Educational aims

- To describe the impact of COPD exacerbations and the importance of the frequent exacerbator phenotype.
- To describe the spectrum of pharmacological and non-pharmacological interventions that reduce exacerbation frequency and severity.
- To discuss the role of novel interventions, such as long term macrolide use and dual bronchodilatation, in COPD exacerbation prevention.

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COPD exacerbations: impact and prevention

Summary

Exacerbations are key events for patients with chronic obstructive pulmonary disease (COPD). Exacerbations drive health status and contribute to disease progression and exacerbation prevention is a key goal of therapy in COPD. The majority of COPD exacerbations are triggered by respiratory viral infections and/or bacterial infections. Some patients are especially susceptible to frequent exacerbations and these patients need to be targeted for preventative therapy.

A number of pharmacological therapies exist that can prevent COPD exacerbations and reduce hospital admissions. Non-pharmacological interventions for exacerbation prevention include pulmonary rehabilitation, long-term oxygen therapy and home noninvasive ventilator support, though the evidence base for these is less well developed. Improved management of the acute exacerbation will also prolong the time to the next exacerbation event.

Impact of COPD exacerbations

The natural course of chronic obstructive pulmonary disease (COPD) is interrupted by episodes of symptom worsening termed exacerbations [1]. COPD exacerbations are major determinant of health status in COPD and we now know that they also drive disease progression, with around 25% of the lung function decline being attributed to exacerbations [2].

COPD is the second largest cause of emergency admissions in the UK, with one in eight emergency admissions to hospital resulting from COPD, and accounts for more than £800 million in direct healthcare costs [3]. COPD exacerbations are an important driver of mortality in COPD and are also associated with cardiovascular events. Patients hospitalised with exacerbations of COPD are a particularly vulnerable group. Each new severe exacerbation requiring hospitalisation increases the risk of a subsequent exacerbation, and every new severe exacerbation increases the risk

Statement of Interest

J.A.Wedzicha has received honoraria for lectures and/or advisory boards from GSK, Novartis, Boehringer Ingelheim, Pfizer, Bayer, Takeda, Vifor Pharma, Chiesi, Almirall, Ventura and Medimmune. She has undertaken consultancy for Novartis and Chiesi. Her institution has received research grants from Novartis, Johnson and Johnson, Takeda, Chiesi, GSK, Almirall, Vifor Pharma and AstraZeneca. A.J Mackay has received payment for lectures from GSK and reimbursement for meeting expenses from GSK and Boehringer Ingelheim.

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of death, up to five times after the tenth compared with after the first COPD hospitalisation [4]. COPD exacerbations are also more common in the winter months, and are more severe, when there are already pressures on numbers of admissions in hospitals.

Thus, the COPD strategy document developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) highlights the importance of avoiding future risk in COPD by preventing exacerbations [5]. In view of the wide impact of COPD exacerbations, any therapy that prevents exacerbations will also improve health status and prevent forced expiratory volume in 1 s (FEV_1) decline.

Definition of exacerbations

The common symptoms of a COPD exacerbation are an increase in dyspnoea, sputum purulence and cough, but other symptoms may include increased wheezing, chest discomfort and symptoms of an upper airway cold.

An exacerbation of COPD is defined in the GOLD strategy in terms of healthcare utilisation as ''an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication''. However, there is now considerable evidence that around half of all COPD exacerbations identified by symptom worsening are not reported to healthcare professionals for treatment [6]. Furthermore, these unreported exacerbations, although generally of a lesser severity than reported or treated exacerbations, also impact on health status [6].

For this reason, considerable interest exists in the potential of patient-reported outcomes in studies of exacerbation and an instrument has been specifically designed for exacerbations called the Exacerbations of Chronic Pulmonary Disease Tool (EXACT). Although it may be useful in assessing the severity of exacerbations and the response to acute exacerbation therapy [7], detection of the exacerbation will probably still have to depend on a patient report. Recently a study has shown that EXACT scores at the peak of the exacerbation were higher in treated than untreated events (fig. 1), suggesting that the symptomatic burden of the exacerbation drives the patient's need for therapy. The scores on the COPD assessment test (CAT) will also rise during an exacerbation and reflect severity, but the CAT has not been developed for use at exacerbation [8].

Causes and pathogenesis of exacerbation

The majority of COPD exacerbations are triggered by respiratory viral infections especially by rhinovirus, the cause of the common cold. Using molecular techniques, respiratory viruses can be identified in up to 60% of exacerbations [9]. Exacerbations associated with viruses tend to have greater airway and systemic inflammatory effects than those without any evidence of viral infection and are more common in the winter months. Airway pollutants may also be associated with precipitating exacerbations, especially by interacting with respiratory viruses, although the effects of pollution are only seen in global areas of high urban pollution.

Bacteria are present in the lower airway and are known to be present in the stable state and to colonise the airway. Although airway bacterial load increases at exacerbation it is now considered that bacteria are seldom the primary infective cause of the exacerbation but are secondary invaders after a viral trigger. The effect of the infective trigger is to increase inflammation further in a chronically inflamed airway and this leads to an increase in bronchoconstriction, oedema and mucus production, resulting in an increase in dynamic hyperinflation and symptoms of increased dyspnoea characteristic of an exacerbation (fig. 2) [1]. Thus, any intervention that reduces inflammation in COPD will reduce the number and severity of exacerbations, while bronchodilators will impact exacerbation *via* their effects on reducing dynamic hyperinflation.

The frequent exacerbator phenotype

Exacerbations become more frequent and severe as COPD severity increases. However, one distinct group of patients appears to be susceptible to exacerbations, irrespective of disease severity. This COPD phenotype of frequent exacerbations is relatively stable over time and the major determinant of developing frequent exacerbations is a history of prior exacerbations [10]. This phenomenon is seen across all GOLD stages, including patients with stage 2 disease of whom 22% had frequent exacerbations

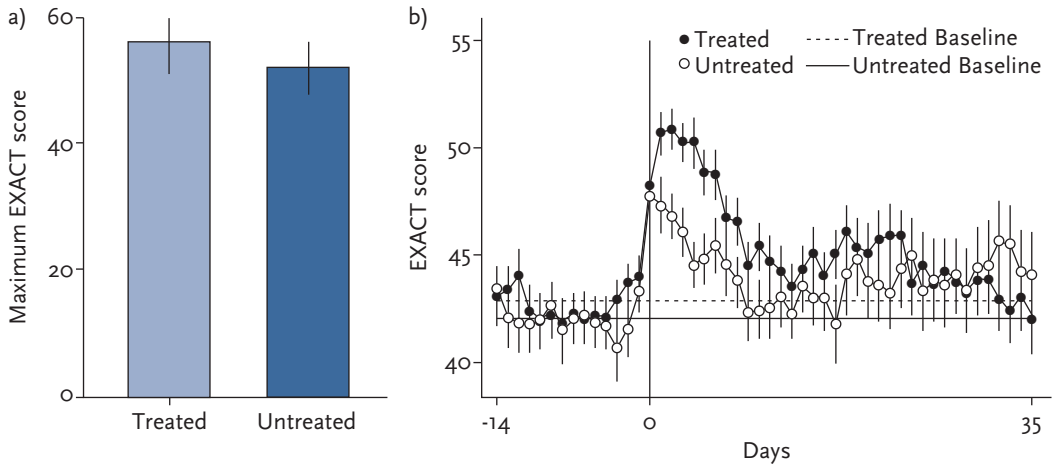

Figure 1
a) Maximum Exacerbations of Chronic Pulmonary Disease Tool (EXACT) scores and b) time course of EXACT scores during treated and untreated exacerbations. Vertical lines represent standard errors. Reproduced from [7].

in the first year of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study [11].

Patients with a history of frequent exacerbations are at particular future risk of further events and death (fig. 3) [12]. Studies have shown that this group of patients has a worse quality of life, increased risk of hospitalisation and a greater chance of recurrent exacerbations. Frequent exacerbators also exhibit a faster decline in lung function and may have worse functional status. Thus, it is vital to identify patients at risk of frequent exacerbations and target this group for therapy.

Exacerbation prevention

Vaccines

In retrospective cohort studies of community-dwelling elderly patients, influenza vaccination is associated with a 27% reduction in the risk of hospitalisation for pneumonia or influenza and a 48% reduction in the risk of death [13]. Thus, influenza vaccines are recommended in the majority of patients with COPD. There is less evidence for the role of pneumococcal polysaccharide vaccine in preventing exacerbations and hospital admissions in COPD, but large studies are currently underway with vaccines with improved immunogenicity. Nevertheless, pneumococcal vaccine is commonly administered to COPD patients.

Inhaled corticosteroids and long-acting bronchodilators

Both inhaled corticosteroids (ICS) and long-acting β-agonists (LABAs) reduce exacerbation frequency. In the TORCH (Towards a Revolution in COPD Health) study, in which patients were followed over 3 years, both inhaled fluticasone and salmeterol reduced exacerbation frequency when administered separately in comparison with placebo [14]. The combination of fluticasone and salmeterol reduced exacerbation frequency further, in addition to improving health status and lung function when compared with placebo. The combination of ICS and LABA also resulted in fewer hospital admissions over the study period. Reduction in exacerbation frequency has been also found with other LABA/ICS combinations, such as formoterol and budesonide. Guidelines now indicate an LABA/ICS combination for treatment of patients with an FEV_1 <50% predicted (Group C and D) and where there is a history of two or more exacerbations.

Long-acting antimuscarinics (LAMAs) also reduce exacerbation frequency. In the UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) trial, patients were randomised to tiotropium or placebo for 4 years, with concomitant therapy

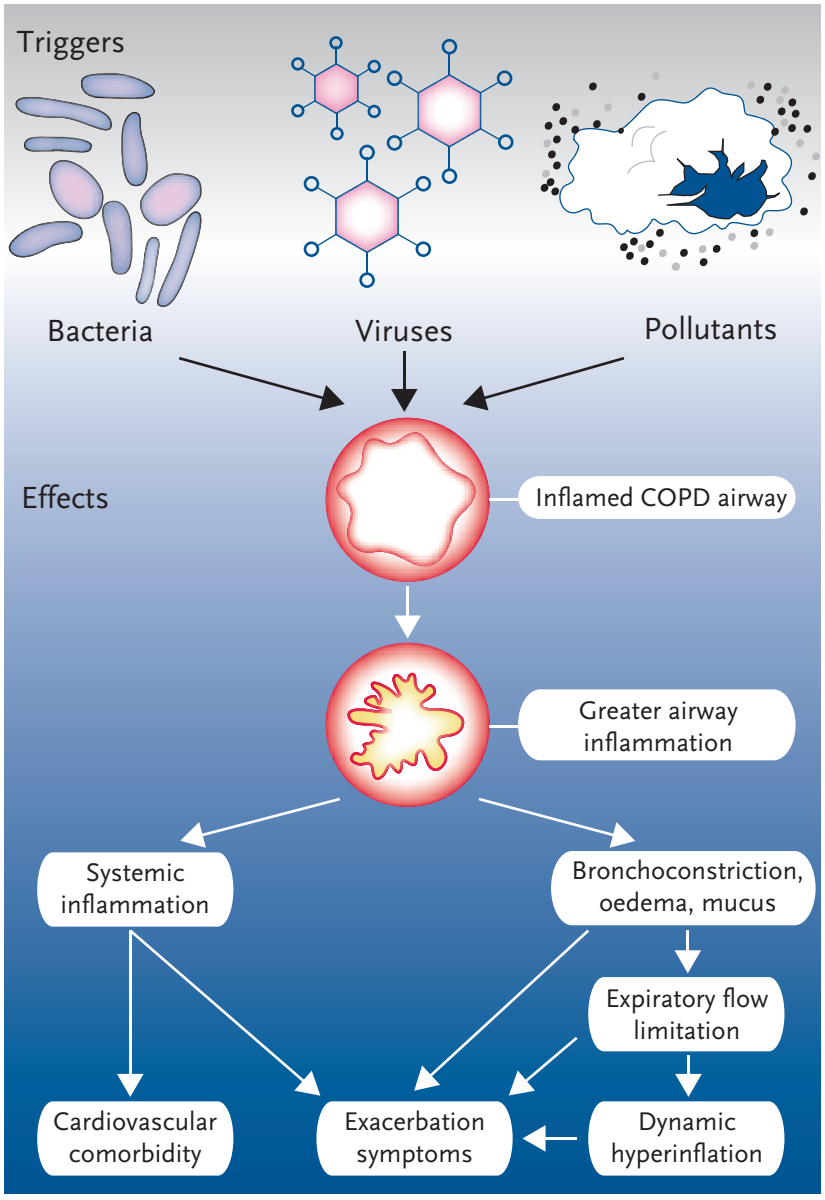

Figure 2
Triggers of chronic obstructive pulmonary disease (COPD) exacerbations and the associated pathophysiological changes leading to increased exacerbation symptoms. Reproduced from [1] with permission from the publisher.

allowed [15]. Although the primary end-point of the trial (reduction in rate of decline in FEV_1) was negative, tiotropium was associated with a reduction in exacerbation risk, related hospitalisations and respiratory failure. The POET-COPD (Prevention of Exacerbations with Tiotropium in COPD) trial showed that, in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations [16]. Both the National Institute for Health and Clinical Excellence guidelines and the GOLD strategy document indicate that LAMAs can be used as an alternative to LABA/ICS to reduce exacerbations or in addition to the LABA/ICS combination as a triple therapy.

Dual bronchodilators

Dual inhaled long-acting bronchodilators contained in one inhaler are now being introduced. Recently, QVA, which is a combination of a LABA (indacaterolol) and a LAMA (glycopyrronium), became the first one to be approved by European regulators. QVA has been shown to produce increased bronchodilation compared to its components. In the SPARK study, which included COPD patients with an FEV_1 of <50% predicted and a history of COPD exacerbations, QVA reduced healthcare utilisation defined exacerbations compared with glycopyrronium [17]. However, diary cards were used in the SPARK study to collect all exacerbation events and QVA was superior to both glycopyrronium and open label tiotropium in the reduction of all exacerbations, *i.e.* mild, moderate and severe exacerbations combined. Thus, future studies of dual bronchodilators must be designed to collect data on all exacerbation events, as in the SPARK study. Availability of the new dual bronchodilators will change treatment algorithms as these therapies reduce both symptoms and prevent exacerbations.

Phosphodiesterase inhibitors

Phosphodiesterase-4 inhibitors inhibit the airway inflammatory processes associated with COPD. Evidence from a pooled analysis of two large placebo-controlled, double-blind multicentre trials revealed a significant reduction of 17% in the frequency of moderate (glucocorticoid treated) or severe (hospitalisation/death) exacerbations [18]. However, only patients with an FEV_1 <50% predicted (GOLD stage 3 and 4), presence of bronchitic symptoms and a history of exacerbations were enrolled. There currently are no comparator studies with ICS. Weight loss was also noted in the roflumilast group, with a mean reduction of 2.1 kg after 1 year, and was highest in obese patients. Therefore, following treatment with roflumilast, weight needs to be carefully monitored. Recent evidence also suggests that roflumilast may

reduce the number of patients in the frequent exacerbator group after 12 months of therapy [19].

Long-term antibiotics

At present there is insufficient evidence to recommend routine prophylactic antibiotic therapy in the management of stable COPD, but some studies have shown promise. Erythromycin reduced the frequency of moderate and/or severe exacerbations (treated with systemic steroids, treated with antibiotics, or hospitalised) and shortened exacerbation length when taken twice daily over 12 months by patients with moderate-to-severe COPD [20]. The macrolide azithromycin has been used as prophylaxis in patients with cystic fibrosis and when added to usual treatment azithromycin has also been shown to decrease exacerbation frequency and improve quality of life in COPD patients [21]. However, the benefits were most significant in treatment-naïve patients with mild disease (GOLD stage 2) and significant rates of hearing decrement (as measured by audiometry) and antibiotic resistance were found. Also, a recent large epidemiological study has suggested a small increase in cardiovascular deaths in patients receiving azithromycin, particularly in those with a high baseline risk of cardiovascular disease.

Furthermore, intermittent pulsed moxifloxacin, when given to stable patients, has been shown to significantly reduce exacerbation frequency in a per-protocol population, and in a *post hoc* subgroup of patients with bronchitis at baseline [22]. However, this reduction did not meet statistical significance in the intention-to-treat analysis and further studies are required on non-macrolide antibiotics, including assessment of safety.

Thus, before prescription of long-term antibiotics in COPD, patients should be treated with an optimum combination inhaled therapy, show evidence of ongoing frequent exacerbations, and be carefully assessed for risk of potential cardiovascular and auditory side-effects.

Pulmonary rehabilitation and home oxygen and ventilatory support

There is some evidence from clinical trials that pulmonary rehabilitation programmes reduce hospital stay. Epidemiological studies in COPD patients have provided some evidence that long-term oxygen therapy and noninvasive ventilatory support may reduce hospital admission and prevent exacerbations [23], but controlled trials have not yet addressed these issues. Although it is now difficult to perform controlled trials of long term oxygen therapy, there are ongoing studies on the role of home noninvasive ventilation in COPD patients who are hypercapnic and at risk of further events.

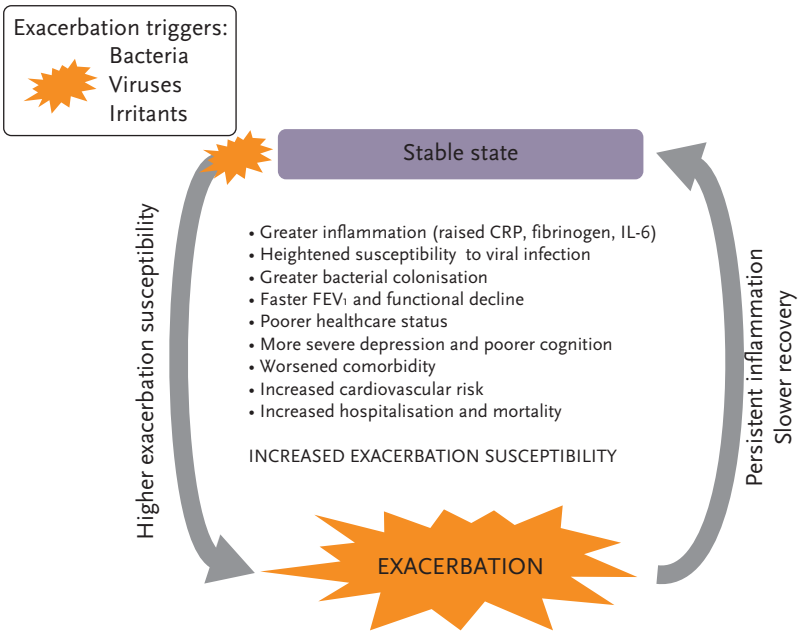

Figure 3
Effect of chronic obstructive pulmonary disease exacerbations in the group with frequent exacerbations. CRP: C-reactive protein; IL: interleukin; FEV1: forced expiratory volume in 1s. Reproduced and modified from [12] with permission from the publisher.

Management of the acute exacerbation

The standard management of an acute exacerbation consists of antibiotics if there is evidence of increased sputum purulence or increased sputum volume. Short courses of oral corticosteroids are also added depending on the individual exacerbation severity. There is evidence that the earlier that therapy is started at onset of exacerbation, the shorter the recovery of the event [6]. COPD exacerbations may show early recurrence especially in patients who are frequent exacerbators. There is evidence

that exacerbation therapy may prolong the time to subsequent events [24]. Thus, prompt and appropriate management of the exacerbation event will have an effect not only on optimising recovery but will also delay the time to the next event.

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