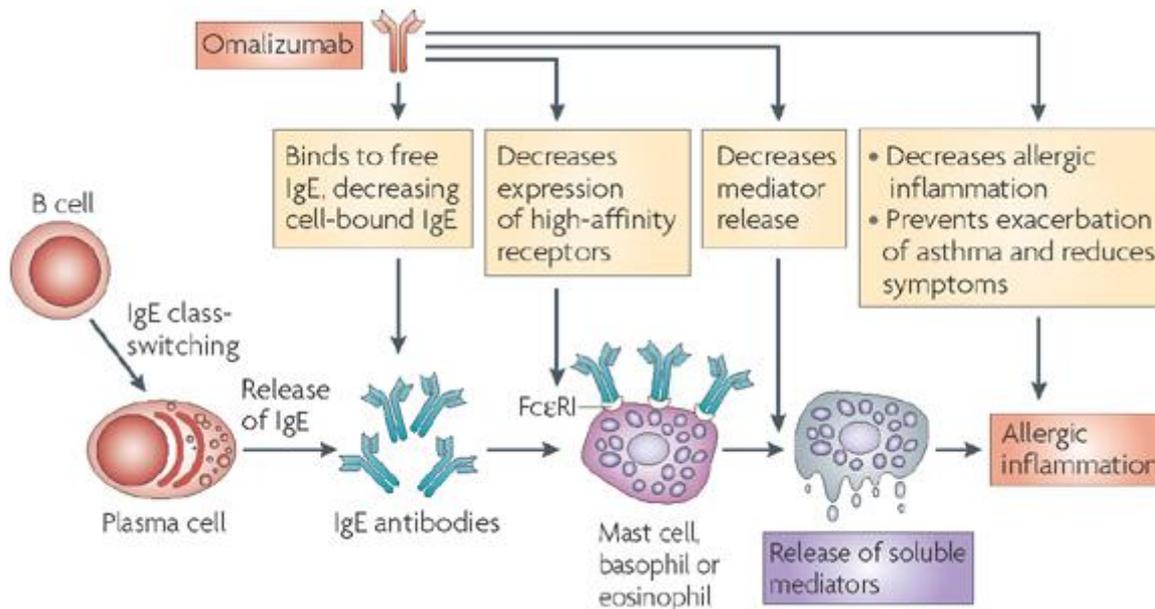


Anti-IgE Monoclonal - Omalizumab

- Used in allergic asthma for those who have failed all conventional treatment.
- Initiated only by specialists (£250 per 1ml).
- Given by subcutaneous injection every 2-4 weeks – dose varies for bodyweight and IgE concentration

- Little evidence so manufacturer advises caution in hepatic and renal disease.

- Side effects are legion. Can cause hypersensitivity reactions.



Other Asthma Medications

Note, you can get compound medications which are mixtures of two drugs, e.g.:

- β 2-agonist and steroid e.g Symbicort
- β 2-agonist and anti-muscarinic e.g. Combivent

Magnesium Sulphate

- 1.2-2g given by IV infusion over 20 minutes
- Used in acute severe asthma.
- Believed to antagonise calcium; raised intracellular calcium causes histamine release and bronchospasm.
- Caution in kidney disease due to renal excretion. Side effects: As per hypermagnesaemia – nausea, vomiting, thirst, hypotension, arrhythmias, weakness, respiratory depression, coma.

Cromoglicate

- Inhaled 10mg qds up to 6-8 times daily.
- Mode of action is not completely understood although believed to stabilise mast cells, reducing cytokine release.
- Side effects are usually local – throat irritation, cough. Paradoxical bronchospasm can occur.

Pregnancy and Breastfeeding with Asthma

- It is important to maintain adequate control of asthma during pregnancy.
- Medications should be converted to oral if possible although most are generally safe to use (including intravenous medications, but see below)



Cautions

- There have been reports of neonatal apnoeas and irritable infants when Xanthines are used, but still indicated as safe.
- There is little evidence with the leukotriene inhibitors. Manufacturers advise to avoid their use unless mandatory for adequate control.
- Omalizumab manufacturer advises to avoid

Other COPD Medications

Roflumilast

- Given orally – 500µg od.
- Is a Phosphodiesterase Type-4 Inhibitors
- Licensed as an adjunct to bronchodilators in severe COPD associated with bronchitis.
- Caution in hepatic disease, latent infection and past psychiatric disease. Side-effects: gastrointestinal disturbance, myalgia and mood change.

Carbocisteine

- Given orally – 2.25g → 1.5g in divided doses.
- Mucolytic which reduces mucus viscosity. Shown to reduce exacerbations in those with productive coughs.
- Caution in those with previous gastric ulcer disease due to effects on gastric mucosal barrier

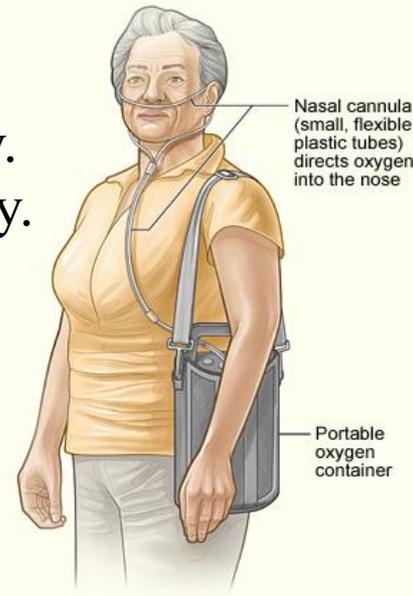
Doxapram

- 1.5-4mg/min
- Is a respiratory stimulant and only recommended when non-invasive ventilation is considered inappropriate
- Stimulates chemoreceptors in the carotid bodies of the carotid arteries, which in turn, stimulates the respiratory centre in the brain stem.
- Side-effects/Cautions – see BNF!

(Briefly:) Long Term Oxygen Therapy

Main eligibility:

- Patients with PaO₂ of <7.3 when stable (no infection) in air.
- Patients with a PaO₂ of 7.3-8kPa with evidence of polycythaemia, nocturnal hypoxaemia, peripheral oedema or pulmonary hypertension.
- Also used in chronic severe asthma, cystic fibrosis, neuromuscular conditions and more.
- Benefit is only seen with use of more than 15 hours a day.
- Substantial benefit only seen with over 19 hours use a day.
- Patients require lots of education and regular review.
- Smoking can cause burns and explosions!



Acute Oxygen delivery, including NIV, is covered in a separate talk

Summary

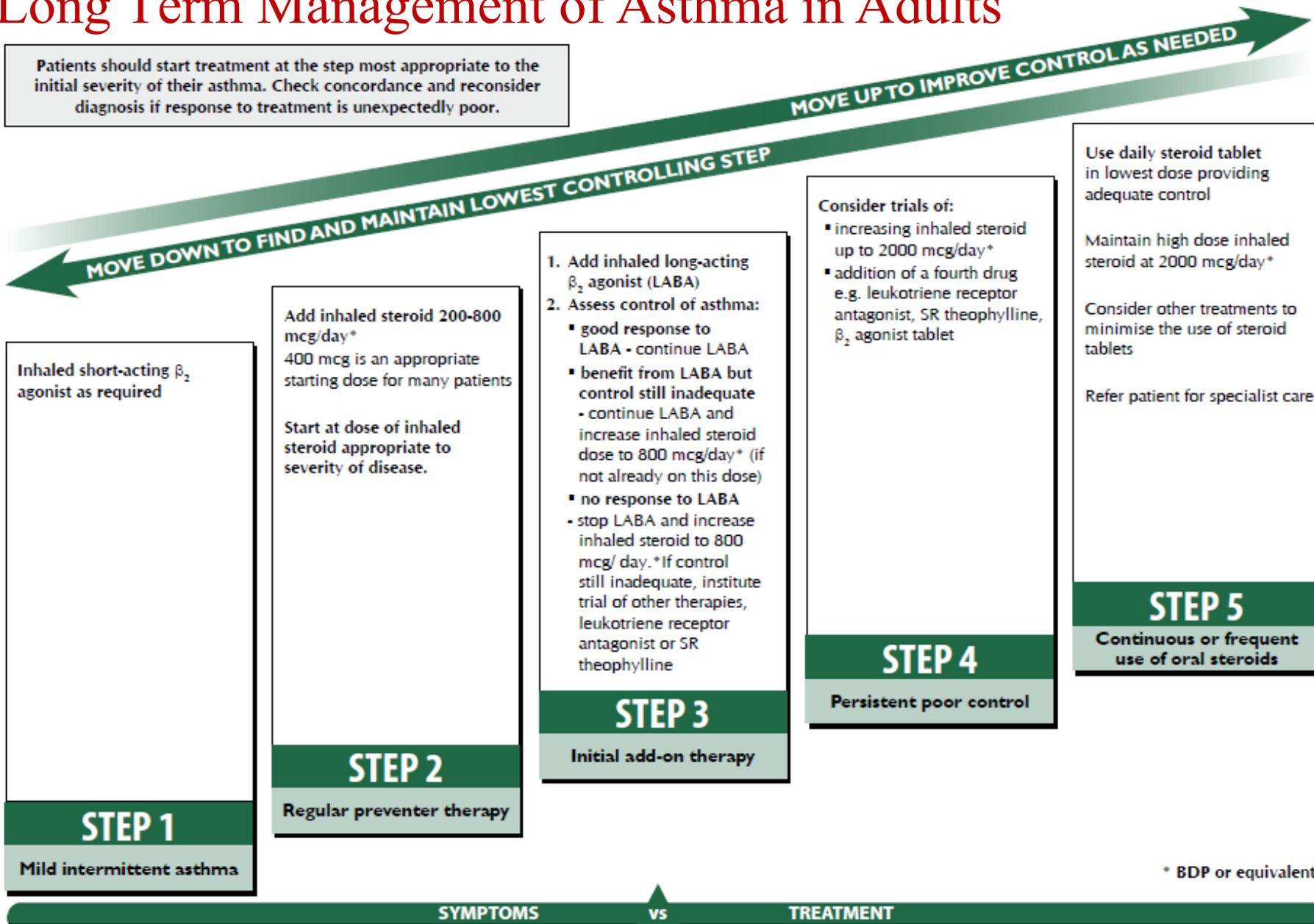
- Many of the same drugs are used in both asthma and COPD, albeit with differing importance.
- Inhaled treatments are preferred where possible, so as to limit systemic absorption.
- Nebulised treatments are the mainstay in the acute setting.
- As with most conditions, MDT input, education and lifestyle advice is important.

- *The following slides provide brief summaries of the management of acute and chronic asthma/COPD. They should be supplemented with further reading!*



Long Term Management of Asthma in Adults

Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response to treatment is unexpectedly poor.



Inhaled short-acting β_2 agonist as required

STEP 1
Mild intermittent asthma

Add inhaled steroid 200-800 mcg/day*
400 mcg is an appropriate starting dose for many patients

Start at dose of inhaled steroid appropriate to severity of disease.

STEP 2
Regular preventer therapy

- Add inhaled long-acting β_2 agonist (LABA)
- Assess control of asthma:
 - good response to LABA - continue LABA
 - benefit from LABA but control still inadequate - continue LABA and increase inhaled steroid dose to 800 mcg/day* (if not already on this dose)
 - no response to LABA - stop LABA and increase inhaled steroid to 800 mcg/day.* If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline

STEP 3
Initial add-on therapy

Consider trials of:

- increasing inhaled steroid up to 2000 mcg/day*
- addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, β_2 agonist tablet

STEP 4
Persistent poor control

Use daily steroid tablet in lowest dose providing adequate control

Maintain high dose inhaled steroid at 2000 mcg/day*

Consider other treatments to minimise the use of steroid tablets

Refer patient for specialist care

STEP 5
Continuous or frequent use of oral steroids

* BDP or equivalent



*Acute Asthma Exacerbation Management

R
E
A
S
S
E
S

- O₂ via Non-Rebreathe mask
- Nebulised Salbutamol (2.5-5mg)
- Nebulised Ipratopium (500µg)
- Corticosteroids (100-200mg IV, 40mg PO)
- IV MgSO₄ (1.2-2g)
• IV Salbutamol (5µg/min)
• IV Aminophylline (5mg/kg loading then 500mcg/kg/hr)

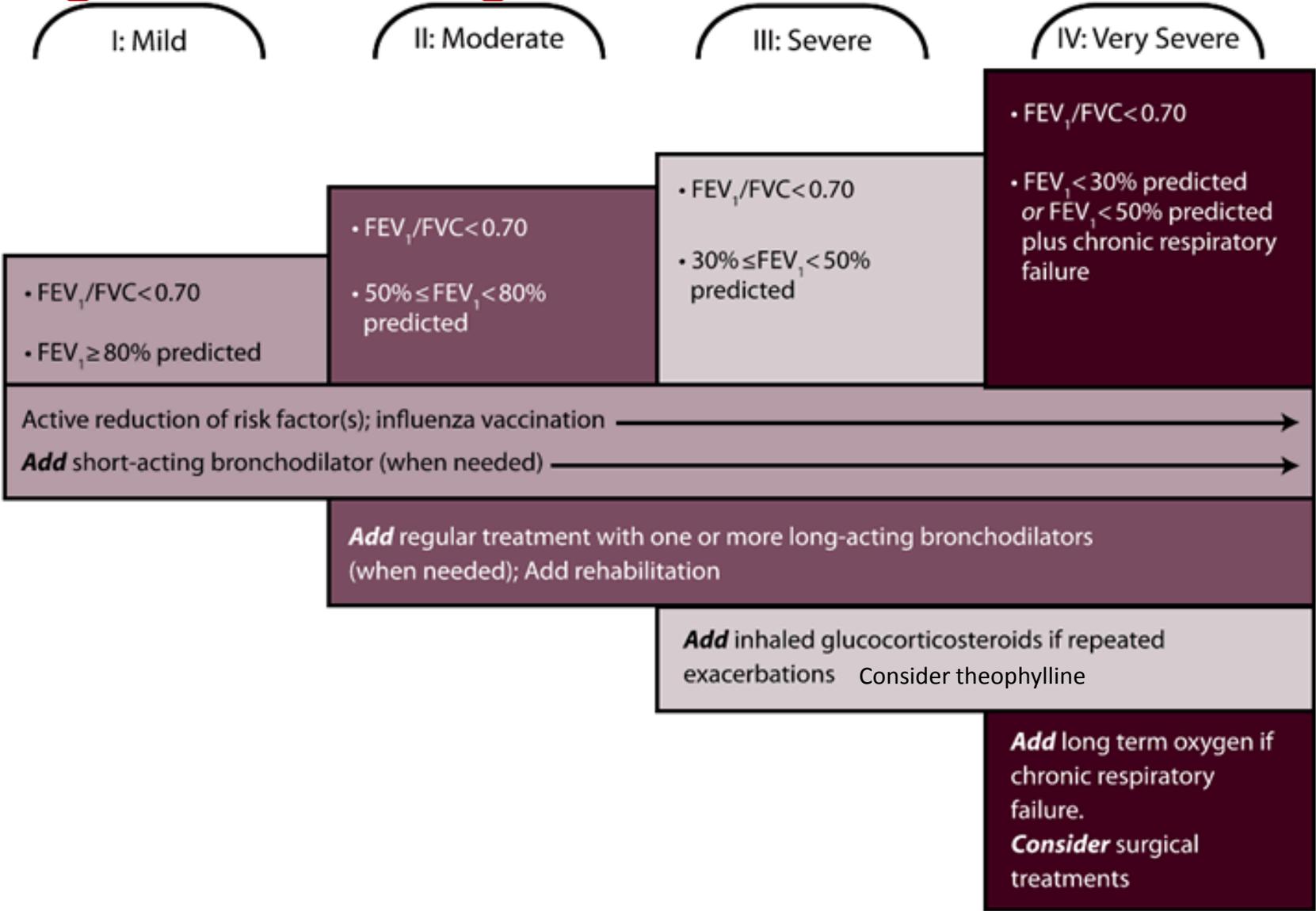
C
A
L
L

F
O
R

H
E
L
P

*Brief overview of... (See www.sign.ac.uk/pdf/qrg101.pdf or Oxford Handbook for more detail)

Long Term Management of COPD



*Brief overview of... (See www.nice.org.uk/nicemedia/live/13029/49399/49399.pdf or OHCM)

*Acute COPD Exacerbation Management

R
E
A
S
S
E
S
S

- Controlled Oxygen Therapy
- *(remember, hypoxia kills before hypercapnia)*

- Nebulised Salbutamol and Ipratropium

- IV or PO corticosteroids

- Are Antibiotics Needed?

- Consider Non-invasive ventilation

C
A
L
L

F
O
R

H
E
L
P

Thank-You

Any Questions?

