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Nicolas Roche

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## **Systemic medications in COPD: use and outcomes**

Nicolas Roche

Respiratory Medicine, APHP Centre, Cochin Hospital, Université de Paris (Descartes), Institut Cochin (UMR 1016), Paris, France

**Address for correspondence:** Prof. Nicolas Roche

Pneumologie et Soins Intensifs Respiratoires, Hôpital Cochin

27, rue du Fbg St Jacques, 75014 Paris, France

Ph : 33 1 58 41 12 53; Fax : 33 1 58 41 22 60; Email : [nicolas.roche@aphp.fr](mailto:nicolas.roche@aphp.fr)

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### **Key words**

COPD, theophylline, phosphodiesterase inhibitors, oral corticosteroids, macrolides, mucoactive agents, alpha1 antitrypsin, morphine

### **Key Points**

- Systemic treatment for COPD are not first line therapeutic options.
- The benefit/risk ratio of oral beta2 adrenergic agonists and xanthines is not favourable.
- Azithromycin, phosphodiesterase 4 inhibitors and mucomodifiers can contribute to exacerbation prevention in patients on inhaled therapy.
- The long-term use of systemic corticosteroids in COPD should be strongly discouraged.
- Several biologics are currently in development for COPD therapy and may prove useful in particular subpopulations identified through the use of specific biomarkers.

## **Synopsis**

Inhaled therapy remains the cornerstone of COPD pharmacological care, but some systemic treatments can be of help when the burden of the disease remains high, especially due to the persistence of exacerbations. Azithromycin, phosphodiesterase-4 inhibitors, mucoactive agents can be used in such situations. The major difficulty remains in the identification of the optimal target populations, i.e., the characteristics of the best responders. Another difficulty is to determine how these treatments should be positioned in the global treatment algorithm. For instance, should they be prescribed in addition to other anti-inflammatory agents (i.e., corticosteroids) or should they replace them in some cases? Ongoing research is very active, aiming at identifying new therapeutic targets.

## **Introduction.**

COPD is now defined by the coexistence of chronic respiratory symptoms and permanent (i.e., not fully reversible) airflow limitation, due to airways and parenchymal disease [1]. The development of airflow obstruction and emphysema is the consequence of a close interplay between inflammation, innate and adaptive immune reactions, protease-antiprotease imbalance, oxidative stress, leading to airway wall and parenchymal remodelling and mucous hypersecretion [2–6]. Associated phenomena include chronic infection/colonization/microbiota modifications, autoimmunity, senescence and systemic inflammation [7,8].

Although some decades ago systemic treatments (i.e., theophylline and oral corticosteroids for very severe cases) represented the main therapeutic approach for patients with COPD, inhaled medications are now the cornerstone of COPD treatment [1]. They have the obvious advantage of delivering high local concentrations of effective medication, while minimizing systemic absorption and side-effects. However, because of these properties they don't exert any significant effect on the systemic components of the disease, which have been repeatedly emphasized in the last 15 years [9].

The comorbidities and systemic effects frequently seen in patients with COPD including muscle deconditioning, malnutrition, osteoporosis, psychological distress (anxiety-depression), cognitive impairment, metabolic and cardiovascular diseases, anemia and lung cancer [10–12]. In the mid 2000's there was a great enthusiasm around the concept of systemic inflammation as a common trigger for all of these conditions with many studies demonstrating increases in several systemic inflammatory biomarkers. However, the exact relation between COPD and precise pathophysiological mechanisms remained uncertain. Currently, decreased physical activity (also associated with systemic inflammation) is viewed as a major common contributor to most systemic aspects of COPD [13]. The increased frequency of cardiovascular events and treatments in patients with COPD also led to some interest in the possible interaction between inflammatory bursts with COPD outcomes. Indeed, this is the most plausible mechanism helping explain the increased risk of major cardiovascular events following acute exacerbations [10].

In addition to their lack of effects on the systemic component of COPD, inhaled treatments may not be sufficiently effective to deliver pharmaceutical agents to the small airways, where most of the disease processes outlined above resides [14].

Here we will review the effects of systemic agents with a main focus on clinical outcomes and long-term maintenance use. Pharmaceutical families of interest will include oral beta2 agonists, theophylline, phosphodiesterase inhibitors, macrolides with anti-inflammatory properties and other antibiotics, muco-active agents, corticosteroids, antileukotrienes, cardiovascular drugs and biologics.

### **Oral beta2 adrenergic agonists**

The benefit-risk ratio of oral beta2 agonists is much less favourable than their inhaled counterparts, since relatively high systemic levels are required to achieve sufficient local concentrations leading to bronchodilation. At therapeutic doses, side-effects (tremor, tachycardia) are more frequent and intense while bronchodilation is similar[15] or less pronounced [16] than the inhaled presentation. In

addition, these agents have been assessed only in small short-term studies with no patient-reported outcome endpoints. As a consequence, they are not recommended for COPD treatment except when the use of any inhaled treatment is impossible.

### **Xanthines, theophylline**

Theophylline is a xanthine structurally similar to caffeine that was initially developed for asthma in the late 1930's, at a time when COPD was not even well recognized [17–19]. Its main mechanisms of action are adenosine receptors (A1 and A2) inhibition (high potency at therapeutic concentrations) and (weak) phosphodiesterase (PDE) 3 and 4 selective inhibition at higher and poorly tolerated concentrations [20]. Through these pathways, it exerts numerous immunomodulatory and anti-inflammatory effects and has weak bronchodilator properties. Interestingly, theophylline decreases neutrophilic and eosinophilic airways inflammation, which can both be involved in patients with COPD, depending on the underlying endotype (i.e., pathophysiological profile). It also modulates lymphocytes functions.

The acute physiological effects of theophylline include bronchodilation, lung deflation, improved gas exchanges, increased diaphragmatic function, reduced work of breathing, improved mucociliary clearance. How these numerous demonstrable effects translate into clinical improvements is less clear, which is largely explained by the narrow therapeutic index of the drug: for instance, bronchodilation and diaphragmatic improvements need relatively high doses to be clinically meaningful, which exposes to risks of serious dose/concentration-dependent side-effects such as gastro-intestinal perturbations (nausea, vomiting, exacerbated gastro-oesophageal reflux), tremor, sleep disturbance, headache, seizures, arrhythmias and heart failure. In addition, many factors can interact with theophylline serum concentrations including diseases that are frequently seen in patients with COPD, such as heart failure, liver disease and smoking. In addition, theophylline serum concentrations will vary depending on its interaction with several concomitant drugs (including

antibiotics used in COPD exacerbations) the elimination of which is modulated by the CYP1A2 or CYP3A4 co enzymatic activity (**Table 1**). Thus, using theophylline often requires monitoring its blood concentrations, further influencing its ease-of-use. As a consequence and particularly in acute situations, the use of theophylline has been widely abandoned due to the need for high serum concentrations to achieve clinically meaningful bronchodilation or diaphragmatic improvement, due to the high risk of significant toxicity.

Regarding long-term use, there has been some interest in one particular property of theophylline, i.e., restoration of histone-deacetylase 2 (HDAC2) activity [21]. HDAC2 is an important cofactor of corticosteroids effects since it interacts with the corticosteroid-glucocorticoid receptor, contributing to chromatin condensation and thereby inhibiting the transcription and subsequent expression of pro-inflammatory genes (trans-repression)[22]. In smokers and even more in patients with COPD, the oxidative stress impairs HDAC2 function, representing one of the numerous mechanisms of corticosteroid resistance [23]. Thus, conceptually theophylline could restore the effects of corticosteroids that is reduced in smokers and in COPD. This mode of action could be of particular interest since it occurs at serum concentrations that are approximately half the threshold of toxicity. Following encouraging results from in vitro experiments on HDAC2 activity and corticosteroid cellular effects, this hypothesis has been clinically tested in two randomized controlled trials, with completely disappointing results regarding all variables of clinical interest, i.e., lung function, exacerbations, symptoms and quality of life [24,25].

As a consequence, the use of theophylline has been largely abandoned as part of long-term maintenance therapy. However, in some areas of the world cost-issues are such that theophylline is one of a few affordable options, together with a few “low-cost” (but still very effective) inhaled drugs as salbutamol and beclomethasone.

The theophylline/xanthines family includes not only theophylline itself but also its derivatives aminophylline (the oldest one), bamiphylline and doxophylline. The main potential difference

between these agents is the efficacy/safety profile, which might be better for doxophylline according to a recent network metaanalysis [19]. How this translates into clinical superiority at the individual patient level is not fully clear.

### **Phosphodiesterase (PDE) 4 inhibitors**

PDE-4 inhibitors are often wrongly considered as modern theophyllines. This is actually not a valid concept because most of the clinical effect of theophylline observed at non-toxic doses are linked to adenosine receptor antagonism, while effective PDE inhibition occurs only at toxic or close-to-toxic doses. “Real” selective phosphodiesterase inhibitors commercially available at present, are limited to one agent, roflumilast, which is not authorized or reimbursed in all countries. Another agent, cilomilast, was provisionally approved in the early 2000’s but its development has been finally abandoned due to concerns about its efficacy/safety profile [26].

There are many subtypes of PDE4 (A, B, C and D) and more than 25 isoforms, many of which are expressed in various inflammatory and resident cell types in the airways [17,27,28]. The potential beneficial effects of PDE-4 inhibition are numerous since PDE-4 is involved in cAMP (3’5’-cyclic adenosine monophosphate) degradation. Thus, PDE-4 inhibition increases cellular levels of cAMP, which acts as an anti-inflammatory second messenger decreasing the release of inflammatory mediators and the expression of pro-inflammatory surface receptors (e.g., adhesion molecules) by neutrophils and other cell types including macrophages, eosinophils and T-lymphocytes. Roflumilast (through its active metabolite roflumilast N-oxide) reduces the recruitment of inflammatory cells in the airways. cAMP is also involved in smooth muscle relaxation, but the bronchodilator effect of roflumilast at therapeutic concentrations is limited. In animal models, roflumilast prevents cigarette smoke-induced lung inflammation and emphysema [18].

In human, following the first studies and their subgroup analyses, roflumilast has been shown to reduce the risk of exacerbations in patients with COPD and frequent exacerbations (or previous

hospitalization), severe airflow obstruction (GOLD 3-4, post-bronchodilator FEV1<50% predicted), symptoms of chronic bronchitis and receiving bronchodilator therapy [29]. This beneficial effect occurs even in patients receiving concomitant treatment with inhaled long-acting bronchodilator(s) and corticosteroids and is accompanied by an improvement in lung function, although the increase in FEV1 (mean, 51 ml) does not reach the “classical” (but debatable for therapies administered on top of active medications) threshold for clinical significance (100 ml)[30]. These effects have been confirmed by a Cochrane systematic reviews collating data from 20 studies using roflumilast in over 17,000 participants [31], in which small improvements in symptoms and quality of life were also noted.

Roflumilast shares GI side-effects with xanthines but in contrast to those agents, it is not associated with an increased risk of cardio-vascular effects. It can induce moderate weight loss (3 kilograms on average), mostly related to a decrease in fat mass. GI side-effects can lead to treatment interruption.

Compounds with both PDE-3 and PDE-4 inhibitory activity have been assessed in humans with no success due to lack of safety and/or unacceptable side-effects. A new agent of this family administered through the inhaled route, Ensifentrine, is currently tested in clinical trials [32].

Currently available data are insufficient to draw conclusions.

### **Macrolides and other antibiotics**

The most studied macrolide for long-term maintenance therapy in COPD is azithromycin [33,34], although earlier clinical studies were reported using erythromycin [35]. Anti-inflammatory and immune-modulating properties are a feature of these macrolides [18,36]. Their first applications were the successful treatment of diffuse pan-bronchiolitis with erythromycin, and cystic fibrosis colonized by *Pseudomonas aeruginosa* with azithromycin. Animal models have confirmed the anti-inflammatory effects of this agent, which can also prevent cigarette-smoke induced development of

emphysema [18,36]. Macrolides also have the potential to augment HDAC2 expression, thereby restoring corticosteroid sensitivity.

During the late 2000's, 3 studies showed the preventive effect of erythromycin on exacerbations occurrence. Subsequent trials demonstrated a similar effect using azithromycin. Although some individual studies failed to achieve the same success and overall positive effect was shown in a meta-analysis [37]. Studies with roxithromycin and clarithromycin did not provide convincing evidence but did not have a sufficiently robust design because they had a low sample size and were of limited duration)[36].

Considering the beneficial effect of both erythromycin and azithromycin (although they have never been directly compared), 4 main questions arise. First, selection of the best agent and the best scheme of administration. In terms of convenience of use, azithromycin is clearly the preferred drug: once vs twice or three times a day for erythromycin. Trials used a 250 mg/day or >500 mg three times a week scheme [36], although 250 mg three times a week is probably used more often in clinical practice as in cystic fibrosis (in which the efficacy of this protocol was demonstrated), despite a lack of formal evaluation in COPD.

Secondly, the most appropriate target population. The largest study with erythromycin recruited 109 patients in a single center. There was no exacerbation-related inclusion criteria but more than one third of the population reported at least 3 exacerbations during the 12-month preceding inclusion and median exacerbation frequency in the placebo group was 2, suggesting a population of relatively frequent exacerbators [38]. The rate reduction of exacerbations in the active arm was 36% and in addition, erythromycin reduced not only the rate but also the duration of exacerbations. Responders analysis was not performed and would have been difficult considering the limited sample size. The effect on exacerbation was not associated with effects on biomarkers of inflammation nor bacterial loads in the airways, preventing any firm conclusions regarding the mechanisms of observed efficacy. Azithromycin was studied over 12-months in the largest macrolide trial (n=1142)[33]. Patients were

on supplemental oxygen, had received systemic corticosteroids or had been hospitalised for an exacerbation during the previous year. There was a 17% overall risk reduction in exacerbations. Responders analysis found the greatest benefit in ex-smokers, older subjects and milder GOLD stages [39]. However this analysis was post-hoc, requiring further confirmation before drawing firm conclusions. The other 12-month study on azithromycin was performed in patients with a history of 3 or more exacerbations in the previous year, most of whom received triple inhaled therapy. Overall it remains difficult to define a specific target subgroup, although obviously baseline exacerbation risk is an appropriate selection criteria.

The third question relates to risks associated with long-term macrolide therapy [36]. GI side-effects (diarrhea), impairments in liver function and a minimal increase in hearing loss have been reported. Although there is a theoretical risk of increased cardiac arrhythmias, due to the potential increase in the QTc electrocardiographic interval, this was not observed in any of the trials. However, patients with prolonged QTc interval were excluded from those trials. In practice, it may be important to consider its use primarily in patients with normal ECG. An increase in the proportion of macrolide-resistant microorganisms in nasal swabs has been observed, although the absolute number of patients colonized by such bacteria did not change. The bacteriological consequences of long-term macrolide use in COPD populations remains unknown. The last important question is the duration of treatment. For this question, there is no firm answer at present. Conclusive trials have lasted 6-12 months, and no trial of sequential administration (e.g., during the winter period) has been performed.

Regarding other (non-macrolide) antibiotics, the only sufficiently powered trial was performed with pulsed moxifloxacin (400 mg/day 5 days every 8 weeks), which produced a non-significant trend towards a reduction in exacerbations and is thus considered a negative trial [40].

## **Muco-modifiers**

There are two main potential reasons for considering the use of mucoactive agents in COPD [41]: first, chronic mucous hypersecretion is thought to play an important role in the pathophysiology and natural course of the disease. Indeed, the mucus is more abundant and viscous in many patients with COPD and is responsible for small airways obstruction, which is associated with poor prognosis in patients undergoing lung volume reduction surgery. In smokers and COPD patients, chronic mucus hypersecretion is also associated with several prognostic variables (FEV<sub>1</sub> decline and development of COPD, exacerbation and hospitalisation risk and mortality). Mucins concentrations (MUC5B, MUC5AC) appear to play a key role in the pathogenesis of chronic bronchitis [5].

Several mucoactive agents have antioxidant properties, and oxidative stress is thought to be involved in the pathobiology of COPD, both at local (airways) and systemic levels [6]. Its consequences include inflammatory cells recruitment, protease-antiprotease imbalance and production of pro-inflammatory mediators. Paradoxically, there has been no firm demonstration of an effect of most mucoactive agents on mucociliary clearance in vivo in humans. In vitro data and animal models found effects on airway wall remodelling, chemotaxis and activation of neutrophils and monocytes/macrophages as well as decreasing bacterial adherence. In vivo during acute exacerbations, a reduction in inflammatory markers and an improvement in bacterial elimination and symptoms has been found but was not accompanied by effects on “hard” endpoints such as lung function or length of stay in the hospital, questioning the clinical relevance of biological effects. Some mucoactive agents; carbocysteine, N-acetylcysteine, erdosteine and ambroxol have reduced the occurrence of COPD exacerbations in several trials, a finding that is supported by the results of a meta-analysis [42]. One of those trials found a reduction in exacerbation rate only in patients not taking inhaled corticosteroids (ICS), while the other found a reduction in the overall population, in which only a minority (<20%) of patients received ICS, suggesting that mucoactive agents may prove effective only in patients with suboptimal inhaled therapy. This point was further tested in a specifically designed large study, which did not find any interaction between inhaled corticosteroids and effects of N-acetylcysteine on exacerbations occurrence. This was confirmed in a more recent

network meta-analysis in which a meta-regression was performed to identify factors associated with treatment response [42]. Surprisingly, this analysis identified a trend towards less response in Chinese populations. This needs to be interpreted with caution considering the significant heterogeneity observed in the meta-analysis.

### **Oral corticosteroids**

The long-term use of oral corticosteroids is discouraged in COPD due to the well-known burden of side-effects [43], contrasting with the lack of evidence of clinically relevant beneficial effects.

Systemic dose-dependent side-effects include fractures, diabetes, cataracts, hypertension, open-angle glaucoma, skin bruising, muscular weakness, cardiovascular and cerebrovascular events. Many of these effects can have major consequences leading to severe health status impairment. In addition, the use of oral corticosteroids has been linked to increased mortality and reduced efficacy of nutritional supplementation, a component of pulmonary rehabilitation [44,45]. The combination of COPD and oral corticosteroids also increases the risk of infections that may have particularly disastrous consequences in patients with severe lung function impairment, such as *Mycobacteriae*, *Aspergillus* spp. and various types of bacteria involved in chronic airways colonization/infection and pneumonia.

The most recent meta-analysis by the Cochrane Collaboration on oral corticosteroids for stable COPD was published in 2005 [46]. Treatment lasted more than 3 weeks in only 5 studies among the 24 that were identified. Combining all studies, the mean FEV1 improvement was 53 ml, half the minimal clinically important difference. The proportion of FEV1 responders (>20% increase relative to baseline) was approximately 2.5 times higher with oral steroids than on placebo. Effects were more prominent with higher doses (>30 mg/day vs 7-15 mg/day), associated with more risks of side-effects. Increases in walking distance were statistically significant but not clinically relevant (29 m with the 12-min walk test), and most of these studies were short-termed. Some symptomatic and

health status differences were reported but considered insignificant from a clinical perspective. Oral corticosteroids did not prevent exacerbations but the studies were not designed to test this endpoint in a robust manner.

As all the content of this article, the considerations presented here are valid only for patients with COPD and no associated asthma. The situation may be completely different in patients with COPD associated with predominating severe asthma, a subject of another chapter in this issue of the Clinics.

### **Anti-leukotrienes**

Anti-leukotrienes agents are not recommended in COPD [1]. Only very few properly designed studies have been performed to assess their effects in this population. There are two types of available agents [18]: 5-Lipoxygenase (LO) or 5-LO activating Protein (FLAP) inhibitors and Cysteinyl-leukotrienes (Cys-LTs: LT-C4, D4, E4) receptor antagonists. Their purpose is to reduce the production of leukotrienes with proinflammatory activity (LTB<sub>4</sub>, product of the 5-LO pathway) or to decrease effects on airway smooth muscle, mucous secretion, vascular permeability and mucociliary clearance (Cys-LTs). In 2015, 7 studies were identified, 3 of which were non-randomized (2 with Montelukast, one with Zafirlukast). Among the 4 others, one dealt with Zileuton (for acute exacerbations), one with Montelukast and 2 with products that have been secondarily abandoned. All these randomized trials were short-term, while two observational studies (one prospective, one retrospective) had a duration of at least 12 months [47]. Thus, review of all of these studies, it is clear that anti-LT have not been properly assessed in COPD. In only one (short-term) RCT with Montelukast, some non-significant effects on symptoms (dyspnea, sputum production) and lung function were reported [47].

### **Cardiovascular / metabolic treatments**

There is a strong interaction between COPD and cardiovascular diseases, both sharing common risk factors [10]; however, the increased cross prevalence of these conditions is not explained simply by smoking. As mentioned earlier, this association may relate to systemic inflammation and/or decreased daily physical activity, both of which are interrelated. Impairment of cardiac function due to lung hyperinflation may also play a role, as well as chronic or intermittent hypoxia. In addition, the burden (in terms of, e.g., dyspnea and exacerbations) and prognosis of COPD is impaired in the presence of cardiovascular diseases. Reciprocally, there is an increased frequency of COPD in patients with CV conditions and COPD impairs their prognosis. Consequently, CV drugs are frequently used in patients with COPD. In addition, cardiovascular events are more frequent during and after COPD exacerbations, of which they can represent either complications or part of its differential diagnoses. Because of these strong interactions, there has been a lot of interest in the potential effects of CV drugs in patients with COPD.

The first question that was raised related to the safety of beta-blockers in patients with COPD: these agents, especially those with poor beta1-adrenoreceptor selectivity, can enhance airway smooth muscle contractions and, thereby worsen airflow limitation, through beta2 adrenoreceptor antagonism. In clinical trials of beta-blockers for ischemic heart disease, patients with COPD were found to benefit at least, or even more than those with no COPD in terms of survival [48]. The effect of cardio-selective beta1-blockers on lung function appears very limited, if any, and these agents do not increase the occurrence of respiratory symptoms. In addition, they do not impair respiratory outcomes when continued during acute exacerbations. Observational studies had even suggested that beta-blockers could decrease the risk of COPD exacerbations and related hospitalisations and mortality. However, a recent large controlled trial in the USA did not confirm this hypothesis, and actually had a worse outcome, including risk of death in patients randomized to receive beta-blocker and who had no cardiovascular indication of beta1 blockade [49].

Similarly, retrospective database or prospective cohort studies suggested some benefits from statins in terms of exacerbation risk. Such effects could be explained by the pleiotropic anti-inflammatory effects of statins, which could control the systemic inflammation observed in many patients with COPD. However, again a randomised controlled trial did not report any effect on exacerbation rate or mortality in patients with no cardiovascular or metabolic indication [50].

Renin–angiotensin–aldosterone system inhibitors can have anti-inflammatory, anti-fibrotic and anti-oxidant effects that could be of interest in COPD [10]. It has even been suggested that these agents have some potential to prevent emphysema progression [51]. However, no clinical advantage related to the use of these agents has ever been formally demonstrated in adequately designed studies.

## **Biologics**

Inflammation, oxidative stress, airway and parenchymal remodelling including fibrosis all represent potential targets for biologics directed at modulating (upstream or downstream) their mediators, biological triggers or signalling pathways. Their intimate mechanisms are involved in the clinical manifestations of COPD including dyspnea and exacerbations as well as in disease progression. However, this involvement is highly heterogeneous and the disease biology is still incompletely deciphered, making it difficult to identify the most relevant targets and define the corresponding patients populations. Heterogeneity applies not only to stable state but also to exacerbations. In addition, COPD is a slowly evolutive disease with an overall low reactivity to any pharmacological intervention to date. This creates additional hurdles when testing new agents clinically. While clinical phenotypes correspond to clinical features or combinations of features associated with disease progression and/or treatment responses, endotypes are underlying biological mechanisms that can be identified through biomarkers[52,53]. How the disease can be split into phenotypes and endotypes is much less clear in COPD than in asthma [54]. In addition, since there is some marked overlap and discrepancies between phenotypes and between them and endotypes, the current trend

is to adopt the concept of individual treatable traits that can be independently targeted by dedicated interventions [55]. Altogether these traits cover the entire spectrum of asthma, COPD and complex overlapping /intricated situations. Among them, “eosinophilic” COPD triggers particular interest.

The central role of systemic and local inflammation in COPD pathophysiology suggested that anti-TNF agents could have some potential to influence the natural history of the disease. In addition, TNF-alpha has been shown to induce emphysema in animal models. However, clinical trials gave disappointing results, in terms of both effects on markers of local (sputum) and systemic inflammation, and clinical outcomes [56,57].

More recently, anti-IL-5 agents have been tested in COPD. These agents (IL-5 inhibitor or IL-5 receptor blocker) primarily target eosinophilic inflammation. In two parallel randomized controlled trials using mepolizumab (IL-5 inhibitor), one of the trials showed a reduction in the risk of COPD exacerbations (-23%) in patients with higher ( $> 300/\mu\text{L}$ ) blood eosinophil counts (considered as a relatively reliable surrogate for sputum eosinophils)[58]. However, these results were not significant in the other study. Further, there was no difference in lung function or health status in either study when compared with the placebo arm. The larger and more recent study using benralizumab (IL-5 receptor blocker) did not reduce exacerbation rate in patients with eosinophilic COPD ( $> 220$  cells/ $\mu\text{L}$ ). Therefore, additional data need to be gathered before these treatments can be recommended.

### **Alpha1 antitrypsin augmentation therapy**

Since severe alpha1 antitrypsin (AAT) deficiency is a rare disease, randomised controlled trials (RCTs) are difficult to conduct. An European Respiratory Society taskforce recently performed a systematic review that identified 8 RCTs and 17 observational studies (11 of which were uncontrolled) assessing the effects of augmentation therapy on various clinical and imaging outcomes [59]. Only 3 RCTs were placebo-controlled. They found a beneficial effect on emphysema progression as assessed by CT-

scan, but could not demonstrate efficacy in terms of clinical outcomes. However, such efficacy (although subject to more biases) was suggested by some observational studies. In addition, emphysema progression on CT-scan is associated with mortality and quality of life, suggesting that it may represent a clinically relevant outcome. Therefore, several guidelines recommend augmentation therapy in AAT-deficient patients with emphysema and progressive disease [1].

### **Systemic treatments for dyspnea**

Dyspnea is the most important and relevant symptom of patients suffering from COPD. It is the limiting element of exercise capacity/tolerance and daily activity. Therefore, relieving dyspnea is one of the major goals of COPD care. First-line approaches include bronchodilators and rehabilitation. Interventional techniques such as lung volume reduction can be considered in highly selected patient populations. In some patients, dyspnea remains refractory to those therapies. In such instances benzodiazepines and morphine have been considered, but they remain seldom prescribed as part of routine practice [60]. In 2016, a Cochrane review identified 26 randomized controlled trials with over 500 patients with refractory breathlessness in the context of advanced disease and terminal illness. In 14 studies, recruited subjects were primarily or exclusively COPD patients. Altogether the quality of evidence was deemed low or very low, but some evidence of dyspnea alleviation was found. In parallel, drowsiness, nausea and vomiting, and constipation were relatively frequent (13%, 20% and 18%, respectively)[61]. Thus, the benefit-risk ratio needs to be carefully considered on an individual basis, balancing the risk of side-effects and the burden of dyspnea. In summary, for a very breathless patient, a trial can be initiated under close monitoring and stopped if the benefits are not evident or if side effects limit its use.

In a similar way, the last Cochrane review on benzodiazepines for dyspnea was performed in 2016 and included 8 studies in patients with advanced cancer or COPD, in which benzodiazepines were

compared to placebo, promethazine or morphine. No demonstration of positive effects was found, although the authors found less drowsiness than with morphine.

### **Summary and conclusion**

Although numerous systemic treatments for COPD do exist, they are positioned relatively late in treatment algorithms, with inhaled therapy remaining the cornerstone of treatment. However, when inhaled therapy is not sufficient to control the burden of disease, oral therapies such as phosphodiesterase 4 inhibitors, azithromycin or mucoactive agents can be of help in some patients (**Table 2**), especially to reduce the risk of exacerbations. The major difficulty here is to choose the appropriate responder and how these treatments should be positioned in the global treatment algorithm. For instance, should they be prescribed in addition to other anti-inflammatory agents (i.e., corticosteroids) or should they replace them in some specific sub-groups of patients. Some currently available biologics used in severe asthma could also be effective in some patients' categories ("eosinophilic COPD"), but additional studies centered on well selected candidates are needed. Some oral agents such as beta 2 adrenergic agents and particularly theophylline remain widely used in some countries due to its low cost, although its benefit/risk profile is unfavourable compared to inhaled therapy. Alpha1 antitrypsin augmentation therapy is useful in patients with AAT deficiency and progressive emphysema. Cardiovascular drugs should be used in COPD only if those patients have underlying cardiovascular compromise supporting their indication. Ongoing research aims at identifying new therapeutic targets and agents in the fields of inflammation, destruction/repair mechanisms, immune regulation, microbiota homeostasis, mucus modulation and lung regeneration.

### References

- 1 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease.

- 2 Bagdonas E, Raudoniute J, Bruzauskaite I, *et al.* Novel aspects of pathogenesis and regeneration mechanisms in COPD. *Int J Chron Obstruct Pulmon Dis* 2015;**10**:995–1013. doi:10.2147/COPD.S82518
- 3 Eapen MS, Myers S, Walters EH, *et al.* Airway inflammation in chronic obstructive pulmonary disease (COPD): a true paradox. *Expert Rev Respir Med* 2017;**11**:827–39. doi:10.1080/17476348.2017.1360769
- 4 Hussell T, Lui S, Jagger C, *et al.* The consequence of matrix dysfunction on lung immunity and the microbiome in COPD. *Eur Respir Rev* 2018;**27**. doi:10.1183/16000617.0032-2018
- 5 Kesimer M, Ford AA, Ceppe A, *et al.* Airway Mucin Concentration as a Marker of Chronic Bronchitis. *N Engl J Med* 2017;**377**:911–22. doi:10.1056/NEJMoa1701632
- 6 Fischer BM, Voynow JA, Ghio AJ. COPD: balancing oxidants and antioxidants. *Int J Chron Obstruct Pulmon Dis* 2015;**10**:261–76. doi:10.2147/COPD.S42414
- 7 Barnes PJ. Senescence in COPD and Its Comorbidities. *Annu Rev Physiol* 2017;**79**:517–39. doi:10.1146/annurev-physiol-022516-034314
- 8 Caramori G, Ruggeri P, Di Stefano A, *et al.* Autoimmunity and COPD: Clinical Implications. *Chest* 2018;**153**:1424–31. doi:10.1016/j.chest.2017.10.033
- 9 Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009;**33**:1165–85. doi:10.1183/09031936.00128008
- 10 Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? *Eur Respir Rev* 2018;**27**. doi:10.1183/16000617.0057-2018
- 11 Pelgrim CE, Peterson JD, Gosker HR, *et al.* Psychological co-morbidities in COPD: Targeting systemic inflammation, a benefit for both? *Eur J Pharmacol* 2019;**842**:99–110. doi:10.1016/j.ejphar.2018.10.001
- 12 Corlateanu A, Covantev S, Mathioudakis AG, *et al.* Prevalence and burden of comorbidities in Chronic Obstructive Pulmonary Disease. *Respir Investig* 2016;**54**:387–96. doi:10.1016/j.resinv.2016.07.001
- 13 Gimeno-Santos E, Frei A, Steurer-Stey C, *et al.* Determinants and outcomes of physical activity in patients with COPD: a systematic review. *Thorax* Published Online First: 20 February 2014. doi:10.1136/thoraxjnl-2013-204763
- 14 Higham A, Quinn AM, Cançado JED, *et al.* The pathology of small airways disease in COPD: historical aspects and future directions. *Respir Res* 2019;**20**:49. doi:10.1186/s12931-019-1017-y
- 15 Cazzola M, Calderaro F, Califano C, *et al.* Oral bambuterol compared to inhaled salmeterol in patients with partially reversible chronic obstructive pulmonary disease. *Eur J Clin Pharmacol* 1999;**54**:829–33. doi:10.1007/s002280050561
- 16 Shim CS, Williams MH. Bronchodilator response to oral aminophylline and terbutaline versus aerosol albuterol in patients with chronic obstructive pulmonary disease. *Am J Med* 1983;**75**:697–701. doi:10.1016/0002-9343(83)90459-x

- 17 Spina D, Page CP. Xanthines and Phosphodiesterase Inhibitors. *Handb Exp Pharmacol* 2017;**237**:63–91. doi:10.1007/164\_2016\_71
- 18 Pleasants RA. Clinical Pharmacology of Oral Maintenance Therapies for Obstructive Lung Diseases. *Respir Care* 2018;**63**:671–89. doi:10.4187/respcare.06068
- 19 Cazzola M, Calzetta L, Barnes PJ, *et al.* Efficacy and safety profile of xanthines in COPD: a network meta-analysis. *Eur Respir Rev* 2018;**27**. doi:10.1183/16000617.0010-2018
- 20 Barnes PJ. Theophylline. *Am J Respir Crit Care Med* 2013;**188**:901–6. doi:10.1164/rccm.201302-0388PP
- 21 Cosio BG, Tsaprouni L, Ito K, *et al.* Theophylline restores histone deacetylase activity and steroid responses in COPD macrophages. *J ExpMed* 2004;**200**:689–95.
- 22 Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. *Lancet* 2009;**373**:1905–17. doi:10.1016/S0140-6736(09)60326-3
- 23 Ito K, Ito M, Elliott WM, *et al.* Decreased histone deacetylase activity in chronic obstructive pulmonary disease. *N Engl J Med* 2005;**352**:1967–76.
- 24 Devereux G, Cotton S, Fielding S, *et al.* Effect of Theophylline as Adjunct to Inhaled Corticosteroids on Exacerbations in Patients With COPD: A Randomized Clinical Trial. *JAMA* 2018;**320**:1548–59. doi:10.1001/jama.2018.14432
- 25 Cosío BG, Shafiek H, Iglesias A, *et al.* Oral Low-Dose Theophylline on Top of Inhaled Fluticasone-Salmeterol Does Not Reduce Exacerbations in Patients with Severe COPD: A Pilot Clinical Trial. *Chest* Published Online First: 20 April 2016. doi:10.1016/j.chest.2016.04.011
- 26 Compton CH, Gubb J, Nieman R, *et al.* Cilomilast, a selective phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: a randomised, dose-ranging study. *Lancet* 2001Jul28;358(9278):265-70;**358**:265–70.
- 27 Lipworth BJ. Phosphodiesterase-4 inhibitors for asthma and chronic obstructive pulmonary disease. *Lancet* 2005;**365**:167–75.
- 28 Contreras S, Milara J, Morcillo E, *et al.* Selective Inhibition of Phosphodiesterases 4A, B, C and D Isoforms in Chronic Respiratory Diseases: Current and Future Evidences. *Curr Pharm Des* 2017;**23**:2073–83. doi:10.2174/1381612823666170214105651
- 29 Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017;**9**:CD002309. doi:10.1002/14651858.CD002309.pub5
- 30 Martinez FJ, Rabe KF, Sethi S, *et al.* Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting  $\beta$ 2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE(2)SPOND). A Randomized Clinical Trial. *Am J Respir Crit Care Med* 2016;**194**:559–67. doi:10.1164/rccm.201607-1349OC
- 31 Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017;**9**:CD002309. doi:10.1002/14651858.CD002309.pub5

- 32 Cazzola M, Calzetta L, Rogliani P, *et al.* Enfisentrine (RPL554): an investigational PDE3/4 inhibitor for the treatment of COPD. *Expert Opin Investig Drugs* 2019;**28**:827–33. doi:10.1080/13543784.2019.1661990
- 33 Albert RK, Connett J, Bailey WC, *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011;**365**:689–98. doi:10.1056/NEJMoa1104623
- 34 Uzun S, Djamin RS, Kluytmans JAJW, *et al.* Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2014;**2**:361–8. doi:10.1016/S2213-2600(14)70019-0
- 35 Seemungal TA, Wilkinson TM, Hurst JR, *et al.* Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008;**178**:1139–47.
- 36 Huckle AW, Fairclough LC, Todd I. Prophylactic Antibiotic Use in COPD and the Potential Anti-Inflammatory Activities of Antibiotics. *Respir Care* 2018;**63**:609–19. doi:10.4187/respcare.05943
- 37 Cui Y, Luo L, Li C, *et al.* Long-term macrolide treatment for the prevention of acute exacerbations in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2018;**13**:3813–29. doi:10.2147/COPD.S181246
- 38 Suzuki T, Yanai M, Yamaya M, *et al.* Erythromycin and common cold in COPD. *Chest* 2001;**120**:730–3.
- 39 Han MK, Tayob N, Murray S, *et al.* Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. *Am J Respir Crit Care Med* 2014;**189**:1503–8. doi:10.1164/rccm.201402-0207OC
- 40 Sethi S, Jones PW, Theron MS, *et al.* Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Respir Res* 2010;**11**:10. doi:10.1186/1465-9921-11-10
- 41 Decramer M, Janssens W. Mucoactive therapy in COPD. *Eur Respir Rev* 2010;**19**:134–40. doi:10.1183/09059180.00003610
- 42 Cazzola M, Rogliani P, Calzetta L, *et al.* Impact of Mucolytic Agents on COPD Exacerbations: A Pair-wise and Network Meta-analysis. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2017;**14**:552–63. doi:10.1080/15412555.2017.1347918
- 43 Manson SC, Brown RE, Cerulli A, *et al.* The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respir Med* 2009;**103**:975–94. doi:10.1016/j.rmed.2009.01.003
- 44 Schols AM, Wesseling G, Kester AD, *et al.* Dose dependent increased mortality risk in COPD patients treated with oral glucocorticoids. *Eur Respir J* 2001Mar;**17**(3):337-42;**17**:337–42.
- 45 Schols AM, Slangen J, Volovics L, *et al.* Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**:1791–7.
- 46 Walters J, Walters E, Wood-Baker R. Oral corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;:CD005374.

- 47 Lee JH, Kim HJ, Kim YH. The Effectiveness of Anti-leukotriene Agents in Patients with COPD: A Systemic Review and Meta-analysis. *Lung* 2015;**193**:477–86. doi:10.1007/s00408-015-9743-5
- 48 Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *NEnglJMed* 1998;**20**;339:489–97.
- 49 Dransfield MT, Voelker H, Bhatt SP, *et al.* Metoprolol for the Prevention of Acute Exacerbations of COPD. *N Engl J Med* 2019;**381**:2304–14. doi:10.1056/NEJMoa1908142
- 50 Criner GJ, Connett JE, Aaron SD, *et al.* Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med* 2014;**370**:2201–10. doi:10.1056/NEJMoa1403086
- 51 Parikh MA, Aaron CP, Hoffman EA, *et al.* Angiotensin-Converting Inhibitors and Angiotensin II Receptor Blockers and Longitudinal Change in Percent Emphysema on Computed Tomography. The Multi-Ethnic Study of Atherosclerosis Lung Study. *Ann Am Thorac Soc* 2017;**14**:649–58. doi:10.1513/AnnalsATS.201604-317OC
- 52 Pavord ID. Biologics and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2018;**141**:1983–91. doi:10.1016/j.jaci.2018.04.020
- 53 Yousuf A, Brightling CE. Biologic Drugs: A New Target Therapy in COPD? *COPD* 2018;**15**:99–107. doi:10.1080/15412555.2018.1437897
- 54 Woodruff PG, Agusti A, Roche N, *et al.* Current concepts in targeting chronic obstructive pulmonary disease pharmacotherapy: making progress towards personalised management. *Lancet* 2015;**385**:1789–98. doi:10.1016/S0140-6736(15)60693-6
- 55 Agusti A, Bel E, Thomas M, *et al.* Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016;**47**:410–9. doi:10.1183/13993003.01359-2015
- 56 Rennard SI, Flavin SK, Agarwal PK, *et al.* Long-term safety study of infliximab in moderate-to-severe chronic obstructive pulmonary disease. *Respir Med* 2013;**107**:424–32. doi:10.1016/j.rmed.2012.11.008
- 57 Dentener MA, Creutzberg EC, Pennings H-J, *et al.* Effect of infliximab on local and systemic inflammation in chronic obstructive pulmonary disease: a pilot study. *Respiration* 2008;**76**:275–82. doi:10.1159/000117386
- 58 Pavord ID, Chanez P, Criner GJ, *et al.* Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017;**377**:1613–29. doi:10.1056/NEJMoa1708208
- 59 Miravittles M, Dirksen A, Ferrarotti I, *et al.* European Respiratory Society statement: diagnosis and treatment of pulmonary disease in  $\alpha$ 1-antitrypsin deficiency. *Eur Respir J* 2017;**50**. doi:10.1183/13993003.00610-2017
- 60 Ahmadi Z, Bernelid E, Currow DC, *et al.* Prescription of opioids for breathlessness in end-stage COPD: a national population-based study. *Int J Chron Obstruct Pulmon Dis* 2016;**11**:2651–7. doi:10.2147/COPD.S112484
- 61 Barnes H, McDonald J, Smallwood N, *et al.* Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev* 2016;**2016**. doi:10.1002/14651858.CD011008.pub2

**Table 1.** Main modulators of theophylline’s pharmacokinetics. *Data from Refs* <sup>18, 20</sup>

Effect	Increased bioavailability	Reduced bioavailability
Disease/condition	Viral infections Congestive heart failure Liver diseases	
Age		Children < 16 years
Toxic agents		Cigarette and marijuana smoking
Medications (through CYP1A2 and CYP3A4 modulation)	Erythromycin, clarithromycin (not azithromycin), ciprofloxacin (not ofloxacin), cimetidine (not ranitidine) allopurinol, serotonin uptake inhibitors, flu vaccinatuion	Phenytoin, phenobarbitone, rifampicin

**Table 2.** Examples of systemic treatments targeting specific subpopulations / treatable traits in COPD

Treatment	Subpopulation / treatable trait
Established	
PDE-4 inhibitors (roflumilast)	Severe airflow obstruction, repeated exacerbations, chronic mucus hyperproduction, on top of long-acting bronchodilators
Alpha1 antitrypsin	Alpha1 antitrypsin deficiency
Putative	
Azithromycin	Ex-smokers, older patients, milder airflow obstruction Airway bacterial colonization / chronic infection Repeated bacterial exacerbations
Anti-IL-5 agents	“Eosinophilic” COPD
Mucoactive agents	Chronic mucus hyperproduction