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COPD exacerbations: defining their cause and prevention

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Lancet 2007; 370: 786–96

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Exacerbations of chronic obstructive pulmonary disease (COPD) are episodes of worsening of symptoms, leading to substantial morbidity and mortality. COPD exacerbations are associated with increased airway and systemic inflammation and physiological changes, especially the development of hyperinflation. They are triggered mainly by respiratory viruses and bacteria, which infect the lower airway and increase airway inflammation. Some patients are particularly susceptible to exacerbations, and show worse health status and faster disease progression than those who have infrequent exacerbations. Several pharmacological interventions are effective for the reduction of exacerbation frequency and severity in COPD such as inhaled steroids, long-acting bronchodilators, and their combinations. Non-pharmacological therapies such as pulmonary rehabilitation, self-management, and home ventilatory support are becoming increasingly important, but still need to be studied in controlled trials. The future of exacerbation prevention is in assessment of optimum combinations of pharmacological and non-pharmacological therapies that will result in improvement of health status, and reduction of hospital admission and mortality associated with COPD.

Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) impose a substantial burden on health-care systems worldwide; they are a major cause of morbidity, mortality, and reduced health status.¹ COPD exacerbations are now the most common cause of medical hospital admission in the UK (accounting for 15·9% of hospital admissions), at a cost to the National Health System of over £253 million a year.² Exacerbations are also important outcome measures in COPD, and thus a reduction in their frequency is a key target for intervention.

Although in half of community-treated exacerbations, patients recover to baseline symptoms by 7 days, a study of the time course showed that in 14% of these events patients had still not returned to baseline symptoms within 35 days of onset, and in a small proportion of exacerbations, symptoms never returned to the baseline level.³ Thus COPD exacerbations can be quite protracted, which accounts for some of the considerable morbidity associated with such an event. An audit of hospital admissions showed that around 30% of patients presenting with an index exacerbation will be seen again

and possibly readmitted with another (or recurrent) event within 8 weeks.⁴ In a cohort of patients with moderate to severe COPD followed-up after exacerbation, 22% had a recurrent event within 50 days of the first (index) exacerbation. Thus, such events are complex, and an initial exacerbation seems to increase susceptibility to a subsequent one.⁵

Definition

An exacerbation of COPD is described as an acute worsening of respiratory symptoms associated with a variable degree of physiological deterioration.³ The guidelines of the WHO and US National Heart Lung and Blood Institute Global Initiative for Chronic Obstructive Lung Disease (GOLD)⁶ define an exacerbation as “an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD”.⁶

Definitions based on use of health care have also been proposed, eg, unscheduled physician visits, changes or increases in medication, use of antibiotics or oral steroids at exacerbation, and hospital admission.⁷ However, health-care use in COPD can vary depending on access, and thus there could be substantial difficulty in the standardisation of such a definition. Additionally, many COPD exacerbations are not reported to health-care professionals and are either self-treated or left untreated.¹ The latest GOLD guidelines also indicate that exacerbations can be self-limiting, especially if of mild severity, and the phrase “may warrant a change in regular medication” has been incorporated.⁷ However, health-care use can be used to define exacerbation severity: often defined as mild if increases in regular inhaled medication are needed, moderate if courses of steroids or antibiotics are needed, and severe if the patient requires hospital admission.

Exacerbations are usually inflammatory events, with several airway and systemic inflammatory markers increasing.³ There has been substantial interest in developing a systemic biomarker as a diagnostic test for

Search strategy and selection criteria

We searched Medline (1997–May, 2007), Embase (1997–May, 2007), and CINAHL (1956–April, 2006) with the search terms “acute exacerbation of COPD”, “COPD exacerbation prevention”, “COPD exacerbation impact”. Thus we largely selected publications in the past 10 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Decisions to include specific references were based on authors’ knowledge of published work, participation in expert meetings, and many years of research on the subject. Thus, this work is not an exhaustive systematic review of the burden and prevention of COPD exacerbations. However, it is an overview of current thinking on the importance of COPD exacerbations and how to prevent them based on research evidence and clinical practice.

an exacerbation. Hurst and colleagues⁸ did a large study of plasma biomarkers for COPD exacerbations, with 36 candidate molecules assessed in paired baseline and exacerbation plasma samples, and tested against a standard definition, meeting both health-care use and symptom-based criteria. To confirm the diagnosis of exacerbation, the most selective biomarker was C-reactive protein (CRP) but this was neither sufficiently sensitive nor specific alone. However, the combination of CRP with any increased major exacerbation symptom on that day (dyspnoea, sputum volume, or sputum purulence) increased the sensitivity and specificity. Further research will aid in the understanding of mechanisms of COPD exacerbations and will lead to the development of more specific biomarkers.

Pathophysiological changes

COPD exacerbations are associated with increased upper and lower airway and systemic inflammation (figure 1).⁹⁻¹³ There is little information available on the nature of the airway inflammatory changes especially when studied close to an exacerbation, because taking bronchial biopsies at exacerbation in patients with moderate to severe COPD is difficult. In stable COPD there is an increase in the CD8+ lymphocytes and macrophages in the bronchial mucosa and an increase in neutrophils with more severe

disease.¹⁴ In one study, where biopsies were done at exacerbation in patients with chronic bronchitis, increased airway eosinophilia was reported, although the patients studied had only mild COPD.¹⁰ Modest increases were seen in neutrophils, T lymphocytes (CD3), and TNF alpha positive cells. However, in patients with more severe COPD, increases have been seen in airway neutrophils when stable that increase further at exacerbation.¹⁰⁻¹² Qiu and colleagues¹¹ have studied biopsies from patients with severe COPD, who were treated at exacerbation with tracheal intubation, and showed that there was pronounced airway neutrophilia, neutrophil elastase expression, and upregulation of neutrophil chemokine expression. However, studies in intubated patients with COPD are difficult, since the results can be complicated by secondary infection. Oxidative stress is a key factor in the development of airway inflammation in COPD. A study has shown that patients with severe exacerbations who needed hospital admission or assisted ventilation have evidence of increased large airway interleukin-8 (IL-8) levels and increased oxidative stress.¹² Various markers of oxidative stress have been shown to rise in the airways with exacerbation such as hydrogen peroxide and 8-isoprostane and these markers can take some time to recover to baseline.¹⁵ Upper airway inflammation is increased in COPD patients, increases further at exacerbation, and is associated with lower airway inflammatory changes.^{13,16}

Systemic inflammation increases at exacerbation and although the causes of this response in COPD are not clear, there is probably a spill-over of inflammatory markers from the lungs. By contrast with stable disease,¹⁶ exacerbations seem to be associated with a direct correlation between the degree of airway inflammation and the size of the systemic acute-phase response.¹³ Systemic inflammation increases when the exacerbation is associated with bacterial and viral infection.¹⁷ Several inflammatory markers increase at exacerbation, such as plasma fibrinogen and CRP, that have been linked to increased cardiovascular risk. Respiratory infections have been associated with increased cardiac events¹⁸ and thus a COPD exacerbation, especially if triggered by an infection, might also be associated with increased cardiac morbidity.

The airway inflammatory responses during COPD exacerbations cause airway oedema, bronchospasm, and increased sputum production, leading to worsening airflow limitation and development of dynamic hyperinflation.¹⁹ Such hyperinflation is the main cause of dyspnoea, the most common symptom of an exacerbation, and has other effects including modulating gas exchange, mechanical, and cardiovascular effects.¹⁹ Generally the more severe the underlying disease, the greater the degree of physiological change at exacerbation leading to worsening of airflow limitation, and thus the more likely the patient is to develop respiratory failure.

Changes in airflow limitation result in changes in peak expiratory flow rate, but available data suggest that changes in peak flow are too small to be useful in

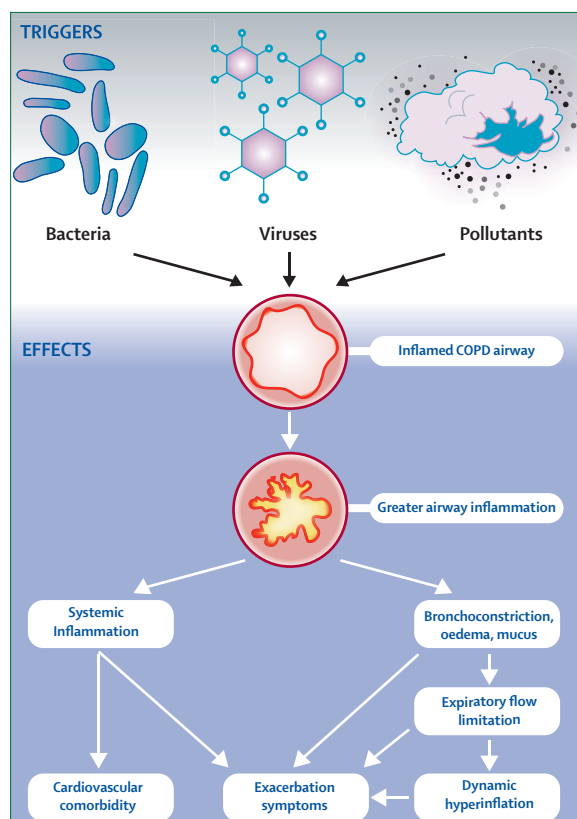


Figure 1: Triggers of COPD exacerbations and associated pathophysiological changes leading to increased exacerbation symptoms

assessing individual patients.³ This limitation might be because peak expiratory flow is mainly an assessment of large airway obstruction, although in COPD, most of the airflow limitation occurs in the small airways. Changes in exhaled nitric oxide also occur and are greater in the presence of viral infections, but are not suitable for monitoring of current exacerbations.²⁰ Novel physiological methods to monitor exacerbations are being developed, and some data now suggest that inspiratory capacity measurements²¹ or within-breath forced oscillation measurements²² might be more useful to assess COPD exacerbations and indicate the degree of physiological impairment.

Causes of COPD exacerbations

COPD exacerbations are heterogeneous events that are now thought to be caused by complex interactions between the host, respiratory viruses, airway bacteria, and environmental pollution, leading to an increase in the inflammatory burden (panel).²³

Panel: Most common bacterial and viral pathogens isolated from patients with COPD exacerbations

Bacteria

Haemophilus influenzae
Moraxella catarrhalis
Streptococcus pneumoniae
Pseudomonas aeruginosa

Viruses

Rhinovirus
 Coronavirus
 Influenza
 Parainfluenza
 Adenovirus
 Respiratory syncytial virus

Viral infections

COPD exacerbations are frequently triggered by upper respiratory tract infections, which are more common in the winter months, when respiratory viral infections are prevalent in the community. Lung function also shows small but significant falls with reduction in outdoor temperature.²⁴ Exacerbations triggered by respiratory viral infections are more severe and are associated with longer recovery times than those triggered by other factors.^{25,26} Molecular diagnostic techniques have now enabled detection of respiratory viruses at exacerbation, which have been isolated in around half of exacerbations,^{27,28} although this finding might be an underestimate due to difficulties in sampling at onset of symptoms. There have been few such studies in the developing world, but a study from Hong Kong detected viruses in only 22% of exacerbations.²⁹ However, this study differed from others in the choice of assay and in that samples were taken from the upper airway rather

than directly from the lower airway. A smaller study of 14 COPD patients admitted to hospital in Singapore reported that 64% of COPD exacerbations were associated with viruses although, like the Hong Kong study, most were associated with influenza virus,³⁰ which was possibly due to less frequent use of the influenza vaccine.

The most common viruses isolated are human rhinoviruses (the most frequent viruses associated with exacerbations), and other viruses including coronavirus, respiratory syncytial virus, influenza, parainfluenza, and adenovirus. Since the introduction of influenza immunisation for patients with chronic lung disease, the virus has become a less prominent cause of exacerbation, though it is still likely to be an important factor at times of epidemics. Although respiratory syncytial virus infection has been seen at exacerbation,³¹ whether it was the sole cause is not entirely clear, since this virus has been detected in the airways of COPD patients when they are stable and is associated with increased airway inflammation in stable COPD.³² Latent expression of adenoviral E1A protein in alveolar epithelial cells can amplify the effects of lung inflammation induced by cigarette smoke.³³ Thus, chronic viral infection might be linked to disease severity in COPD and further work is required on the relation between viruses detected in the stable state and at exacerbation.

With PCR techniques, rhinoviruses can be recovered from induced sputum more frequently than from nasal aspirates at exacerbation,²⁶ suggesting that wild-type rhinoviruses can infect the lower airway and contribute to inflammatory changes at exacerbation. Low-dose experimental rhinovirus infection in patients with mild COPD has been shown produce symptoms that are typical of an exacerbation, confirming that respiratory viruses can infect the lower airway.³⁴ Exacerbations triggered by respiratory viruses are also more severe, associated with longer recovery times,²⁷ and have more chance of hospital admission than exacerbations where respiratory viruses were not detected.³⁵

Bacterial infections

The precise role of bacteria at COPD exacerbations has been difficult to assess, since airway bacterial colonisation in the stable state is associated with the same organisms as those isolated at exacerbations, including *Haemophilus Influenzae*, *Streptococcus Pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.³⁶ In one study in patients with moderate to severe COPD, bacteria were seen in 48.2% of patients in the stable state, rising to 69.6% at exacerbation, with an associated rise in airway bacterial load.³⁷ Purulent sputum production has been regarded as a surrogate marker of bacterial infection, because COPD exacerbations associated with purulent sputum are more likely to produce positive bacterial cultures than those where the sputum

production was mucoid.^{38,39} Evidence for the involvement of bacteria has come from studies of antibiotic therapy, since exacerbations are often associated with increased sputum purulence and volume, and antibiotics have traditionally been used as first line therapy. A study investigating the benefit of antibiotics in more than 300 acute exacerbations showed a greater treatment success rate in patients treated with antibiotics, especially if their initial presentation was with the symptoms of increased dyspnoea, sputum volume, and purulence, than in patients who did not receive such treatment.⁴⁰ Patients with mild COPD obtained less benefit from antibiotic therapy than those with more severe COPD. The results of a meta-analysis have shown that antibiotic treatment offered a small but significant benefit in treatment failure and mortality.⁴¹

Substantial progress has been made on investigating the role of bacterial infection at exacerbation, with the development of molecular typing methods allowing the detection of changes in bacterial strains, rather than species. Sethi and colleagues⁴² have suggested that isolation of a new bacterial strain in COPD patients who were regularly sampled was associated with an increased risk of an exacerbation. However, this finding does not conclusively prove that bacteria are direct causes of exacerbations, because not all exacerbations were associated with strain change, and not all strain changes resulted in exacerbation. The strain-specific immune responses to colonising bacterial species⁴³ provide some further evidence that bacteria are not just innocent bystanders in the lower airways during exacerbations.

However, the situation with airway infection is further complicated, since in many COPD exacerbations both respiratory viruses and bacteria could be isolated. A greater systemic inflammatory response has been reported in those exacerbations associated with both *H influenzae* and rhinovirus isolation, and if the isolation of *H influenzae* was associated with new or worsening coryzal symptoms (a surrogate of viral infection), such infections were more severe as assessed by changes in symptoms and lung function at exacerbation onset.³⁷ This change has been confirmed in a further study which reported greater lung function impairment and longer hospitalisations in patients with exacerbations associated with viral and bacterial coinfection than in those without coinfection.⁴⁴ Thus bacterial coinfection with viruses might be of greater importance than bacterial infection alone at COPD exacerbation but consensus within the field has not yet emerged.

Atypical bacteria such as chlamydia, legionella, and mycoplasma have also been implicated at COPD exacerbation, although evidence on their role is conflicting, and these microorganisms might also interact with airway bacteria and viruses.⁴⁵⁻⁴⁸ A recent study using real-time PCR detection methods found no role for these three atypical bacteria at COPD exacerbation.⁴⁹

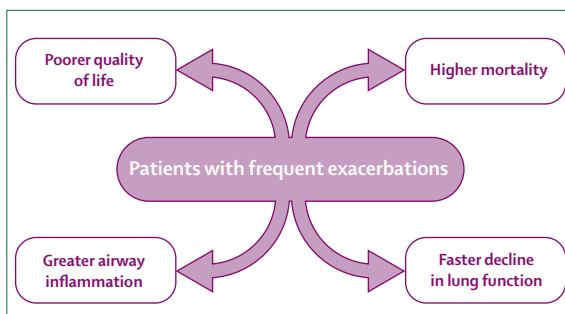


Figure 2: Effect of COPD exacerbations in the group with frequent exacerbations

Pollution

COPD patients can have increased exacerbations and hospital admissions with increasing environmental pollution.⁵⁰ In the APHEA study in six European cities, Anderson and colleagues⁵¹ reported a significant effect of air pollution levels on hospital admission for COPD, and similar results have also been seen in Taiwan⁵² and Brazil.⁵³ However, common pollutants, especially nitrogen oxides and particulates, can interact with viral infection in asthma⁵⁴ to precipitate exacerbation rather than acting alone, and a similar mechanism might occur in COPD. A study from Hong Kong has shown adverse effects of ambient concentrations of air pollutants (sulphur dioxide, nitrogen dioxides, ozone, and particulate matter with an diameter of less than 10 $\mu\text{g}/\text{m}^3$ [PM_{10}] and 2.5 $\mu\text{g}/\text{m}^3$ [$\text{PM}_{2.5}$]) on hospitalisation rates for COPD, especially during the winter season.⁵⁵ Thus measures to improve air quality can have an effect on exacerbation frequency.

Effects

In general, exacerbations become both more frequent and more severe as the severity of the underlying COPD increases.⁵⁶ However, there remain large differences in yearly exacerbation incidence rates between patients of similar COPD severity.¹ There is no agreed definition of a patient with frequent exacerbations, but in several studies they were defined as those with yearly exacerbation rates of greater than the median for the study, usually around three symptom-defined exacerbations per year or two per year if the exacerbation is defined by the requirement for therapy with courses of antibiotics, corticosteroids, or both.

Patients with a history of frequent exacerbations have worse quality of life than patients with a history of less frequent exacerbations, and have consistent exacerbation frequencies when studied from year to year.¹ These patients also have an increased risk of hospital admission⁵⁷ and greater mortality (figure 2).⁵⁸ A UK study suggested that COPD exacerbations do not affect lung function decline, though this study was done in men of working age with fairly good lung function.⁵⁹ However, results of subsequent studies suggest that exacerbations do play a part in disease progression in patients who are active

smokers⁶⁰ and those who have frequent exacerbations,⁶¹ although this effect is fairly small, at around 25% of the total decline in lung function. This observation might be due to the fact that not all exacerbations recover to baseline levels of symptoms and lung function.³ The results of one audit showed that around 30% of patients seen at hospital with an index exacerbation will be seen again and possibly readmitted with a recurrent exacerbation within 8 weeks.⁶² Patients with a history of frequent exacerbations also have increased airway inflammation,⁹ which could also contribute to the disease progression.⁶³ Why some patients have frequent exacerbations is not clear, although they possibly have increased susceptibility to respiratory viral infection.²⁵ Thus this group of COPD patients is important for targeting interventions that have the potential of reducing exacerbation frequency.

COPD exacerbations have functional consequences. Spruit and colleagues⁶⁴ have shown that peripheral muscle weakness worsens during exacerbation, potentially contributing to reduced functionality and therefore to deconditioning (loss of fitness). Patients who do not improve their walking distance within a month after exacerbation are more prone to be readmitted to hospital.⁶⁵ Donaldson and colleagues⁶⁶ have also shown that exacerbations are associated with a decline in outdoor activity for up to 5 weeks after the onset of symptoms. Patients who have frequent exacerbations had a faster decline in functional status, as measured by time spent outdoors, than patients with infrequent exacerbations (figure 3). Thus, patients with frequent exacerbations are more likely to become

housebound and are a subpopulation that needs targeting for pulmonary rehabilitation programmes.

COPD is associated with other comorbid conditions, and patients who are admitted to hospital are more likely to have associated comorbid conditions such as ischaemic heart disease, pneumonia, and diabetes than patients without a diagnosis of COPD.⁶⁷ Increasing blood glucose concentrations have been shown to be associated with adverse clinical outcomes in patients with COPD exacerbations.⁶⁸ Thus the disease burden of COPD exacerbations is likely to be much higher when these comorbidities are taken into account.⁶⁷

There have been several reports of associations between pulmonary embolism, deep venous thrombosis, and COPD exacerbation.⁶⁹⁻⁷¹ Exacerbations could trigger pulmonary embolic events, since acute infections are known to predispose to deep venous thrombosis and pulmonary embolism.⁷² There might also be diagnostic difficulties because both COPD exacerbations and pulmonary embolism might present solely with dyspnoea. However, a recent study has shown that pulmonary embolism is not a common feature in uncomplicated exacerbations,⁷³ but some patients with exacerbations can have prolonged recovery periods, complicated by respiratory failure and comorbidity, when the risk of pulmonary embolism could become greater.

Prevention

Pharmacological therapies

A few studies have shown that a decreased exacerbation rate is associated with improved quality of life.⁷⁴⁻⁷⁷ Thus lowering the exacerbation rate would be expected to decrease hospitalisations and have important health economic benefits. Several classes of drugs with potential for reducing exacerbations have been investigated, with variable evidence for their use: vaccines, bacterial extracts, inhaled steroids and long acting bronchodilators, phosphodiesterase inhibitors, and mucolytic agents.

Vaccines and immunostimulants

There are several studies of influenza and pneumococcal vaccinations, which are now routinely recommended for all patients with COPD of significant severity.⁷⁸⁻⁸¹ One study that reviewed the outcome of influenza vaccination in a cohort of elderly patients with chronic lung disease found that influenza vaccination is associated with significant health benefits with fewer outpatient visits, fewer hospitalisations, and reduced mortality.⁷⁸

A Cochrane database review of four studies in COPD saw no evidence of efficacy for injectable anti-pneumococcal vaccines;⁸² however, in a study of the 23 serotype pneumococcal polysaccharide vaccine in COPD patients, Alfageme and colleagues⁸³ showed that the vaccine was effective in the prevention of community acquired pneumonia, compared with placebo in patients younger than 65 years or those with severe airflow obstruction. However, no difference in mortality between

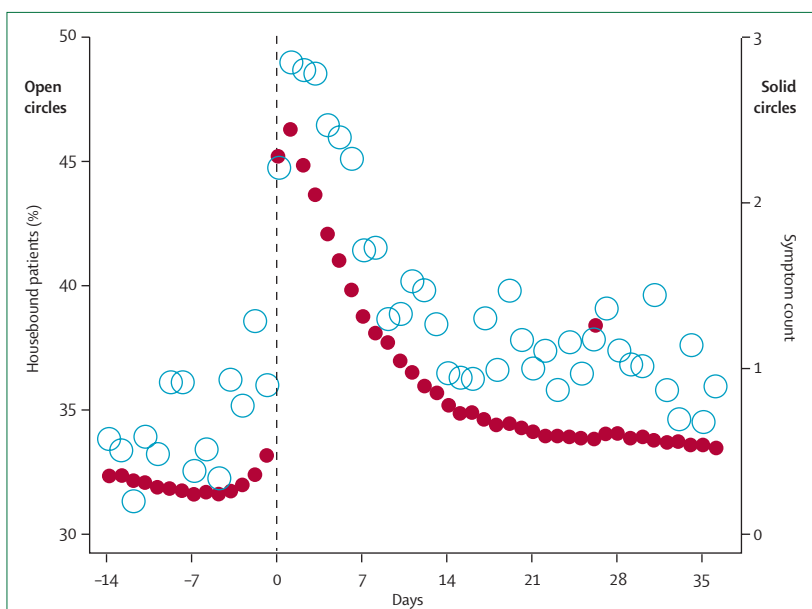


Figure 3: Time course of a COPD exacerbation over 51 days of time spent indoors (open circles) and symptom count (solid circles) for 136 patients who were monitored daily and had an exacerbation. Reproduced with permission from Fletcher and colleagues.⁵⁹

the groups was seen in the study. Larger well designed studies are needed to examine the effects of pneumococcal vaccine in patients older than 65 years with COPD.

Immunostimulatory agents have also been reported to reduce COPD exacerbation frequency. 10 years ago, a study of the immunostimulant OM-85, a detoxified oral immunoactive bacterial extract, reported a reduction in the severe complications of exacerbations and hospital admissions in COPD patients, with a follow-up study confirming the economic benefits of using this agent.⁸⁴ A recent randomised study has also found benefits but the patients had heterogeneous pathology.⁸⁵ A systematic review of 13 trials involving 2066 patients saw no consistent evidence of a benefit though the agent is currently in use in Europe.⁸⁶ Further study is needed to understand the mechanisms of action of this immunostimulant before its role in COPD can be defined.

Inhaled corticosteroids and long acting bronchodilators

The success of oral corticosteroids in the treatment of COPD exacerbations with reduction of hospital length of stay^{87,88} has prompted much interest in the use of inhaled steroids to reduce exacerbation frequency in COPD. One of the early studies, the ISOLDE (Inhaled Steroid in Obstructive Lung Disease in Europe) study, was a 3-year study, powered to detect a significant change in FEV₁ decline, was negative for the primary outcome but showed that exacerbation frequency can be reduced with inhaled steroids by about 25%.⁷⁴ Generally the effect of inhaled steroids was greater in patients with more impaired lung function, suggesting that this is the group to target with long-term inhaled steroid therapy.⁸⁹ In another study from the USA⁹⁰ (The Lung Health Study), the inhaled steroid (triamcinolone) group had significantly fewer visits to a physician due to respiratory illness, suggesting that triamcinolone also reduced the frequency of COPD exacerbations.

Inhaled long-acting beta 2 agonist (LABA) therapy has been shown to cause small reductions in exacerbation frequency, although most studies involved short periods of therapy at 12 weeks.⁹¹⁻⁹² Mahler and colleagues⁹¹ found that the time to the first exacerbation was longer with therapy with the long-acting beta agonist salmeterol, although the overall number of exacerbations during the study was small. The larger TORCH study⁹³ of 6112 COPD patients reported that salmeterol reduced exacerbation frequency compared with placebo over a 3-year period. In another study comparing salmeterol with the short-acting ipratropium and placebo, there was no difference in the effect in either treatment arm on exacerbation frequency.⁹⁴ Rossi and colleagues⁹⁵ compared two different dosages of the inhaled bronchodilator formoterol with placebo or theophylline and concluded that formoterol was more effective and better tolerated than therapeutically appropriate doses of oral slow-release theophylline in symptomatic COPD patients. Furthermore, two studies

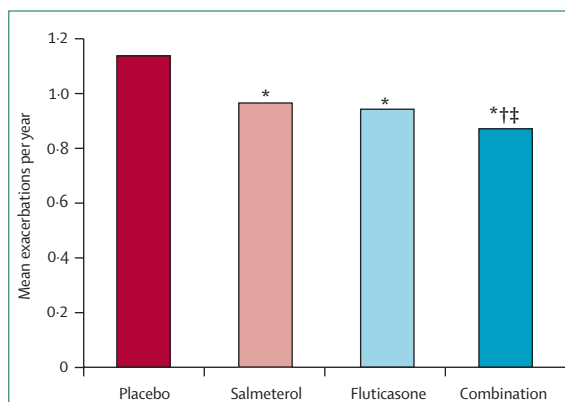


Figure 4: Effect of salmeterol (100 µg/day), fluticasone (1000 µg/day), both (combination), or placebo on the mean number of moderate and severe exacerbations of COPD per year, over 3 years

*p<0.001 vs placebo. †p=0.002 vs salmeterol. ‡p=0.024 vs fluticasone. Adapted with permission from Calverley and colleagues.⁹³

reported that formoterol had no effect on total exacerbation frequency relative to placebo, though these studies did find that the rates of steroid-treated exacerbations were decreased in the formoterol group.^{96,97}

The balance of evidence favours a positive role for LABAs in decreasing exacerbation frequency, which might be the result of the inhibitory effect of β_2 -adrenoceptor agonists on plasma exudation and neutrophil migration, or possibly indicating an additional reduction in the expression of adhesion molecules. However, the likely pathway of action could be through a synergistic action on airway inflammatory cells in those patients already receiving inhaled corticosteroid therapy.^{98,99} All of the major recent studies of combination therapy^{75,93,96,97} have reported that the combination of inhaled steroid and LABA is more effective than either individual drug alone in reducing exacerbation frequency. Thus, inhaled steroids are unlikely to be used as sole therapy for COPD patients in the future. The data from the TORCH study have confirmed the effectiveness of the inhaled steroid-LABA combination in reducing exacerbation frequency, and the study has reported that the combination reduces hospital admission rates in COPD patients.⁹³ However, most of these studies have been done in patients with more severe COPD with an FEV₁ at less than 60% predicted (figure 4). The effect of the inhaled steroid-LABA combination on reducing exacerbations in patients with milder COPD is not clear, especially in those patients who have an increased exacerbation frequency.

Long-acting anticholinergic agents such as tiotropium also reduce exacerbation frequency, and tiotropium has been shown to reduce exacerbations by 24%, compared with ipratropium when studied over a 1-year period.^{76,77} Niewoehner and colleagues¹⁰⁰ in a well designed study have confirmed the potential of tiotropium to reduce exacerbation frequency and also have shown a reduction in hospitalisation. Tiotropium does not have any known

anti-inflammatory effect,¹⁰¹ and its effect on reducing exacerbations is most likely due to the reduction of dynamic hyperinflation that is the major cause of dyspnoea in COPD (figure 5).¹⁹ The combination of tiotropium with inhaled LABA and inhaled steroids has been explored in the Optimal Study.¹⁰² This randomised trial compared tiotropium-fluticasone-salmeterol versus tiotropium-salmeterol versus tiotropium-placebo, and the triple combination reduced hospitalisation as a result of exacerbation, but not the total number of exacerbations. However, a trend was seen in the reduction of the number of exacerbations with the triple combination, which failed to reach significance possibly due to the small size of the study and the high dropout rate. Triple therapy could be more effective than dual therapy, but further studies of these combinations are required with adequately powered studies.

Phosphodiesterase inhibitors and other anti-inflammatory agents

The phosphodiesterase inhibitors now form a class of non-steroidal anti-inflammatory drugs that might be useful in the prevention of COPD exacerbations. Studies of the phosphodiesterase inhibitor theophylline have suggested that small reductions in exacerbation rates can be achieved with therapy,^{95,103} though further studies are needed on the effect of low dose theophylline on exacerbation frequency in COPD. Two new receptor-specific phosphodiesterase inhibitors have been studied in COPD: cilomilast and roflumilast, which are both phosphodiesterase-4 inhibitors. A trial of cilomilast in COPD patients showed reduction in exacerbations in the cilomilast group.¹⁰⁴ Two studies of roflumilast in COPD

have been recently reported: Rabe and colleagues¹⁰⁵ have reported a reduction in exacerbations after 24 weeks therapy with roflumilast, while Calverley and colleagues¹⁰⁶ studied roflumilast in patients with GOLD stage III and IV in a 1-year trial and showed no overall effect on exacerbation rate, although patients with severe disease (GOLD stage IV) had fewer during the study period. Prevention of COPD exacerbations using this class of drugs is evolving and newer agents and more effective phosphodiesterase inhibitors will be developed with fewer adverse events.

Tumour necrosis factor (TNF)- α has an important role as a key mediator in COPD and has been a target for study. However, a trial of the anti-TNF α antibody, infliximab, showed no benefit on any of the main trial outcomes and no effect of the therapy on exacerbation rate.¹⁰⁷

Mucolytic agents

The BRONCUS trial¹⁰⁸ using N-acetylcysteine has shown no overall benefit of mucolytics on reduction of COPD exacerbations, except a small effect was noted in those patients who were not taking inhaled steroids. A follow-up meta-analysis of 26 randomised trials involving mucolytic therapy in COPD revealed a 20% reduction in exacerbations, with a large number of patients treated with mucolytics having no exacerbations.¹⁰⁹ A study from North America has shown that small airways occluded with inflammatory exudate in COPD patients were associated with early death. This finding might stimulate further research into the role of mucolytic agents in COPD therapy.¹¹⁰ However, the consensus view is that the evidence for mucolytics preventing COPD exacerbations is not convincing; this view is supported by the GOLD guidelines, although mucolytics are still used quite widely in some parts of the world.

Long-term antibiotics

Long-term antibiotic treatment has been used by physicians in clinical practice previously in patients with very frequent exacerbations, either continuously or in rotation, though there is little evidence for their effectiveness. There are some problems with using long-term antibiotics as resistant bacteria could emerge and cause increased airway inflammation and exacerbations. However, in view of the presence of lower airway bacterial colonisation in these patients¹¹¹ and data from Patel and colleagues¹¹² that such colonisation is related to exacerbation frequency, there has been renewed interest in this type of intervention and some continuing studies will soon be reporting their findings.

Non-pharmacological therapies

Pulmonary rehabilitation and self management

Pulmonary rehabilitation is now an accepted intervention in COPD and although it has important benefits for patients, its effect on preventing exacerbations is less clear.¹¹³ In a randomised trial from South Wales, UK, Griffiths and colleagues¹¹⁴ reported that those patients

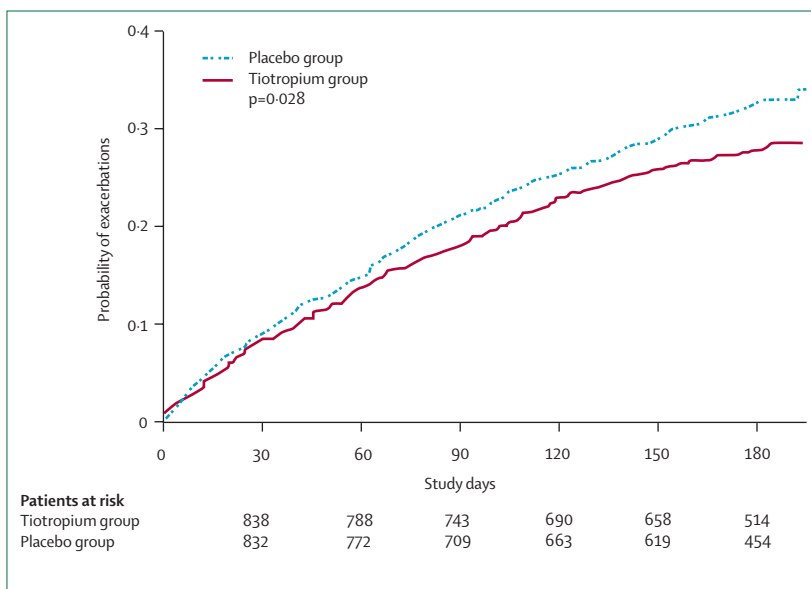


Figure 5: Kaplan-Meier estimates of the rate of first treatment failure at 6 months for the first COPD exacerbation treated with either tiotropium (continuous line) or placebo (dotted line). Reproduced with permission from Niewoehner and colleagues.¹⁰⁰

treated with a pulmonary rehabilitation programme including exercise training and education had shorter hospital stays than the control group and fewer primary-care home visits. This finding suggests that a course of pulmonary rehabilitation might reduce exacerbation severity rather than frequency by increasing the patient's knowledge of COPD and how to access health care or self-manage during an exacerbation. Pulmonary rehabilitation could thus reduce hospital stay but also encourage early presentation for exacerbation therapy, which reduces exacerbation length and thus the severity of the event.¹¹⁵

Garcia-Aymerich and colleagues¹¹⁶ have also shown in a 1-year study that patients with high levels of usual physical activity were at reduced risk of readmission to hospital. An intensive disease-specific self-management programme done in Canada has been shown to reduce hospital admission rate,¹¹⁷ though a systematic review of nurse-led interventions failed to show a consistent effect on hospitalisation.¹¹⁸ Casas and colleagues¹¹⁹ have extended this approach by using a similar integrated care plan in two different environments (Barcelona, Spain, and Leuven, Belgium), with similar effects on decreased readmission rates for COPD exacerbation. Patients with COPD are elderly, often with a degree of cognitive impairment and might have difficulty with self-management at exacerbations. How optimum community support should be provided for patients who are at particular risk of hospital admission is not clear.

Home oxygen therapy and ventilatory support

Long-term oxygen therapy has several benefits in COPD patients who are chronically hypoxaemic, including reducing mortality, anxiety, and depression.^{120–122} In an epidemiological study, Garcia-Aymerich and colleagues⁵² noted that patients with hypoxaemia but not treated with long-term oxygen therapy had a higher risk of hospital admission. Another observational study from the Danish Oxygen Register¹²³ has also suggested that long-term oxygen therapy reduces hospital admission rate. Controlled studies on home oxygen therapy and COPD exacerbations are difficult, since withholding therapy in a control hypoxaemic group would not be ethically justifiable.

COPD patients with chronic respiratory failure are particularly susceptible to exacerbations. After the early experience of domiciliary long-term non-invasive ventilation in patients with chest wall and neuromuscular disease, non-invasive ventilation has also been assessed in patients with hypercapnic COPD. Early observations on the effect of non-invasive ventilation in COPD showed a significant beneficial effect on health status, although data for exacerbations were not recorded.¹²⁴ Because health status is such an important determinant of exacerbation frequency,¹ improvement in health status could be due to a reduction of exacerbation frequency. In a controlled study lasting a year, no effect was seen of non-invasive ventilation

on exacerbations but there was a reduction in hospital admission at the 3-month follow-up point.¹²⁵ Thus, larger controlled studies are now required to assess the effect of non-invasive ventilation on exacerbation in hypercapnic COPD patients, particularly at risk of hospital admission.

Conclusion

COPD exacerbations are often triggered by airway infection and are an important cause of morbidity, impairment of health status, and mortality. Although many pharmacological and non-pharmacological interventions prevent exacerbations, the degree of reduction in exacerbation frequency is still restricted and we now need new interventions to be urgently developed and studied in well designed and adequately powered randomised trials. Combinations of these interventions will probably be most effective and this approach will need future development and assessment. One of the main objectives of therapy for COPD is to reduce the morbidity associated with exacerbations and thus improve the quality of life of patients with this disabling condition.

Conflict of interest statement

JAW has received research grant funding from AstraZeneca, GlaxoSmithKline, and Boehringer Ingelheim, who all manufacture pharmacological therapies for prevention of COPD exacerbations. She has also received honoraria for lectures or attended advisory boards from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Bayer Healthcare, and Novartis Pharma. TARS has received honoraria for attendance of research meetings from AstraZeneca, GlaxoSmithKline, and Boehringer Ingelheim.

Acknowledgments

We are very grateful to John Hurst for assistance in the preparation of this Review.

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