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Prescribing in Chronic Obstructive Pulmonary Disease (COPD)

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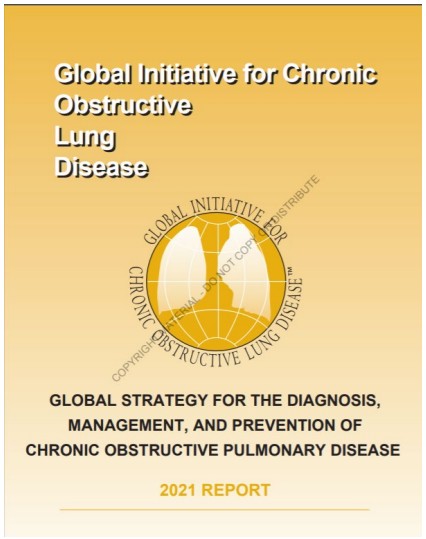
Aims

- RPS (2020) Competency framework for prescribers
- Guidelines
  - NICE (Updated 2019)
  - GOLD (2021)
- Assessment / Diagnosis
- Management of stable COPD
- Management of acute exacerbations

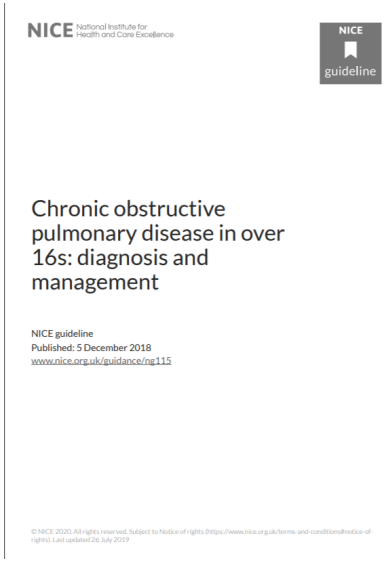
Guidelines

GOLD (2021)



https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf

NICE (2018, Update 2019)



https://www.nice.org.uk/guidance/ng115/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-pdf-66141600098245

COPD Definition

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COPD, a common preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and /or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

GOLD 2021 (www.goldcopd.org)

Emphysema

Pathological diagnosis

Chronic Bronchitis

Clinical diagnosis

COPD

PHYSIOLOGICAL DIAGNOSIS:
Post-BD
FEV_1/FVC <0.7

When to suspect COPD

- **Smokers or ex-smokers (including cannabis) over 35 with a 10 year history of smoking or greater who have any symptoms of COPD:**
  - **Exertional breathlessness**
  - **Chronic cough**
  - **Regular sputum production**
  - **Frequent winter 'bronchitis'**
  - **Wheeze**
- **No signs of asthma**
  - **Significantly variable breathlessness**
  - **Night-time wakening with breathlessness and/or wheeze**
  - **Significant diurnal or day-to-day variability of symptoms.**

Spirometry

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- **Post-bronchodilator FEV1 / FVC < 0.7**

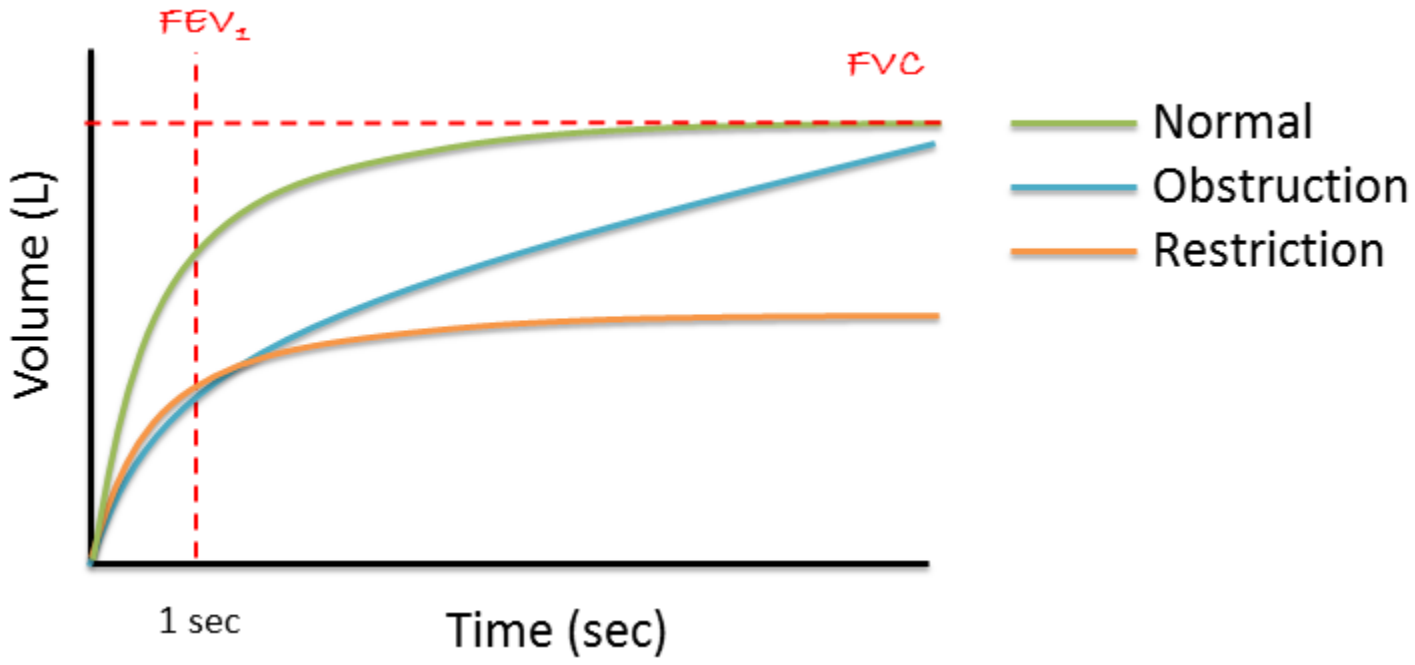
  FEV1 (Forced Expiratory Volume in one second)

  FVC (Forced Vital Capacity)

- **Bronchodilation:**
  - **Nebulised 2.5mg – 5mg salbutamol.**
  - **Inhaled via pMDI and disposable spacer 4 puffs x 100 micrograms salbutamol.**
  - **Measure lung function 15 minutes after β2-agonist.**

FEV1 % predicted	Severity of airflow obstruction
≥ 80%	Stage 1 - Mild
50-79%	Stage 2 - Moderate
30-49%	Stage 3 - Severe
<30%	Stage 4 - Very Severe

Volume time curve



Goals of COPD assessment:

- **Symptom burden**
  - **COPD Assessment Test (CAT) 0-40**

MRC DYSPNOEA SCALE (for COPD patients)	
Grade	**Impact**
1	Not troubled by breathlessness except on vigorous exertion
2	Short of breath when hurrying or walking up inclines
3	Walks slower than contemporaries because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100 m or stops after a few minutes' walking on the level
5	Too breathless to leave the house or breathless on dressing or undressing

- **Exacerbation risk**
  - **Frequent = 2 or more per year or 1 requiring hospital admission**
  - **No. of exacerbations in previous year**
  - **Declining airflow obstruction**
- **Comorbidities**

GOLD classification

Exacerbation risk

≥2 exacerbations or 1 requiring hospital	**C** High risk, less symptoms	**D** High risk, more symptoms
0-1 exacerbation	**A** Low risk, less symptoms	**B** Low risk, more symptoms
	mMRC 0-1 **CAT < 10**	**mMRC2-4** **CAT > 10**

Symptom burden

Other Investigations

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Investigation	Role
CXR CT scan	Rule out other pathologies Investigate symptoms disproportionate to spirometry, suitability for LVR surgery
Full blood count Hb, Hct, Eosinophil count	Anaemia, polycythaemia, eosinophilia
BMI	Nutritional status, prognostic factor
Serial PEFR	Exclude asthma
ECG Serum natriuretic peptides ECHO	If cardiac disease / pulmonary hypertension suspected
Alpha-1 Antitrypsin	If early onset, minimal smoking history, family history
Transfer Factor for carbon monoxide (TLCO)	Investigate symptoms disproportionate to spirometry
Pulse oximetry	To assess need for oxygen therapy, if cyanosis or cor pulmonale present or FEV1 < 50%
Sputum Culture	To identify organisms if sputum is persistently present and purulent or frequent exacerbator

Differential diagnosis

- **Further investigation required:**
  - **Copious / purulent sputum**
  - **Restriction on spirometry**

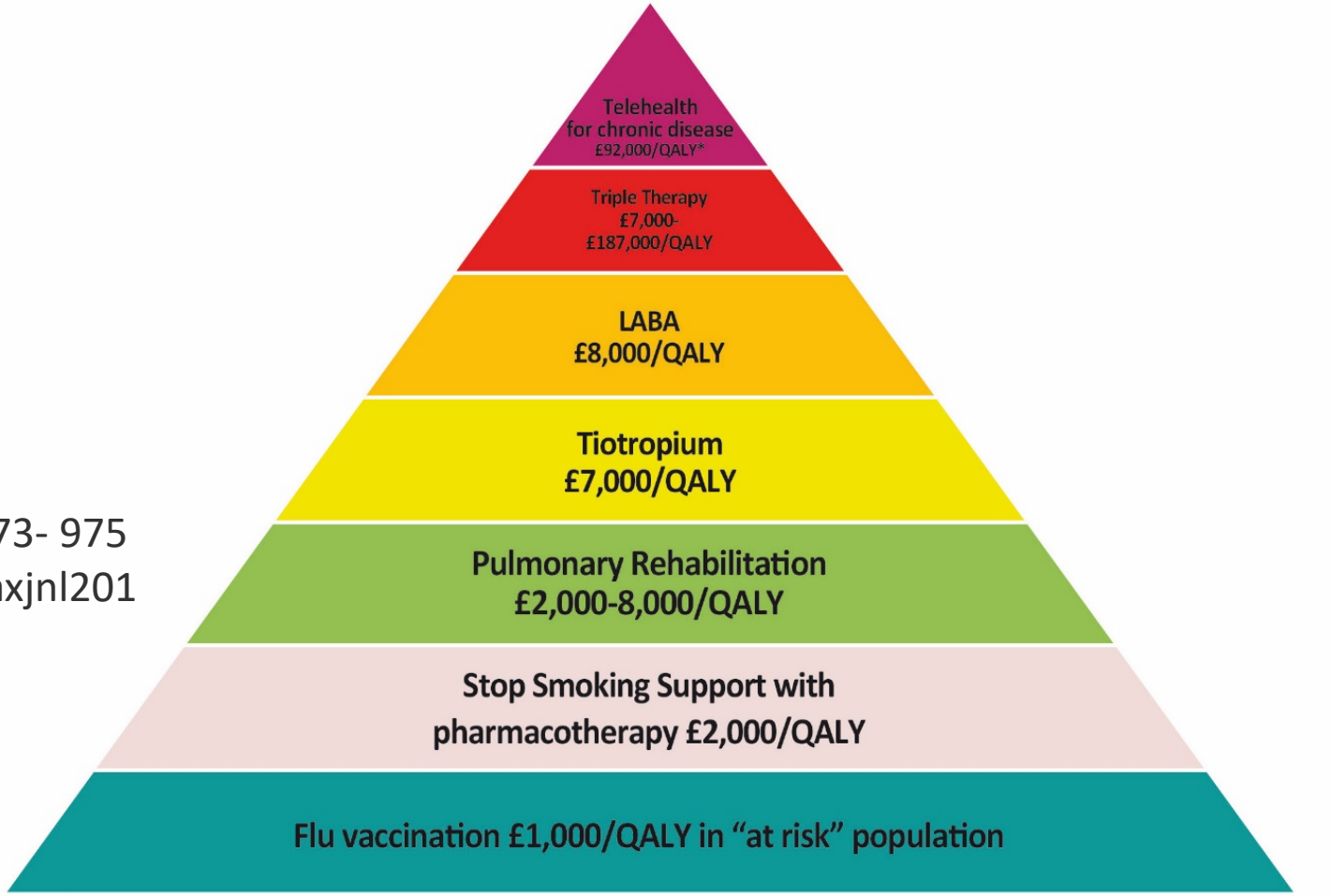
- **Red flags**
  - **Haemoptysis**
  - **Clubbing**
  - **Weight loss**
  - **Night sweats**

Management of Stable COPD

Aims:

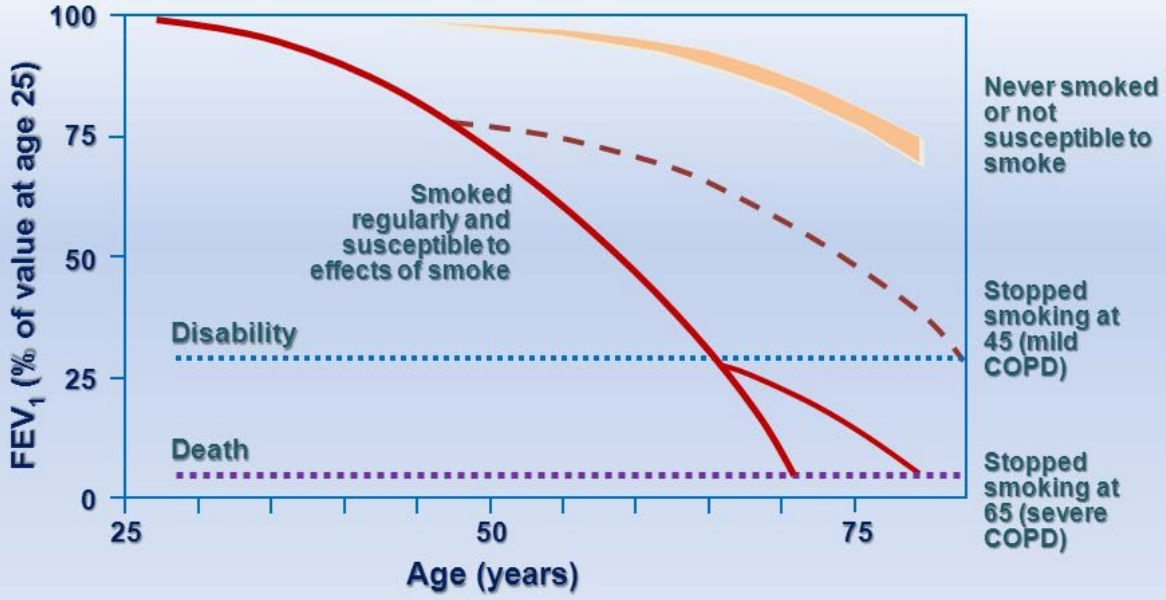
- Reduce symptoms
- Reduce frequency and severity of exacerbations
- Improve exercise tolerance
- Improve health status

London Respiratory Network "Value Pyramid"



Thorax 2014;69:973- 975
doi:10.1136/thoraxjnl2014-205667

COPD Risk and Smoking Cessation



Fletcher CM, Peto R. *BMJ*. 1977;1:1645-1648

- **National centre for smoking cessation and training**

https://www.ncsct.co.uk/publication_very-brief-advice.php

- **Smoking is an enzyme inducer (CYP1A2)**

Pulmonary rehabilitation

- **Offer to every patient with:**
  - **Confirmed COPD diagnosis**
  - **BREATHLESSNESS MRC≥3**
  - **Hospital admission for COPD or frequent exacerbations irrespective of MRC score, provided COPD diagnosis confirmed).**
- **If MRC score 1 or 2 offer EXERCISE ON REFERRAL and local LIFESTYLE EDUCATION program.**
- **https://www.blf.org.uk/support-for-you/keep-active/pulmonary-rehabilitation**

Inhaled therapy options for COPD

- **Bronchodilators:**
  - **Beta 2 agonists (Short Acting - SABA / Long Acting - LABA)**
  - **Muscarinic antagonists (SAMA / LAMA)**

- **Inhaled corticosteroids (ICS)**

- **Combinations**
  - **LABA / LAMA**
  - **ICS / LABA**
  - **ICS / LABA / LAMA (triple therapy)**

Inhaled therapy guide

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Step 1 – MILD – Few symptoms, ≤1 exacerbation / year

- PRN SABA / SAMA

Step 2 – MODERATE – MRC 2, ≤1 exacerbation / year

- Regular LAMA or LABA
- Continue SABA, Stop SAMA

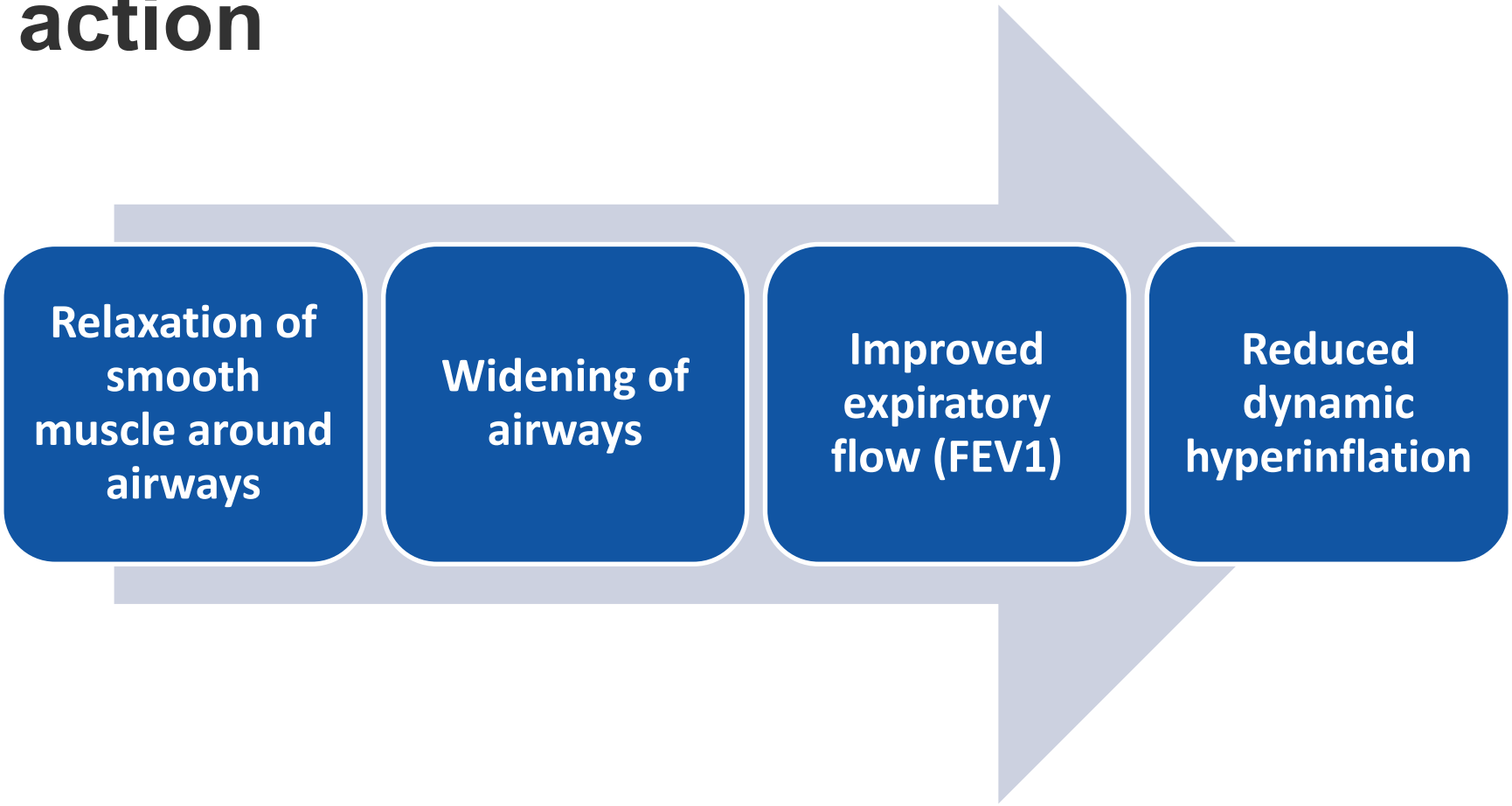
Step 3 – SEVERE – MRC 3 and /or ≥ 2 exacerbations / year

- Regular LAMA / LABA combination
- Or Regular ICS / LABA combination (if concomitant asthma)

Step 4 – VERY SEVERE – Progressive breathlessness or ongoing exacerbations

- "Triple therapy"
- ICS / LABA / LAMA combination

Bronchodilators – Mechanism of action



Beta 2 agonists

Short acting (SABA)	Long acting (LABA)
Salbutamol 100mcg 2 doses Four times daily	Salmeterol 25mcg (Serevent®) 2 doses Twice daily

Beta$_2$-adrenoceptor – Sympathetic

- Bind to beta$_2$-adrenoceptors in bronchial smooth muscle wall
- Receptors are coupled to a G-stimulatory protein
- Stimulates the formation of cAMP (cyclic adenosine monophosphate)
- cAMP inhibits myosin light chain kinase
- MLC phosphorylation leads to cross-bridge formation between the myosin heads and the actin filaments and hence, smooth muscle contraction.
- Inhibition of this process prevents contraction of muscle

Side effect

Site	Type	Effect
Cardiac muscle	$beta_1$	Tachycardia Arrhythmia
Vascular smooth muscle	$beta_2$	Systemic vasodilation
Skeletal muscle	$beta_2$	Fine tremor

Caution

- **Can cause hypokalaemia**
  - **Higher doses**
  - **In conjunction with corticosteroids / theophylline**

Beta Blockers (for treatment of co-existing heart failure)

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- Beta blockers (predominantly cardio-selective) may confer reductions in mortality, exacerbations, and hospital admissions in patients with COPD, in addition to the benefits attributable to addressing cardiovascular risk.
- COPD is not a contraindication to beta blockers
- BMJ (2011) https://www.bmj.com/content/342/bmj.d2549

Muscarinic antagonists

Short acting (SAMA)

- Ipratropium (Atrovent)
  - (Atrovent® pMDI)
  - 20 mcg
  - Two doses, four times daily or as required

Long acting (LAMA)

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Inhaler name	Drug name	Frequency	
Spireva® handihaler®	Tiotropium 18mcg	One dose Once daily	
Braltus® Zonda®	Tiotropium 10mcg	One dose Once daily	
Incruse® Ellipta®	Umeclidinium 55 mcg	One dose Once daily	

Antimuscarinic - parasympathetic

- Binds to muscarinic receptors on bronchial smooth muscle
- Inhibit action of acetylcholine
- Prevents increase in intracellular concentration of Calcium ion
- Calcium binding required to expose active binding sites on actin for myosin
- Prevent bronchoconstriction

Side effects

- Poorly absorbed therefore relatively mild side effects
- Dry mouth
- GI Motility disorder
- Urinary retention

Caution

Ipratropium - Glaucoma

LAMA or LABA?

Both:

- Improved lung function
- Improved dyspnoea
- Improved health status

LAMA:

- Greater effect on exacerbation reduction
- Reduce hospitalisation

Cochrane Review, 2012: Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. https://doi.org/10.1002/14651858.CD009157.pub2

Dual bronchodilator (LABA/LAMA)

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Inhaler name	LAMA	LABA	Frequency	
Anoro® Ellipta®	Umeclidinium 55 mcg	Vilanterol 22 mcg	One dose Once daily	
Ultibro Breezhaler®	Glycopyrronium 50mcg	Indacaterol 110mcg	One dose Once daily	
Spiolto® Respimat®	Tiotropium 2.5mcg	Olodaterol 2.5mcg	Two doses Once daily	
Duaklir® Genuair	Aclidinium 340mcg	Formoterol 12mcg	One dose Twice daily	

Dual bronchodilator (LABA/LAMA)

Compared with other dual therapy combinations and with monotherapy:

- Reduced risk of moderate to severe exacerbations
- Greater improvement in symptoms and QOL scores
- Improved lung function

Cochrane review, 2018: Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. https://doi.org/10.1002/14651858.CD012620.pub2

- Most cost-effective option.

Inhaled corticosteroids

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- Reduce frequency of exacerbations
- Reduce severity of exacerbations
  - Oral corticosteroids
  - Hospitalisation
- Risk:
  - Pneumonia
  - Local and systemic side effects
- Use for people with features of asthma/steroid responsiveness
- Always in combination with LABA

Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. European Respiratory Journal 2009 34: 641-647; DOI: 10.1183/09031936.00193908

Combination (ICS / LABA)

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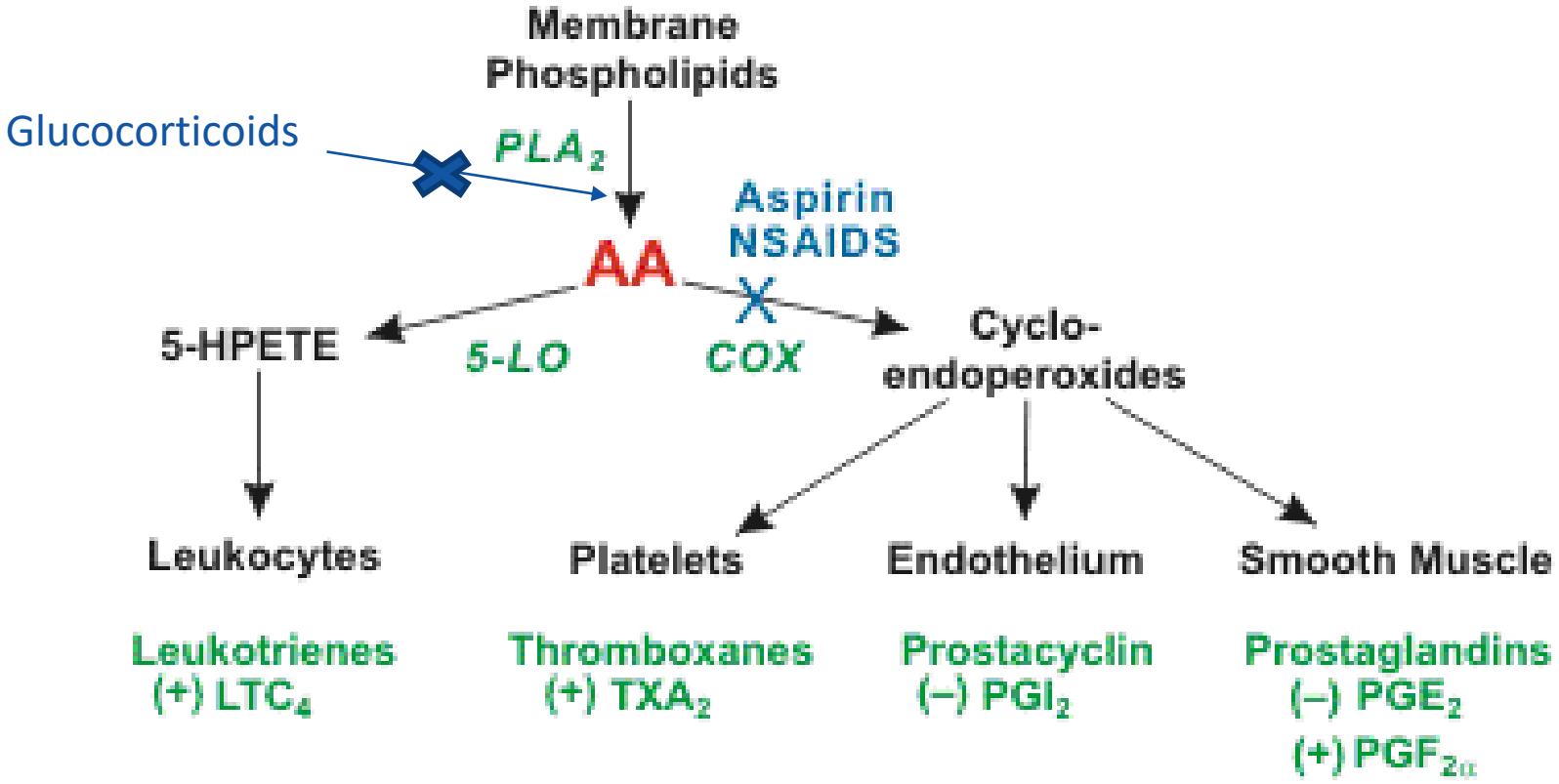
Name	ICS	LABA	Frequency	
Fostair® pMDI	Beclometasone 100mcg	Formoterol 6mcg	Two doses Twice daily	
Relvar® Ellipta®	Fluticasone Furoate 92 mcg	Vilanterol 22 mcg	Once daily	
DuoResp® Spiromax®	Budesonide 160mcg <u>Or</u> 320mcg	Formoterol 4.5mcg <u>Or</u> 9mcg	Two doses Twice daily <u>Or</u> One dose Twice daily	
Seretide® Accuhaler	Fluticasone propionate 500mcg	Salmeterol 50mcg	One dose Once daily	

Triple therapy

Name	ICS	LAMA	LABA	Frequency	
Trelegy® Ellipta®	Fluticasone furoate 92mcg	Umeclidinium bromide 55mcg	Vilanterol 22mcg	One dose Once daily	
Trimbow ®	Beclomethasone fine particle 87mcg	Glycopyrronium 9mcg	Formoterol 5mcg	Two doses Twice daily	

Inflammatory pathway



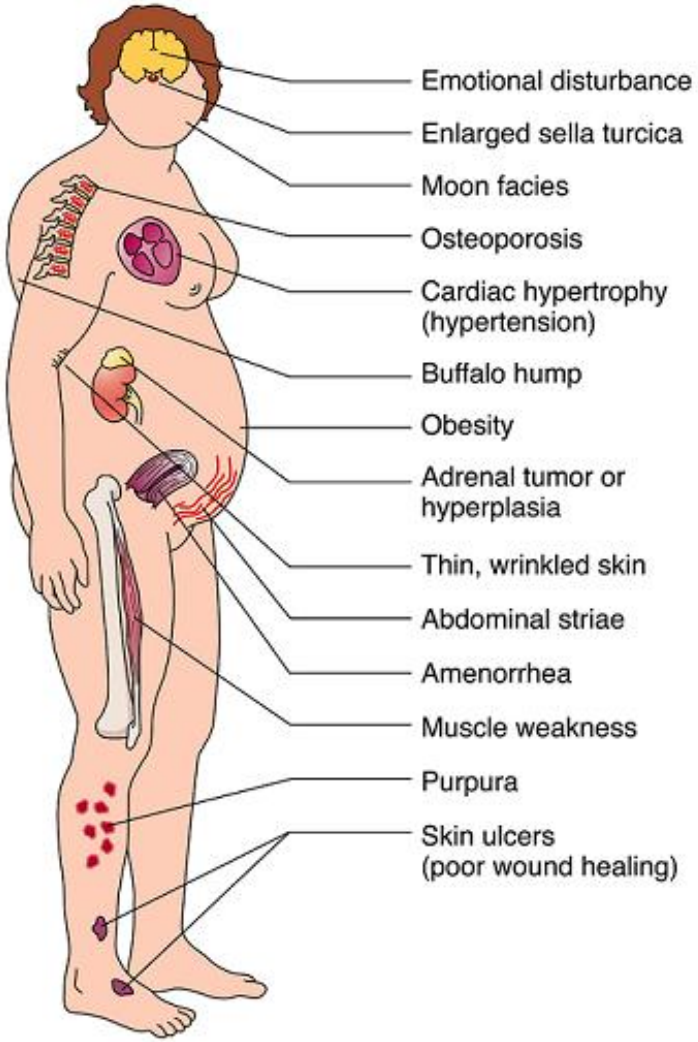
Abbreviations: AA, arachidonic acid; PLA_2, phospholipase A_2; PLC, phospholipase C; COX, cyclooxygenase; NSAIDS, non-steroidal anti-inflammatory drugs; +, vasoconstriction; –, vasodilation.

https://www.cvphysiology.com

Corticosteroids

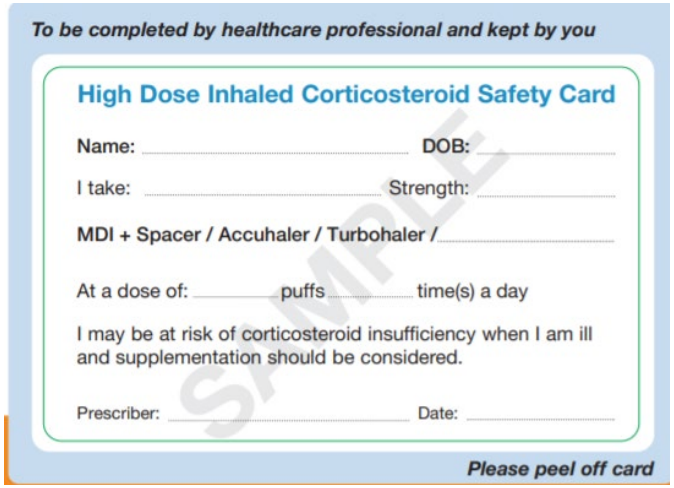
- Bind to glucocorticoid receptor to form receptor-ligand complex.
- Activated complex translocates into the cell nucleus
- Causes up-regulation of anti-inflammatory proteins.
- Also represses expression of pro-inflammatory proteins in the cytosol by preventing translocation of other transcription factors from the cytosol into the nucleus.
- Reduced inflammation in airways
- Reduced mucus secretion

Side effects



High dose inhaled corticosteroid

- **Any patient on long-term high dose ICS (≥ 1000micrograms of standard beclometasone daily or equivalent) should be provided with a High Dose Inhaled Steroid card**



To be completed by healthcare professional and kept by you

High Dose Inhaled Corticosteroid Safety Card

Name: _____ DOB: _____

I take: _____ Strength: _____

MDI + Spacer / Accuhaler / Turbohaler / _____

At a dose of: _____ puffs _____ time(s) a day

I may be at risk of corticosteroid insufficiency when I am ill and supplementation should be considered.

Prescriber: _____ Date: _____

SAMPLE

Please peel off card

You have been given this safety card because you are taking a high dose of inhaled corticosteroid.

It is important that you do NOT stop using your inhaled corticosteroid suddenly, particularly if you have been taking this medication for more than 3 weeks.

Be sure to get your repeat prescription of your inhaler before it runs out.

Always carry this card with you and show it to your medical team if you become ill.

NHS England

https://www.networks.nhs.uk/nhs-networks/london-lungs/documents/inhaled-corticosteroids-in-adults

ICS conversion chart

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	Total Daily Dose of Inhaled Corticosteroid		
	Low dose No ICS card required	Intermediate dose Consider an ICS card	High dose ICS card is required
Beclometasone dipropionate			
Aerosol Inhaler (prescribe by brand name)			
Non-proprietary	<800 micrograms	800-1000 micrograms	≥1000 micrograms
Clenil modulite	<800 micrograms	800-1000 micrograms	≥1000 micrograms
Qvar (BDP HFA)	<400 micrograms	400-500 micrograms	≥500 micrograms
Fostair (BDP HFA)	<400 micrograms	400-500 micrograms	≥500 micrograms
Dry Powder Inhaler			
Asmabec Clickhaler	<800 micrograms	800-1000 micrograms	≥1000 micrograms
Budesonide			
Dry Powder Inhaler			
Easyhaler, Novolizer	<800 micrograms	800-1000 micrograms	≥1000 micrograms
Turbohaler (Pulmicort, Symbicort)	<800 micrograms	800-1000 micrograms	≥1000 micrograms
Ciclesonide			
Aerosol Inhaler Alvesco	≤240 micrograms	320 micrograms	≥480 micrograms
Fluticasone propionate (FP)			
Aerosol Inhaler			
Flixotide, Flutiform▼, Seretide	<400 micrograms	400-500 micrograms	≥500 micrograms
Dry Powder Inhaler			
Flixotide and Seretide	<400 micrograms	400-500 micrograms	≥500 micrograms
Fluticasone furoate (FF)*			
Dry Powder Inhaler Relvar▼		Literature not available*	
Mometasone furoate			
Dry Powder Inhaler Asmanex	220 micrograms	440 micrograms	≥880 micrograms

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Device / technique

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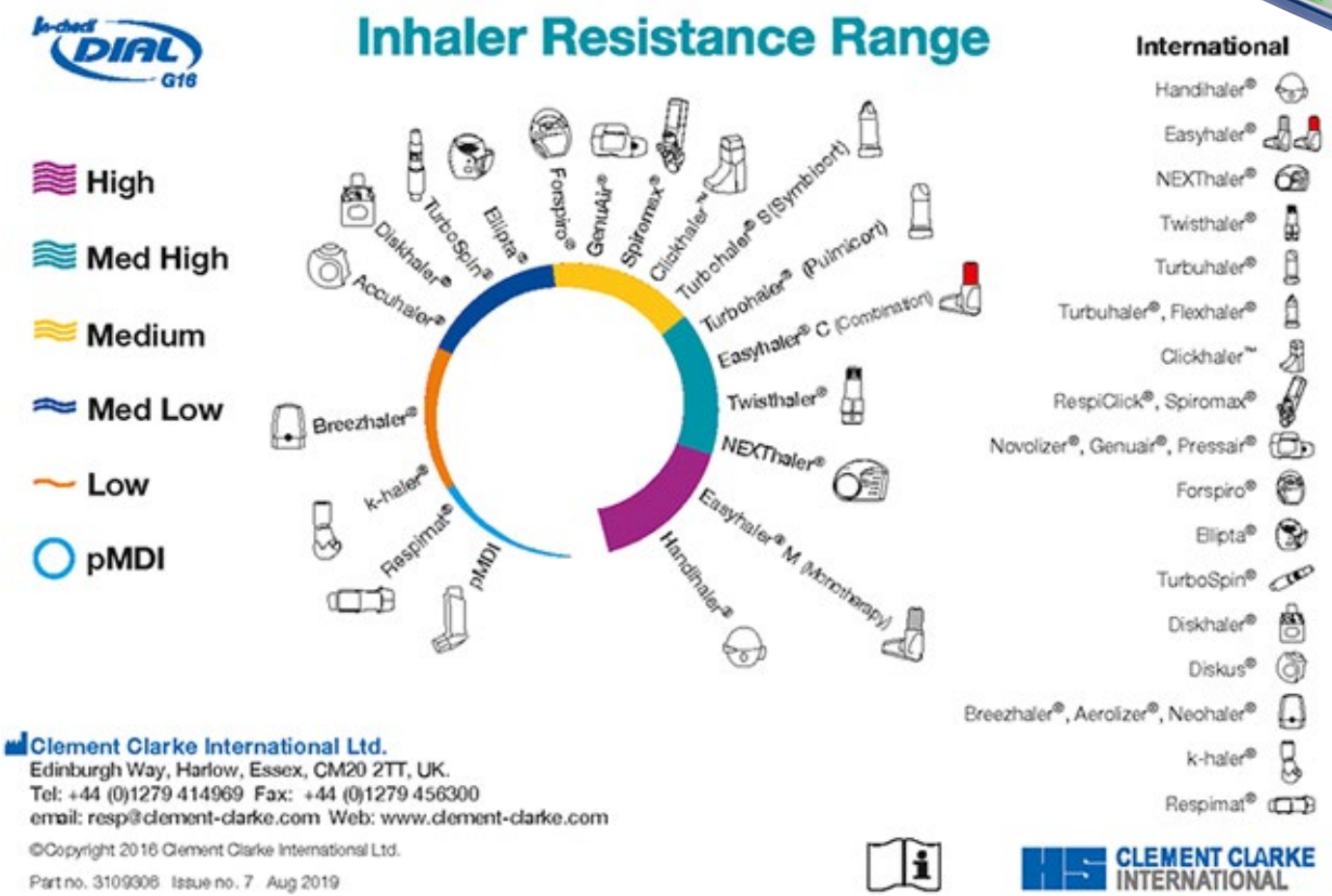
Inhaler Device Types - The inhaler colour will vary depending on drug content						
Aerosol and Spacer devices "*Slow and Steady*" inspiration			**Dry Powder devices** "*Quick and Deep*" inspiration			
Metered Dose Inhaler	**Volumatic®**	**Aerochamber® Plus**	**HandiHaler®**	**Zonda®**	**Ellipta®**	**Spiromax®**
						
			Inspiratory flow required 30-60L/min	Inspiratory flow required 30-60L/min	Inspiratory flow required 30-90L/min NB: Anoro® Ellipta® shown above. Relvar Ellipta® has yellow cap. Incruse Ellipta has green cap	Inspiratory flow required 30-90L/min

- NCL formulary
  - Narrow
  - Based on patient focus groups
  - Ease of use and regime
- Prescribe by BRAND NAME

Inspiratory flow



https://www.haag-streit.com/clement-clarke/products/inhaler-technique/in-check-dial-g16

Choice and competency

- UK inhaler group: Inhaler standards and competency document

https://www.respiratoryfutures.org.uk/media/69775/ukig-inhaler-standards-january-2017.pdf

- NICE patient decision tool for asthma

https://www.nice.org.uk/guidance/ng80/resources/inhalers-for-asthma-patient-decision-aid-pdf-6727144573

Acute exacerbation of COPD

- **"A sustained worsening of a person's symptoms from their stable state beyond usual day-to-day variations and is acute in onset" (NICE, 2018)**

- **Exacerbations can be associated with:**
  - **Breathlessness**
  - **Sputum purulence**
  - **Sputum volume**
  - **Cough**

Management of acute exacerbations

Mild — Short acting bronchodilators

Moderate — Oral steroids +/- Antibiotics

Severe — A+E / Hospitalisation

Management of acute exacerbations

- Oral prednisolone 30mg OD for 5 days (NICE, 2019)
  - Caution hyperglycaemia

- <u>Only if purulent sputum</u>
  - Add Oral antibiotics
    - Amoxicillin 500mg TDS for 5 days
    - Doxycycline 200mg on day 1 then 100mg OD for 4 further days

https://www.gov.uk/government/publications/managing-common-infections-guidance-for-primary-care(as Oral antibiotics

Frequent exacerbations

- Secondary care
- Respiratory physiotherapy

- Prophylactic antibiotic (Azithromycin)
  - May reduce exacerbation rate
- Mucolytic (Carbocisteine)
  - Reduce viscosity of mucus (Break disulphide bond)
  - May reduce exacerbations in select patient group
- Phosphodiesterase inhibitors (Rofumilast)
  - Reduce inflammation (inhibit breakdown of intracellular cAMP)
  - Severe/Very severe COPD, frequent exacerbations
  - Improved lung function and reduced exacerbations

Other respiratory medications - Insufficient evidence

- **Anti-IL-5 monoclonal antibody (Mepolizumab) and Anti-IL-5 receptor-α antibody (Benralizumab)**
  - **Severe COPD, frequent exacerbations, high eosinophil count**
  - **Reduces eosinophils**
  - **Further studies required**
- **Methylxanthine (Theophylline)**
  - **Bronchodilator and vasodilator effect**
  - **Narrow therapeutic index – caution with enzyme inducer / inhibitors**
- **Leukotriene modifier (Montelukast)**
  - **Reduce inflammatory mediator, inhibit bronchoconstriction**

Resources

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- NICE

https://www.nice.org.uk/guidance/ng115/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-pdf-66141600098245

- GOLD

https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf

- CCG

https://gps.northcentrallondonccg.nhs.uk/

- BLF

https://www.blf.org.uk/support-for-you/copd

- BTS

https://www.brit-thoracic.org.uk/quality-improvement/guidelines/home-oxygen/