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Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine

EXPERT REVIEW

Pharmacotherapies for COPD

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Abstract: This review article summarizes the main treatments for chronic obstructive pulmonary disease, their mechanisms, and the key evidence from trials supporting their use. Drug classes covered were short acting beta agonists (SABA), short acting muscarinic antagonists (SAMA), long acting beta agonists (LABA), long acting antimuscarinics (LAMA), inhaled corticosteroids (ICS), LABA/ICS combinations, specific phosphodiesterase (PDE4) inhibitors, non-specific PDE inhibitors, mucolytics, and oxygen. Non-specific therapies, such as opiates for relief of dyspnoea and therapies for smoking cessation, are also covered briefly. For each class of drug, mechanisms of action are described, key clinical trial results are reported, and available agents compared. Finally, the place of each drug in therapy is compared between current worldwide guidelines.

Keywords: chronic obstructive pulmonary disease, pharmacotherapies, disease management

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Introduction

Chronic obstructive pulmonary disease (COPD) is a multi-component disease which is both preventable and treatable. It is currently the fourth leading cause of death worldwide and predicted to be the third by 2020.[1] Globally the burden of disease is projected to increase in the coming decades due to continued exposure to COPD risk factors and an ageing population.[1]

COPD is characterized by airflow limitation that is progressive and not fully reversible; the latest severity categorization also includes exacerbation frequency and symptom burden as key features.[1] COPD is associated with an enhanced chronic inflammatory response which is responsible for the airway abnormalities and architectural distortion of the lung parenchyma. In affected individuals lung function deteriorates progressively over several years, with increasing symptoms such as cough, sputum production, and dyspnoea. Acute exacerbations are defined by increased cough, dyspnea, or increased sputum purulence from baseline,[2] and punctuate the disease process with a deleterious impact on patients' daily activities and well-being.[3] Frequent exacerbations are associated with more rapid decline of lung function[4] and are one of the greatest costs to the health economy, partly through hospital admissions, and partly through loss of work days.[5] Although mainly categorized by airflow limitation, in many patients the disease seems to be associated with several extra-pulmonary manifestations. What is unclear at present is whether these manifestations are directly related to COPD or are just an independent consequence of the exposure to common causal effects such as tobacco smoking and inactivity. The most widely recognized manifestations include the presence of concomitant cardiovascular disease, skeletal muscle dysfunction, osteoporosis, and clinical depression/anxiety.[6] These co-morbidities interact to increase the risk of hospitalization and mortality in COPD patients, especially as the airway obstruction becomes more severe.[7] The main goals in management of COPD are improving health status, reducing symptoms, preserving lung function decline, preventing exacerbations, and reducing mortality. This review outlines the pharmacological management of stable COPD.

Bronchodilators

Dyspnoea is one of the hallmark symptoms of COPD and one of the most common reasons for health resource utilization and increasing anxiety in affected patients.[8] Dynamic hyperinflation as a result of increased lung volumes is a key reason why patients experience dyspnoea. Long acting bronchodilators reduce lung volumes by a reduction in air trapping and facilitate the emptying of the lungs.[9] The subsequent improvement in inspiratory capacity leads to reduced dyspnoea and improved exercise tolerance.[8] The available long acting bronchodilators include B_2 agonists and anti-muscarinics.

Beta 2 adrenoceptor agonists (B2-agonists)

Mechanism of action

B_2 adrenergic receptors (B_2AR) are present in high density in airway smooth muscle cells. B_2 agonists act by binding to the B_2AR (Fig. 1). Interaction of the receptor with intracellular G proteins stimulates the production of intracellular cyclic adenosine monophosphate (cAMP). This leads to activation of protein kinase A, which results in phosphorylation of various targets mediating smooth muscle relaxation. The exact targets are unknown but probably involve myosin light chain kinase and calcium dependent potassium channels.[10]

B_2AR are also present in vascular endothelium, ciliated cells, circulating inflammatory cells (such as eosinophils), and sub-mucosal glands. The presence of the receptor on these cells explains some of the non-bronchodilator effects, including attenuation of mast cell mediator release, reduction of plasma exudation, and reduced activation of sensory nerves. Other beneficial effects include enhancement of mucociliary transport,[11] attenuation of neutrophil recruitment,[12] and inhibition of smooth muscle cell proliferation.[13]

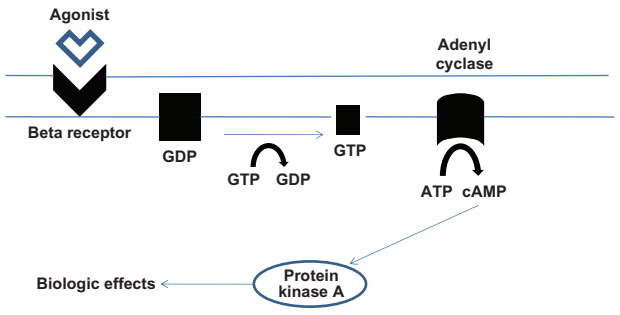

Figure 1. Mechanism of action of Beta agonists.
Notes: Binding of the agonist to the receptor results in a change in protein structure, which enables interaction with intracellular G proteins, production of cAMP and then protein kinase A, which mediates the bronchodilating effects via its actions on smooth muscle.

Short acting B_2AR agonists (SABAs)

Although many patients with COPD do not have reversible airflow obstruction, many have noted symptomatic improvement with the use of SABAs.[14] SABAs are used both in acute and chronic management of COPD, the most commonly used being Salbutamol. Once administered, the onset of action is within 3 minutes with peak activity after 2.5 hours. The duration of action is between 4 and 6 hours.[15] Salbutamol is mainly metabolized to a sulphate conjugate. Approximately 50% is excreted in this form with a smaller proportion as unchanged drug.[16] The most recent Cochrane review showed that use of SABAs for at least seven days improved post bronchodilator lung function in patients with moderate to severe COPD. Patients were also less dyspnoeic and more likely to comply with treatment.[14]

Long acting B_2AR agonists (LABAs)

This class of drug has recently been reviewed and compared to one of the long acting anti-muscarinic agents (LAMAs) by the Cochrane collaboration,[17] although significant trial heterogeneity precluded meta-analysis, primarily due to the fact that indacaterol's effect on health related quality of life (HRQoL) in particular differed from the other LABAs. Most of the primary studies of LABAs did not have exacerbation frequency as a primary outcome measure, although meta-analysis of their data has been carried out;[18] in general there is a class effect showing reduction in exacerbations against placebo. Their place in therapy is generally considered as one of the options for maintenance therapy in patients that are symptomatic despite regular SABA use;[1] treatment algorithms for the disease will be considered at the end of this article.

Salmeterol and formoterol

Salmeterol and formoterol are LABAs with extended duration of action maintained 12 hours after inhalation of a single dose,[19] which has led to their twice daily dosing. Formoterol's potency and speed of action make it effective in both quick relief and for prolonged effect. Despite these characteristics, it appears to be inferior to salmeterol in terms of health related quality of life (HRQoL) scores and its ability to reduce exacerbations, albeit in indirect comparisons only.[17] Salmeterol and formoterol have some important differences which can be explained by their physicochemical properties. Both are lipophilic, with salmeterol being far more so than formoterol; the relative water solubility of formoterol enables it to diffuse rapidly to the B_2AR and cause bronchodilation in between 1 to 3 minutes, similar to that of SABAs.[20] Salmeterol's onset of action is, at least 20 minutes, significantly longer.[21] Both drugs have adequate lipophilic properties that allow them to remain in the airway tissues in close vicinity to B_2AR, explaining the longer duration of action. There is also some evidence to suggest that salmeterol binds to an additional exosite within the receptor, potentiating the longer effect of the drug.[22] Secondly the intrinsic efficacy of the drugs varies—formoterol is a full agonist whilst salmeterol is a partial agonist; hypothetically this implies formoterol should provide better bronchodilation.

Salmeterol xinafoate dissociates in solution to salmeterol and 1-hydroxy-2-naphthoic acid. These two compounds are then absorbed, distributed, metabolized, and excreted independently. The xinafoate moiety has no discernable pharmacological activity, is highly protein bound, and has a long elimination half-life of about 12 to 15 days in healthy individuals. The cytochrome P450 (CYP) isoform 3A4 is responsible for aliphatic oxidation of salmeterol base, which is extensively metabolized by hydroxylation, with the major metabolite being alpha-hydroxysalmeterol and with subsequent elimination predominantly in the feces.[23] Formoterol is metabolized primarily in the liver by CYP450 enzymes and undergoes glucuronidation and O-demethylation. Elimination of formoterol is via the urine and feces in ratios of two thirds and one third respectively, with 10% of urinary excretion being of unchanged drug.[24]

Clinical trials pertaining to the efficacy of formoterol and salmeterol are shown in Table 1. Whilst no head to head trials of the 2 agents have been done, indirect comparison within the Cochrane review[17] suggests that their effects are largely the same. Additionally, reduction in exacerbation rate was not maintained in patients on inhaled corticosteroids (ICS) and formoterol, unlike the other LABAs.[18]

Indacaterol is an ultra-long acting, once daily LABA; it is the only agent of this type currently on the

Table 1. Major randomized controlled trials (RCTs) of salmeterol and formoterol.

Trial	Duration	Outcome	Comparator
Salmeterol			
Boyd et al[25]	16 weeks	↑ FEV_1	Placebo
Mahler et al[26]	12 weeks	↑ FEV_1	Placebo, ipratropium*
Rennard et al[27]	12 weeks	↑ FEV_1	Placebo
Calverley et al[28] (TRISTAN)	1 year	↑ FEV_1 ↓ Exacerbations ↑ HRQoL	Placebo, fluticasone, fluticasone/salmeterol
Calverley et al[29] (TORCH)	3 years	↑ FEV_1 ↓ Exacerbations ↑ HRQoL	Placebo, fluticasone, salmeterol/fluticasone
Formoterol			
Dahl et al[30]	12 weeks	↑ FEV_1 ↓ Symptom scores	Placebo, ipratropium*
De Rossi et al[31]	1 year	↑ FEV_1	Placebo, theophylline*
Calverley et al[32]	1 year	↔ FEV_1 ↑ HRQoL	Placebo, budesonide, budesonide/formoterol
Szafranski et al[33]	1 year	↔ FEV_1 ↔ HRQoL	Placebo, budesonide, budesonide/formoterol

Notes: The table shows results against placebo; for results of the multicomponent trials against ICS and ICS/LABA please see text in relevant section. *Also significant result against active comparator.

market, although others are in development, including vilanterol.[34] It is a partial B_2 agonist which exhibits high intrinsic efficacy at the B_2AR, more than two fold that of salbutamol and salmeterol.[35] Partial agonists can exhibit antagonist behavior in the presence of an agonist with higher receptor efficacy, which could potentially result in inhibitory action of rescue medication, an effect which has been shown with salmeterol but not indacaterol.[35] Studies using indacaterol have demonstrated a relatively rapid onset of action (5 minutes) with peak effect occurring at 15 minutes and lasting 24 hours.[35] The rapid onset of action and length of duration of action is related to both the high affinity of indacaterol to the lipid raft domains within the B_2AR membrane and its intrinsic efficacy at the receptor level.[35] Following administration, the bioavailability of indacaterol is 43%, with a steady state reached after 12 to 14 days. It is primarily metabolized to a hydroxylated derivate by the CYP3A4 enzyme, and subsequent to this, to phenolic O glucuronides and other metabolites. Elimination occurs via the fecal route, with less than 2% being excreted unchanged in the urine.[35]

The clinical trials pertaining to indacaterol's efficacy are shown in Table 2. Current evidence suggests that indacaterol is superior to other LABAs with regard to HRQoL.[17] Sub-group analyses with regard to exacerbations showed that indacaterol had a greater effect on severe exacerbations (ie, hospitalized event rate).[18]

Safety

In general, apart from the occasional episode of tachycardia and tremor, both SABAs and LABAs are well tolerated. However, here has been some concern with regard to cardiovascular safety and use of B_2 agonists. Salpeter et al[41] suggested increased cardiovascular risk with LABAs compared with placebo, a fact hotly debated but disproven in subsequent meta-analyses in COPD.[42] It has also been suggested that tolerance/tachyphylaxis would render LABAs less efficacious over time. Data from Szafranski et al[33] and TORCH[29] has refuted this by demonstrating that the bronchodilator effect of LABA therapy is maintained at 1 and 3 years respectively.

Muscarinic antagonists

Mechanism of action

Para-sympathetic activity mediates both bronchial smooth muscle contraction and the release of mucus into the airway lumen through stimulation of muscarinic receptors, of which there are five distinct types (M1–M5).[43] Whilst the role of subtypes M4 and M5 are unknown, subtypes M1–M3 are expressed in human lungs. M1 receptors are expressed in

Table 2. Major RCTs for indacaterol.

Trial	Duration	Outcome	Comparator
Donohue et al[36] (INHANCE)	26 weeks	↑ HRQoL ↓ Dyspnoea (TDI)	Placebo, tiotropium
Dahl et al[37] (INVOLVE)	I year	↑ Bronchodilation (FEV_1) ↑ HRQoL ↓ Dyspnoea (TDI) Prolonged time to exacerbation	Placebo, formoterol
Buhl et al[38] (INTENSITY)	12 weeks	↔ Bronchodilation (FEV_1) ↑ HRQoL ↓ Dyspnoea (TDI)	Tiotropium
Kornmann et al[39] (INLIGHT-2)	12 weeks	↑ Bronchodilation (FEV_1) ↑ HRQoL ↓ Dyspnoea (TDI)	Placebo, salmeterol
Korn et al[40] (INSIST)	12 weeks	↑ Bronchodilation (FEV_1) ↓ Dyspnoea (TDI)	Salmeterol

Notes: The outcomes shown in the table are against the active comparator; good efficacy was also shown against placebo where this arm was used.
Abbreviations: TDI, transitional dyspnoea index.

peribronchial ganglia, whilst M3 receptors are present on bronchial smooth muscle cells; their relationship to one another is shown in Figure 2. Both mediate bronchomotor tone and reflex bronchoconstriction. M2 receptors are located in the post ganglionic para-sympathetic nerve and act as auto receptors. Agonistic stimulation of these receptors provides feedback and inhibition of further acetylcholine release; thus, optimal inhibition of the parasympathetic pathway would be achieved by selectively blocking M1 and M3 receptors.[43]

Short acting muscarinic antagonists (SAMAs)

Short acting muscarinic antagonists, like SABAs, are used both in the acute and chronic management of COPD. Ipratropium bromide is the most widely used following the discontinuation of Oxitropium bromide in 2004. Ipratropium blocks all muscarinic receptors without sub-type selectivity. Its onset of action is within minutes, with peak activity occurring between 1 and 2 hours and duration of action approximately 4 hours in the majority of patients.[43] In a systematic review, combination of LABAs with ipratropium showed a small benefit in pre bronchodilator FEV_1 of borderline statistical significance;[14] however, for the most part LABAs were superior. Head to head comparison suggested that tiotropium was superior,[44] and thus current guidance places LAMA ahead of SAMA for maintenance therapy.[5]

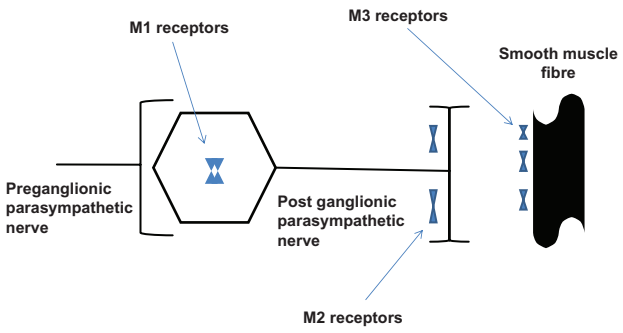

Figure 2. Location of anti-muscarinic receptors.
Notes: M1 receptors are expressed in peribronchial ganglia, whilst M3 are present on bronchial smooth muscle cells; both mediate bronchomotor tone and reflex bronchoconstriction. M2 receptors are located in the post ganglionic para-sympathetic nerve and act as auto receptors. The figure shows their relationship to one another.
Adapted from Lipson DA (2006).

Long acting muscarinic antagonists (LAMAs)

In general, the place of LAMAs in therapy is the same as LABAs. Until recently there was only one LAMA on the market (tiotropium), but two other products have recently been licensed (glycopyrronium and aclidinium). The Cochrane review of LABAs versus LAMAs[17] was only able to consider trials using tiotropium (due to their search dates) and concluded that its effects were superior to LABAs in terms of preventing exacerbations and disease related hospitalization. Nevertheless, drug choice for the individual patient may still suggest LABA as a good choice for some, ie, in patients with severe glaucoma; thus current guidance places the 2 classes of drug equal in therapy algorithms.[1,5] Few head to head trials of LAMAs

have been carried out, with the notable exception of GLOW2 (tiotropium versus glycopyrronium),[45] which concluded that the products were equivalent in terms of trough FEV_1, dyspnoea score, and exacerbation reduction. Aclidinium has been studied alongside tiotropium, but this trial was a small study of crossover design,[46] and therefore larger, more definitive studies are still needed. A summary of clinical effects, as demonstrated by the various LAMA trials, is shown in Table 3; since most effects (with the exception of speed of onset) appear to be roughly equivalent between the 3 drugs they have been tabulated together.

Tiotropium

Tiotropium was the first available LAMA and is administered once daily. It binds to M1–M3 receptors and is 10 times more potent than ipratropium bromide. It dissociates slowly from M1 and M3 receptors, giving it its long acting effect, but dissociates relatively rapidly from the M2 receptor, giving it a unique kinetic selectivity.[55] Once administered the onset of bronchodilation occurs within 30 minutes, with peak activity at 3 hours and sustained over more than 24 hours.[43] Tiotropium has a low bioavailability of between 2%–3% and after regular once daily inhalation, it reaches a steady state after 2 weeks. The drug is not extensively metabolized but the portion that is undergoes hydrolysis into two major metabolites, a carboxylic acid derivative and an alcohol derivative, neither of which have any affinity for any of the muscarinic receptor subtype. A larger proportion of the drug is eliminated via renal secretion which means there is some accumulation in renal impairment.[56]

Glycopyrronium

Glycopyrronium is a novel once daily LAMA licensed for use in Europe in 2012. Like tiotropium it has a

Table 3. Major RCTs for LAMAs.

Trial	Duration	Outcome	Comparator
Tiotropium			
Brusasco et al[47]	26 weeks	↓ Exacerbations ↑ HRQoL	Placebo, salmeterol
Briggs et al[48]	12 weeks	↑ FEV_1	Salmeterol*
Tashkin et al[49] (UPLIFT)	4 years	↓ Exacerbations ↑ HRQoL ↑ FEV_1	Placebo
Vogelmeier et al[50] (POET)	1 year	↓ Exacerbations	Salmeterol*
Glycopyrronium			
D'Urzo et al[51] (GLOW1)	26 weeks	↑ Trough FEV_1 ↑ HRQoL ↓ Dyspnoea (TDI score) ↓ Exacerbations	Placebo
Kerwin et al[45] (GLOW2)	1 year	Similar to GLOW1 v placebo ↑ Bronchodilation on day 1 and week 26 v tiotropium	Placebo, tiotropium*
Beeh et al[8] (GLOW3)	8 weeks	↑ Endurance time ↑ Inspiratory capacity	Placebo
Aclidinium			
Jones et al[52] (ACCLAIM I and II)	1 year	↑ Trough FEV_1 ↑ HRQoL	Placebo
Jones et al[53] (ATTAIN)	6 months	↑ FEV_1 ↑ HRQoL ↓ Dyspnoea (TDI)	Placebo
Kerwin et al[54] (ACCORD)	12 weeks	↑ FEV_1 ↑ HRQoL ↓ Dyspnoea (TDI)	Placebo
Fuhr et al[46]	15 days per treatment	Similar to ACCORD v placebo ↑ Morning FEV_1 v tiotropium	Placebo, tiotropium

Notes: The table shows results against placebo unless otherwise stated. *Also significant result against active comparator.

sustained 24 hour bronchodilator effect,[45] and higher selectivity for the M3 receptor than the M2 receptor.[57] Dissociation from the M3 receptor occurs four times faster than tiotropium[57] and almost twice as fast as aclidinium.[58] This suggests that glycopyrronium would have a more rapid onset of action, which has been confirmed in clinical studies.[45,51] Glycopyrronium bromide undergoes mainly hydrolysis, which results in the formation of a carboxylic acid derivative, and to a lesser extent glucuronidation. Elimination is predominately via the kidneys.[59]

Aclidinium bromide

Aclidinium is a recently developed LAMA administered twice daily which was approved by the FDA in 2012. It is a potent and selective muscarinic antagonist which displays relative selectivity for the M3 receptor with a drug/receptor binding rate similar to that of ipratropium and 2.6 times faster than that of tiotropium.[60] Aclidinium undergoes hydrolysis into two major metabolites, a carboxylic acid derivative and an alcohol derivative. Owing to its short plasma half-life and rapid metabolism, very little is excreted in the urine, such that no adjustments are required in renal disease.[61] Once administered, onset of action occurs within 15 minutes with a peak activity at 2 hours.[60]

The clinical trials pertaining to aclidinium's efficacy are shown in Table 4. Potential differences from other LAMAs include higher nocturnal FEV_1 compared with tiotropium, resulting in better morning symptoms.[46]

Safety

The adverse effects encountered with LAMAs are largely those attributed to its anti-cholinergic activity, with dry mouth being one of the most commonly reported side effects.[49] Clinical trials involving all drugs have reported similar adverse event rates with the active intervention compared with placebo. In the ATTAIN and GLOW2 trials, the most common events reported in the aclidinium and glycopyrronium arm over placebo were nasopharyngitis.[45,53] In the 4 year UPLIFT study, the most commonly encountered adverse events were due to lower respiratory causes; however, this was similar to the placebo arm.[49]

A study prior to the publication of UPLIFT suggested that use of tiotropium increased cardiovascular morbidity and mortality;[62] data from UPLIFT refuted this demonstrating a non-significant reduction in all cause cardiovascular mortality.[63] It is of note that UPLIFT used the Handihaler device, and excluded those with cardiovascular co-morbidity. Later analyses of trial data using the Respimat device (not licensed in the USA, but available in at least 55 countries worldwide) still suggested an adverse cardiovascular mortality effect with tiotropium.[64] Much debate ensued after this, but a more recent Cochrane review[65] and a further independent meta-analysis[66] have confirmed the finding of increased mortality risk associated with the soft mist inhaler (Respimat). Ipratropium and tiotropium are actively transported through the bronchial epithelium using the OCTN2 transporter, which is also present in the human heart.[67] Furthermore the Respimat device results in greater deposition in the lung than the Handihaler.[68,69] Whilst such features may go some way to explaining the mechanism of cardiovascular morbidity and it's apparent device specificity, this will require further study. In the meantime there has been a call in the UK

Table 4. Major RCTs of ICS in COPD.

Trial	ICS	Duration	Outcome	Comparator
Burge et al[76] (ISOLDE)	Fluticasone	1 year	↑ FEV_1 ↓ Exacerbations	Placebo
Calverley et al[23]	Budesonide	1 year	↓ Exacerbations* ↑ HRQoL	Placebo, formoterol, budesonide/formoterol
Szafranski et al[33]	Budesonide	1 year	↑ FEV_1	Placebo, formoterol, budesonide/formoterol
Calverley et al[28] (TRISTAN)	Fluticasone	1 year	↑ FEV_1 ↓ Exacerbations	Placebo, salmeterol, salmeterol/fluticasone
Calverley et al[29] (TORCH)	Fluticasone	3 years	↓ Exacerbations ↑ FEV_1	Placebo, salmeterol, salmeterol/fluticasone

Notes: The table shows results for comparisons of ICS against placebo, although many trials used multiple comparators; see text and table in section on combined ICS/LABA for other results. *Only exacerbations requiring oral corticosteroids.

for withdrawal of the Respimat device as a result of safety concerns.[70]

Inhaled Corticosteroids

It is clear that ICS reduce airway inflammation, airflow limitation, and symptoms in asthma and are therefore the mainstay of treatment.[71] In COPD, however, the role of ICS is more controversial, predominantly because the pattern of inflammation differs. The inflammation in COPD is dominated by neutrophilic infiltration, with an increased numbers of macrophages and CD8 T lymphocytes; neutrophilic infiltration is not as responsive to steroids as the eosinophilic inflammation seen in asthma.[72] Despite this, ICS were used in COPD before any real evidence of their efficacy was known. Their use in COPD has recently been reviewed by the Cochrane collaboration, which concluded that although use of ICS is associated with a reduction in exacerbation rates and possibly a reduced rate of decline in FEV_1, these benefits need to be weighed against increased pneumonia risks and local side effects.[73]

Mechanism of action

The primary actions of glucocorticoids arise by activation of specific glucocorticoid receptors (GCR) which are found in the cytoplasm of most mammalian cell types. The mechanism of action via the GCR is shown in Figure 3. Another method by which the GCR influences inflammatory processes in COPD is the interaction between histone deacetylase-2 (HDAC2) and nuclear factor kappa B (Nf-kB), a key transcription factor. Nf-kB is upregulated in many cell types during inflammation and favors the expression of pro inflammatory genes. HDAC2 mediated deacetylation of the GCR enables it to bind to Nf-kB and nullify its effect as a pro inflammatory molecule.[74] HDAC2 modulation is a current area of interest in COPD therapy.[75] The clinical trials pertaining to the efficacy of ICS are shown in Table 5.

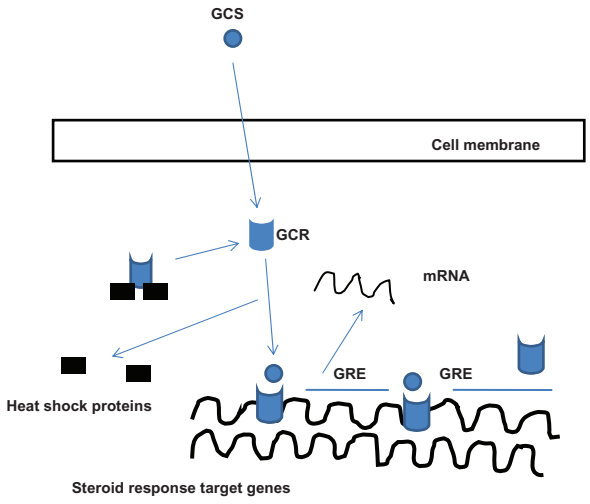

Figure 3. Mechanism of action of ICS.
Notes: When a glucocorticoid (GCS) binds to the GCR the heat shock proteins are detached resulting in a conformational change and formation of a GCR dimer. This dimerization is necessary for the binding of the GCR to the glucocorticoid response element (GRE) which is an area of DNA responsible for up or down regulating gene expression.

Budesonide and fluticasone

Budesonide and fluticasone are the two ICS which have been used most extensively in clinical trials pertaining to COPD. Whilst the potency—and therein pharmacological response—of ICS is related to its affinity at the GCR, other factors such as particle size and pulmonary deposition will determine its therapeutic effect. Table 5 outlines the pharmacokinetic and pharmacodynamic features of both drugs.[77]

Budesonide is several times less lipophilic than fluticasone and, as a result, dissolves more readily in airway mucus and is more rapidly absorbed into the airway tissue and systemic circulation. Fluticasone, being more lipophilic and thus less water soluble, is more likely to be retained in the lumen of the airways; it therefore has a greater chance of being removed from the airways by mucociliary clearance and cough.[78] Recent studies have shown higher proportions of fluticasone expectorated in the sputum of patient with COPD and fluticasone plasma concentration is more affected by airflow limitation than budesonide.[78]

Safety

The adverse effects of ICS are related to its local and systemic absorption. The amount of inhaled steroid

Table 5. Relative therapeutic effects of ICS.

	Fluticasone	Budesonide
Oral bioavailability (%)	<1	11
Pulmonary deposition (%)	16	28
Receptor binding affinity	1800	935
Protein binding (%)	90	88
Half life (hrs)	7.8	2.8
Clearance (l/h)	69	84

Note: 100% is the affinity of dexamethasone, to which the above are compared in the table.

reaching the systemic circulation is the sum of the pulmonary and orally bioavailable fractions. Given that most ICS have relatively low oral bioavailability, it is largely the absorption from the pulmonary vasculature which determines the systemically available steroid. Although adrenal suppression is a theoretical risk, it has not been reported in COPD, though it has been seen in bronchiectasis.[79] Local effects, namely dysphonia and oral candidiasis. are more frequently observed adverse effects demonstrated in the trials in Table 4. One of the main concerns in patients using ICS is the significantly increased risk of pneumonia which was demonstrated in the TORCH trial[29] and noted in the recent Cochrane review of ICS.[73]

Combination Therapy

There are currently two combination inhalers used in the treatment of patients with COPD: Seretide/Advair (salmeterol/fluticasone) and Symbicort (budesonide/formoterol). Both are a combination of a LABA with an ICS; thus, for the purposes of this article, the term combination therapy is synonymous with these drugs. It is important to note that many new combinations of drugs are in development for COPD, eg, LABA/LAMA,[80] such that in future we may not use the term in the same way. The pharmacokinetics and pharmacodynamics of the component drugs have been discussed in the preceding sections. LABA/ICS combinations have been shown to improve lung function and HRQoL and to reduce exacerbations in COPD patients (Table 6). Current national and international guidelines advocate the use of combination inhalers in severe and very severe disease.

Synergistic mechanism of action

The two components of ICS/LABA may have an additive or synergistic effect; there is greater evidence of synergy in allergic inflammation than in COPD patients.[81] Animal studies suggest that the combination of ICS plus LABA behaves synergistically,[82] as ICS may regulate the coupling of β receptors to G proteins and hence cAMP activation, and overall response to LABA. Exposure to exogenous LABA (or SABA) leads to uncoupling by phosphorylation of the receptor via various pathways, which theoretically can lead to drug tolerance. Exposure to corticosteroids restores receptors to their previously sensitized state.[83] Chronic LABA or SABA exposure will also lead to reduced β receptor numbers, as they are internalized and degraded; ICS reverse this effect because the activation of GRE causes gene transcription and hence synthesis of these receptors.[84]

The main RCTS for combination inhalers are shown in Table 6. A number of secondary analyses of TORCH data have also been published, detailing determinants of change in health status,[85] beneficial effects on FEV_1 decline,[86] and stratifying analysis for disease stage.[87]

Table 6. Major RCTs of ICS/LABA.

Trial	ICS/LABA	Duration	Outcome	Comparator
Calverley et al[23]	Budesonide/formoterol	1 year	↓ Exacerbations v P and F ↔ FEV_1 v all ↑ HRQoL v all	Placebo, formoterol, budesonide
Szafranski et al[33]	Budesonide/formoterol	1 year	↓ Exacerbations v P and F ↔ FEV_1 v P and B ↑ HRQoL v P and B	Placebo, formoterol, budesonide
Calverley et al[28] (TRISTAN)	Salmeterol/fluticasone	1 year	↑ FEV_1 v all ↑ HRQoL v all ↓ Exacerbations v P	Placebo, salmeterol, fluticasone
Calverley et al[29] (TORCH)	Salmeterol/fluticasone	3 years	↓ Exacerbations v all ↑ HRQoL v P	Placebo, salmeterol, fluticasone
Wedzicha et al[88] (INSPIRE)	Salmeterol/fluticasone	2 years	↔ Exacerbations ↑ HRQoL ↓ Mortality ↑ Pneumonia	Tiotropium

Notes: The table shows all results for ICS/LABA. See also ICS and LABA sections for individual component results.
Abbreviations: P, placebo; F, formoterol; S, salmeterol; B, budesonide.

Safety

The side effect profiles of LABA/ICS combinations are effectively the sum of their component parts, as described above. Similar to the use of ICS, the most significant adverse event is the risk of pneumonia with combination inhalers.[89] The risk is significantly higher than placebo or LABA but not so when compared with ICS. A recent systematic review and indirect comparison of trials looking at Symbicort and Seretide suggests that the risk of pneumonia is greater with Seretide, perhaps due to overall elevation in steroid load. The caveat to this is that data from the TORCH trial had a large bearing on the overall findings.[90]

Phosphodiesterase Inhibitors

Mechanism of action

Roflumilast is a selective phosphodiesterase 4 (PDE4) inhibitor; PDE4 is an enzyme which is expressed in many pro-inflammatory cells. The therapeutic effects of roflumilast are thought to be mediated via increased levels of cellular cAMP and include inhibition of microvascular leakage, inhibition of trafficking, release of cytokines, and chemokines from inflammatory cells, and mild bronchodilation.[91] Roflumilast has a high oral bioavailability and is largely protein bound (98%). Peak plasma concentrations occur within one hour, mean elimination half-life is 17 hours, and a steady state is achieved after 4 days. The major metabolic pathway for roflumilast elimination after oral administration is pyridine N-oxidation, with the formation of roflumilast N-oxide; this metabolite is an active compound with pharmacokinetics distinct from its parent compound. Peak plasma concentrations occur after 4 hours and its elimination half is approximately 27 hours. Although the major elimination route for both the drug and its metabolite is the kidney, studies have shown that dose adjustment is not required in renal impairment.[92] Other selective PDE4 inhibitors were developed and went through trials,[93] but roflumilast is the only one currently on the market.

Theophylline is a non-selective phosphodiesterase inhibitor. Through the enzymatic inhibition of phosphodiesterase, levels of cAMP and cGMP are increased giving it its weak bronchodilator effect.[94] To achieve this, however, fairly high concentrations of theophylline are needed. Recent evidence has shown that theophylline has some anti-inflammatory action and maybe able to modulate inflammatory gene expression by its interaction with the histone deacetylase.[76] Theophylline like Roflumilast has a high oral bioavailability. Peak plasma concentration occurs between 1 and 2 hours, and it has an elimination half-life of 8 hours.[75,77] Metabolism is largely by the liver, whereby the drug undergoes hydroxylation, N-demethylation, and N methylation to various compounds.[75,77] The main RCTs for PDE4 inhibitors are shown in Table 10. Roflumilast appears to work best in the subset of COPD patients who have chronic bronchitis.[95] Despite widespread use, there have been few parallel group studies of oral theophyllines; the Cochrane review in 2002 included 20 relatively small crossover studies and concluded that there were moderate beneficial effects on lung function, with the caveat that results may not be generalizable.[96]

Safety

Treatment-related adverse events were higher in the roflumilast treatment arms of the clinical trials in Table 7. Gastrointestinal side effects, namely weight loss and nausea, were the most common, followed by neuropsychiatric effects. Although dropout rates overall were similar between roflumilast and placebo, more patients in the roflumilast arm dropped out within the first few weeks. Theophylline has been used for a number of years in airway disease and still has a role in the management of COPD.[1] The main adverse effects encountered include tachycardia, nausea, and tremor. Unfortunately it has a narrow therapeutic index and drug monitoring should be undertaken at regular intervals. The propensity for theophylline to interact with other drugs is another drawback to its use.

Mucolytics

Mucus hypersecretion and resultant chronic cough can often be a feature of COPD. Mucolytics have been used to reduce sputum viscosity and to aid expectoration; those most widely used are carbocysteine and N-acetylcysteine (NAC). Others include erdosteine and ambroxol. NAC and to a lesser extent carbocysteine have antioxidant properties. The awareness that oxidative stress and the formation of reactive oxygen species play a role in COPD, especially during exacerbations, has suggested that treatment with mucolytics may be able to influence exacerbation rates.[102]

Table 7. Major RCTs of phophodiesterase inhibitors.

Trial	Drug	Duration	Outcome	Comparator
ZuWhallack et al[97]	Theophylline	12 weeks	↑ FEV_1** ↓ Symptoms**	Salmeterol
Rabe et al[98]	Roflumilast	24 weeks	↑ FEV_1 ↓ Exacerbations	Placebo
Calverley et al[99]	Roflumilast	1 year	↑ FEV_1 ↓ Exacerbations*	Placebo
Calverley et al[100]	Roflumilast	1 year	↑ FEV_1 ↓ Exacerbations	Placebo
Fabbri et al[101]	Roflumilast	1 year	↑ FEV_1	Placebo

Notes: *In GOLD stage 4 patients only; **in combination with salmeterol.

Carbocysteine is a blocked thiol derivative of the amino acid L-cysteine. While the mechanism of action is not completely understood, it has the ability to split glycoprotein bonds in mucus. In vitro studies also suggest a mucoregulatory mechanism. Carbocysteine is well absorbed and peak serum concentration as achieved at between 1 and 1.7 hours after ingestion. Approximately 30%–60% of the drug is excreted unchanged in the urine. The fraction of the drug not excreted in this manner undergoes metabolism via varying pathways with great inter-individual variability.[103]

NAC is recognized as a mucolytic agent with direct and indirect antioxidant properties. It differs from carbocysteine in that it has a free thiol group capable of interacting with reactive oxygen species, leading to NAC disulfide as an end product. NAC's indirect properties arise from its role as a glutathione precursor. It is rapidly absorbed following oral administration with peak plasma concentrations occurring between 2 to 3 hours and has a plasma half-life of 6.3 hours. NAC undergoes mainly hepatic metabolism.[104]

The most recent systematic review of clinical effectiveness of mucolytics included 30 studies and demonstrated a small but significant reduction in exacerbations in treated patients with COPD.[105] Mucolytic agents however do not seem to have any effect on lung function. One of the largest trials with the power to demonstrate this was undertaken by Decramer et al. The use of NAC had no effect on lung function in those with mild or more severe COPD; additionally, mucolytics had no effect on HRQoL.[106]

Oxygen

Overt or relative hypoxia is one of the hallmarks of COPD, especially in the latter stages of the disease. Oxygen therapy to ameliorate this has been proven to be effective for patients who have severe resting hypoxia, and it is considered a prescription intervention in many countries. Whilst it is beyond the scope of this article to review all evidence pertaining to oxygen in detail, some key points and major studies can be included.

The basis for LTOT (>15 hours daily) is derived from two landmark RCTs: the NOTT trial which compared 12 hour (nocturnal) and 24 hour oxygen therapy,[107] and the MRC trial which compared > 15 hour oxygen therapy to placebo.[108] The main outcome in both trials was improved survival in patients receiving oxygen for at least 15 hours daily, though this improved survival was not seen in the MRC trial until one year after the initiation of oxygen therapy. The NOTT trial also demonstrated a fall in mean pulmonary artery pressure (PAP). Whilst a fall in mean PAP was not shown in the MRC trial, increases in PAP seen in the control arm did not occur in the patients undergoing oxygen therapy. LTOT is indicated for patients in a clinically stable state who have PaO2 < 7.3 kPa (55 mmHg) or 7.3–8 kPa (55–60 mmHg) in the presence of pulmonary hypertension, nocturnal hypoxia, or secondary polycythaemia when assessed on two separate occasions. Aside from LTOT, two other modes of oxygen therapy exist: ambulatory and short burst (SBOT); both have been reviewed relatively recently.[109] Ambulatory oxygen is indicated in mobile patients who meet the LTOT criteria and is commonly considered in other COPD patients who exhibit exertional desaturation to less than 90%. SBOT criteria are poorly defined, and in general no benefits are seen;[110] it should therefore be used only in a palliative setting.

Smoking Cessation

Tobacco smoke is arguably the most important etiological factor for the development of COPD in the developed world. The impact of continued smoking and its cessation on lung function (FEV_1) is well known and illustrated via the Fletcher-Peto Curve.[111] Despite the continued advances in pharmacotherapies for COPD, smoking cessation remains the best way to delay progression of COPD at all stages of the disease.

Over the last few years the neurochemical basis of nicotine addiction has been better understood; it is thought that the addictive properties of nicotine are a result of dopamine release mediated via stimulation of the alpha4beta2 nicotinic receptors.[112] Currently, the most common therapeutic strategies employ the use of Varenicline, Bupropion, and Nicotine replacement therapy (NRT). Varenicline is a selective nicotinic receptor partial agonist. It mimics the effects of nicotine on dopamine release in the nucleus accumbens when given alone but attenuates this response to a subsequent nicotine challenge and reduces nicotine self-administration.[112] Bupropion inhibits the reuptake of dopamine, noradrenaline, and serotonin in the central nervous system.[112] During nicotine withdrawal, levels of these neurotransmitters fall, leading to withdrawal symptoms. Therefore, in limiting reuptake the symptoms of withdrawal are attenuated. All three modalities[113–115] have proven to be effective compared to placebo in smoking cessation, with available evidence favoring the superiority of Varenicline over Bupropion. There is limited direct evidence between Varenicline and NRT, and only a few heterogeneous trials comparing Bupropion to NRT; overall it is likely that both are superior to NRT.[113–115] Post-marketing surveillance has raised subsequent concerns about possible between Varenicline and suicidal ideation, such that a recent systematic review (mainly of evidence in populations unselected for psychiatric disease) advised using it only with caution in patients with pre-existing psychiatric problems.[116] Conversely a recent RCT specific to schizophrenic patients found if effective and safe.[117]

Opiates

Despite optimal management of COPD with the above pharmacotherapies, dyspnoea can be problematic, especially in the advanced stages of the disease process. It pervades all aspects of patients' life leading to a detrimental effect on its quality; opiates are widely used in a palliative setting to reduce the sensation of dyspnoea.[118] Endogenous opioids might modulate dyspnoea by a reduction in ventilatory drive in response to carbon dioxide,[119] hypoxia,[119] and exercise.[120] This decrease in respiratory effort may lead to a reduction in breathlessness. In addition, the sedative effect of opiates may reduce anxiety. The use of opiates to manage dyspnoea was the subject of a systematic review in 2002.[121] This demonstrated a significant beneficial effect of oral and parenteral opiates over placebo. This benefit was also seen when the subgroup analysis for patients solely with COPD was undertaken. One of the major concerns and possibly barriers to opiate usage is respiratory depression, especially in opioid naive patients. However, when appropriately administered and monitored at lower doses, they do not appear to cause significant respiratory depression.[122]

Other Potential Pharmacotherapies

The multicomponent nature of COPD has meant that therapeutic strategies have been trialed in an attempt to gain additional benefit to the interventions outlined above. Ameliorating sequelae such as pulmonary hypertension (PH), improving nutrition, and trying to reduce systemic inflammation all have theoretical merits.

PH in COPD adversely affects survival and exercise capacity. Although the use of oxygen therapy has a protective effect on the progression of PH in patients with advanced COPD, its use is limited to patients who meet the LTOT criteria. Vasoactive compounds used in primary PH (sildenafil, bosentan, and nitric oxide) have been investigated in COPD and are shown in Table 8. Since some trials have shown worse HRQoL in treated patients, these drugs are not used routinely, although trial periods to see if benefit is seen are sometimes employed in selected patients by specialist centers.[123]

Over the last few years a number of studies have shown a relationship between vitamin D deficiency and severe COPD, whereby its deficiency seems to correlate with the degree of airflow obstruction.[129,130] Clearly on this basis it would seem reasonable to replenish vitamin D levels. In a yearlong RCT, Lehouck et al[131] used high dose vitamin D supplementation in patients

Table 8. RCTs of drugs for PH in COPD.

Trial	Drug	Duration	Outcome	Comparator
Vonbank et al[124]	Nitric oxide + oxygen	3 months	↓ PAP ↔ PaO2	Oxygen
Stolz et al[125]	Bosentan	3 months	↓ PaO2 ↓ HRQoL ↔ 6MWT distance	Placebo
Valerio et al[126]	Bosentan	18 months	↓ PAP* ↑ 6MWT distance*	Placebo
Rao et al[127]	Sildenafil	12 weeks	↓ PAP ↑ 6MWT distance	Placebo
Lederer et al[128]	Sildenafil	4 weeks per intervention	↔ 6MWT distance ↓ HRQoL	Placebo

Notes: *Statistically significant improvement over baseline in treated patients; comparison between groups was not reported.

with COPD. However, no benefit in lung function or exacerbations was seen in the treatment arm, except in the severely deficient in whom supplementation would be indicated for other reasons. Some studies have used other forms of nutritional supplementation in the context of pulmonary rehabilitation,[132] albeit with limited benefits. Consequently, nutritional supplementation is not routinely used therapeutically in COPD.

Treatment Algorithms in COPD

The updated GOLD guidance[1] has made some changes to the way that the therapies detailed above are recommended. Other national guidance (eg, British NICE guidance[5]) differs markedly in the order of which drugs are used. In order to interpret the GOLD guidance, disease stage, symptoms, HRQoL and exacerbation frequency must all be taken into account; this is shown in Figure 4. Table 9 compares the main differences between guidelines, some of which are described below.

First line treatment

The use of bronchodilators is central to the management of COPD and, although not extensively discussed, the use of short acting agents are best used for rescue of symptoms. Both LAMAs and LABAs in the trials above were used across the full spectrum of disease severity and have all been shown to have significant effects on outcome measures in COPD. Consistent clinically and statistically significant improvements in lung function, HRQoL, and reduction in exacerbations in the region of 15%–20% have been demonstrated. International and national guidelines suggest that either a LABA or LAMA be used as maintenance therapy for GOLD2 disease. The choice of which agent depends on patient preference, tolerability, and cost.

Based on current evidence, tiotropium and indacaterol are essentially equivalent, with indacaterol being slightly more favorable at influencing HRQoL. The place of aclidinium and glycopyrronium is likely to be as an alternative to tiotropium or LABA. Thus, when it comes to prescribing maintenance therapy for patients with COPD, a trial of either indacaterol or tiotropium should be used in the first instance as they provide significantly better bronchodilation and reduce the risk of severe exacerbations.

Additions if remains symptomatic

The role of ICS in COPD is contentious. In most of the trials discussed, although FEV_1 was superior to

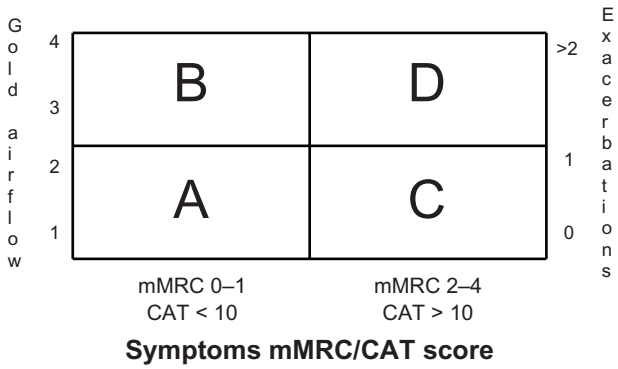

Figure 4. Classifying disease severity by GOLD.
Notes: Patients are categorised by the combination of severity of spirometric impairment (GOLD airflow) or exacerbations and mMRC or CAT. Whilst it is recognised that spirometry or exacerbations and mMRC or CAT may result in different groups for some patients, GOLD recommends that treatment should be according to whichever method chosen results in the higher risk.

Table 9. Comparison of GOLD and UK NICE guidance for COPD management.

FEV_1	GOLD category	GOLD 1st line	GOLD 2nd line	NICE guidance
>50%	A	*SABA*/*SAMA*	LAMA/LABA/SAMA/SABA Theophylline	SAMA/SABA *LABA*/*LAMA*
	B	*LAMA*/*LABA*	LAMA+LABA	LABA+ICS*
<50%	C	*LABA*+*ICS*/ *LAMA*	LAMA+LABA PD4 Theophylline	LABA+ICS LAMA+LABA *ICS*+*LABA*+*LAMA*
	D	*LABA*+*ICS*/ *LAMA*	LAMA+LABA ICS+LAMA ICS+LABA+LAMA ICS+LABA+PD4 LAMA+PD4 Theophylline	

Notes: First choice treatment shown in italics. *Only if persistent symptoms.

placebo the magnitude of improvement in FEV_1 with ICS was inferior to that of the LABA used. TORCH was the only trial to show slower decline in FEV_1 against placebo when fluticasone was used as a monotherapy. What has been proven to be relatively consistent is their ability to reduce exacerbations. This benefit is largely in patients with $FEV_1 < 50\%$ (ie, GOLD ¾). The tradeoff for this benefit is an increased risk of local side effects and pneumonia. It is in these patients who suffer recurrent exacerbations that the risk benefit ratio is greatest. Their use in management of COPD cannot be advocated earlier as both LAMA and LABA monotherapy produce significant increases in lung function outcomes as well as a reduction in exacerbations. Current national guidelines in the UK do not suggest using ICS as monotherapy but in addition to a LABA; GOLD guidelines only recommend ICS monotherapy used with a LAMA as a second choice in patients with severe disease who suffer recurrent exacerbations and have poor functional capacity.

Whilst this section of the review focuses on the use of ICS in COPD, a growing body of evidence suggests that an overlap syndrome of COPD and asthma exists,[133–136] although the syndrome is not clearly defined. However, the general consensus is that patients with incompletely reversible airflow obstruction exhibit sputum eosinophilia, history of atopy, and, following bronchodilator, either improvement in $FEV_1 > 12\%$ (200 mls), or improvement in $FEV_1 > 15\%$ (400 mls). In this subset of patients ICS therapy may have greater benefit and should be employed earlier.[135,136]

Other options

The use of roflumilast in patients has been largely confined to GOLD3/4 disease. In most of the clinical trials patients were selected on the basis of chronic bronchitis, recurrent exacerbations requiring oral corticosteroids, or the need for hospital admission. Its use provided modest but significantly improved FEV_1 compared with placebo and a reduction in exacerbation rates when used with a long acting bronchodilator. International guidelines advocate its use as second line in GOLD 4 patients or as an adjunct to treatment in GOLD 3 patients who are already on LABA/ICS combination inhalers. UK guidance advocates its use in GOLD3 patients with a history of recurrent bronchitis or exacerbations. The place of theophylline is seemingly more variable. International guidelines advocate its use as an alternative to inhaled bronchodilators in mild disease, but also as an adjunct from moderate to very severe disease. UK guidelines only suggest its use after a trial of short or long acting bronchodilators or in those who cannot tolerate inhaled therapy.

Conclusion

The pharmacological management of COPD is driven by symptoms. As a progressive disease it is clear that over time increasing intervention will be required to manage symptoms appropriately. This review has outlined the key pharmacological treatments used.

Unfortunately however, no treatment has been shown conclusively to reduce mortality and very few slow the rate of decline in lung function in COPD. ICS have not proven to be as effective as in asthma and what benefits are derived need to be balanced against the increased risk of pneumonia. Since bronchodilators are the mainstay of current management the search to improve existing bronchodilators will continue; so also will the search for novel anti-inflammatory agents and therapeutic strategies to reverse the corticosteroid resistance seen in COPD.

Author Contributions

Wrote the first draft of the manuscript: SE. Contributed to the writing of the manuscript: AMT. Agree with manuscript results and conclusions: AMT, SE. Jointly developed the structure and arguments for the paper: AMT, SE. Made critical revisions and approved final version: AMT. All authors reviewed and approved of the final manuscript.

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