CLINICAL REVIEW

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Preventing exacerbations in chronic obstructive pulmonary disease

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Drug and Therapeutics Bulletin
Editorial Office, London
WC1H 9JR, UK
dtb@bmjgroup.com

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Acute exacerbations of chronic obstructive pulmonary disease (COPD) are associated with significant morbidity and mortality. Patients with frequent exacerbations have high levels of anxiety and depression, significantly impaired health status and faster disease progression.[1 2] Exacerbations are also the most common cause of emergency respiratory admissions to UK hospitals[3] and are costly to health services.[2] Here we assess whether and how drug and non-drug interventions can help in preventing exacerbations.

Background

COPD is defined by the Global Initiative for Chronic Lung Disease (GOLD) as "a preventable and treatable disease . . . characterised by airflow limitation that is not fully reversible. It is a progressive systemic disease that results in debility over time."[4] Cigarette smoking is the most important causal factor for the development of the disease and smoking cessation is a crucial intervention that can both reduce the rate of decline in lung function and improve survival.[5 6] The severity of COPD is defined in terms of the reduction in forced expiratory volume in 1 second (FEV_1) relative to that predicted for age, height, and sex. This measure is considered the most significant (but not only) predictor of prognosis in the disease.[7] Mild COPD is defined as an FEV_1 of 50-79% of predicted, moderate as 30-49%, and severe as below 30%.[8]

There is no standard definition for an exacerbation. GOLD describes it as "an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum production that is beyond normal day-to-day variation, is acute in onset, and may warrant a change in regular medication."[4] COPD exacerbations develop because of complex interactions between respiratory viruses, airway bacteria, ambient air pollution, and host factors, which then result in an inflammatory cascade. Consequences of the inflammatory processes in the airway include increased sputum production, bronchospasm, and airway oedema and these in turn result in worsening airflow limitation and breathlessness.[9] The frequency of episodes increases with disease severity.[2] On average, people with moderate to severe COPD have around three exacerbations per year compared with an average of around two for patients with mild disease.[2]

In trials of interventions in COPD, exacerbations are sometimes defined according to severity. For example, a moderate exacerbation might be defined as a worsening of respiratory symptoms requiring treatment with an antibacterial and/or oral corticosteroid, while a severe episode is often described as one requiring hospitalisation.

Preventive measures

Single drugs

Long-acting antimuscarinic drugs

A Cochrane systematic review of nine randomised controlled trials (involving a total of 6584 patients with moderately severe COPD) found that, compared with placebo or ipratropium (a shorter-acting antimuscarinic), tiotropium reduced the likelihood of exacerbations (defined as a complex of respiratory symptoms lasting at least three days and usually associated with a therapeutic intervention; odds ratio 0.74, 95% CI 0.66 to 0.83) and related hospitalisations (0.64, 95% CI 0.51 to 0.82).[10] In a more recently published four-year placebo-controlled trial in 5993 patients with moderate to severe COPD (the "Understanding Potential Long-term Impacts on Function with Tiotropium" [UPLIFT] study), tiotropium did not reduce the rate of decline in FEV_1 (the primary outcome measure).[11] However, it did increase the time to the next exacerbation (16.7 months, 95% CI 14.9 to 17.9 *v* 12.5 months, 11.5 to 13.8) and reduced the mean number of exacerbations by 14% (P<0.001; all secondary outcome measures). Exacerbations were defined as an increase in, or the new onset of, more than one respiratory symptom lasting three days or more and requiring treatment with an antibacterial or systemic corticosteroid.

Antimuscarinics can cause unwanted effects such as visual disorders, dry mouth, constipation, micturition difficulties and arrhythmias. A meta-analysis of 17 randomised controlled trials (involving a total of 14 783 patients) assessing tiotropium or ipratropium found that such treatment slightly increased the likelihood of cardiovascular death, myocardial infarction, or stroke in patients with COPD (1.9% *v* 1.2% for control, relative risk 1.60, 95% CI 1.22 to 2.10).[12] However, the UPLIFT study (which did not exclude patients with cardiac disease) showed a lower likelihood of unwanted cardiac events with tiotro-

pium compared with placebo at four years (relative risk of cardiac events 0.84, 95% CI 0.73 to 0.98).[11]

Long-acting beta2 agonists (LABAs)

A Cochrane systematic review of double-blind randomised controlled trials evaluating LABAs in patients who had COPD with poor reversibility to short-acting bronchodilators (and an FEV_1 of 75% or less of predicted) found that the chances of experiencing an exacerbation (undefined in the report) were reduced with salmeterol 50 µg compared with placebo (odds ratio 0.72, 95% CI 0.57 to 0.90; data from six trials involving a total of 1741 patients).[13] The authors calculated a number needed to treat (NNT) of 24 (95% CI 14 to 98) to prevent one exacerbation in the short term. This review found insufficient evidence to draw a conclusion about other LABAs or other doses of salmeterol. Subsequently, a large double-blind randomised controlled trial (known as "Towards a Revolution in COPD Health" [TORCH]) evaluated salmeterol in poorly reversible COPD. The trial included 6112 patients with COPD and an FEV_1 below 60% of predicted.[14] There was no difference in the time to death with salmeterol plus fluticasone compared with each of the components alone (the primary outcome measure). However, compared with placebo, salmeterol 50 µg twice daily reduced the annual rate of moderate or severe exacerbations (a secondary outcome measure, defined as a symptomatic deterioration requiring antibacterial or oral corticosteroid therapy or hospitalisation or a combination of these) by 15% (95% CI 7% to 22%, P<0.001). According to the authors, this corresponded to a NNT of 4 to prevent one exacerbation in one year.

LABAs can cause tremor, nervous tension, headache, muscle cramps, and palpitations. There is a theoretical risk of LABA therapy causing tachyarrhythmias in COPD due to beta-adrenergic stimulation. However, a meta-analysis of individual patient data from seven trials (involving a total of 1410 patients who had received salmeterol 50 µg twice daily for up to one year) found no significant increase in the risk of adverse cardiovascular events.[15]

Inhaled corticosteroids

A Cochrane systematic review included 47 randomised placebo-controlled trials (involving a total of 13 139 patients) of inhaled corticosteroids in the treatment of patients with COPD (FEV_1 36–87% of predicted).[16] Long-term (more than six months) use of inhaled corticosteroids slightly reduced the rate of exacerbations (undefined in the report) (weighted mean difference −0.26 exacerbations per patient per year, P<0.0001).

A more recent meta-analysis of data from 11 published randomised placebo-controlled trials of inhaled corticosteroids (involving a total of 8164 patients with COPD and each lasting at least one year) also showed a moderate reduction in exacerbations (undefined) (0.82, 95% CI 0.73 to 0.92), with a subgroup analysis suggesting that such benefit occurred only in patients with an FEV_1 below 50% of predicted.[17]

Associated unwanted effects of inhaled corticosteroids include oropharyngeal candidiasis and hoarseness. The drugs also increase the likelihood of pneumonia in patients with COPD (relative risk 1.60, 95% CI 1.33 to 1.92).[18] Such evidence led the Medicines and Healthcare products Regulatory Agency (MHRA) to advise that doctors should remain vigilant for pneumonia and other infections of the lower respiratory tract in patients with COPD treated with inhaled products that contain corticosteroids.[19] Inhaled corticosteroid-only preparations are not licensed for use in COPD. The MHRA also advises that they should not be used alone in COPD and should be introduced only when COPD progresses to severe disease.[20]

Drug combinations

LABA plus inhaled corticosteroid

A Cochrane systematic review identified seven double-blind randomised controlled trials (involving a total of 5708 patients with moderate to severe COPD).[21] Adding a LABA to an inhaled corticosteroid was found to reduce the rate of exacerbations relative to control by only 9% (95% CI 3% to 15%). Also, one of the trials (TORCH) showed a reduction in hospital admissions (a secondary outcome measure) with combination therapy compared with placebo, but not compared with either salmeterol or fluticasone alone.[14]

A systematic review of randomised controlled trials assessing the combination of a LABA plus an inhaled corticosteroid (involving 18 studies in a total of 12 446 patients) found such a combination to be no better than a LABA alone at preventing severe exacerbations (that is, requiring hospitalisation or withdrawal), but marginally better at preventing moderate exacerbations (needing antibacterials or systemic corticosteroids) (exacerbation rate 17.5% *v* 20.1% of patients, P=0.008; NNT 31, 95% CI 20 to 93).[22]

A Cochrane systematic review of randomised controlled trials comparing the combination of an inhaled corticosteroid plus a LABA with inhaled tiotropium found three trials (involving a total of 1507 patients).[23] Owing partly to differences in trial durations, no meta-analysis was performed. In the largest trial ("Investigating New Standards for Prophylaxis in Reducing Exacerbations" [INSPIRE], which included 1323 patients with a mean FEV_1 of 39%), the rate of exacerbations (the primary outcome measure, defined as those requiring treatment with oral corticosteroids and/or antibacterials or requiring hospitalisation) were similar with the two treatments.[24]

Antimuscarinic plus corticosteroid plus LABA

A recently published Canadian Health Technology Assessment evaluated the efficacy of triple therapy for moderate to severe COPD through a systematic review of the evidence.[25] It found four randomised trials evaluating triple therapy (either tiotropium together with fluticasone plus salmeterol, or tiotropium with budesonide plus formoterol). The trials were found to have heterogeneous populations and varying methodological problems. Overall, the authors concluded there was insufficient evidence to show whether triple therapy was superior to a combination of a corticosteroid plus a bronchodilator or combination of a LABA plus an antimuscarinic.

Other drugs and vaccinations

A meta-analysis of data from 28 randomised controlled trials (involving a total of 7042 patients with COPD) found

that mucolytic therapy reduced the mean number of exacerbations per patient by 0.04 per month; some of the evidence suggests that this benefit may only be seen in patients who are not already using an inhaled corticosteroid.[26]

There is insufficient clinical trial evidence to support the use of prophylactic antibacterial therapy to prevent exacerbations.

A Cochrane systematic review identified two randomised controlled trials (involving a total of 187 patients with COPD) assessing the effect of influenza vaccination on exacerbations.[27] Vaccination reduced the exacerbation rate relative to placebo (weighted mean difference in number of exacerbations −0.37, 95% CI −0.64 to −0.11, P=0.006). Another Cochrane review, which included four randomised controlled trials (involving a total of 937 patients with COPD), found no overall evidence of benefit for anti-pneumococcal vaccines on morbidity or mortality.[28]

Oxygen therapy and non-invasive ventilation

Long term oxygen therapy (usually given over a minimum of 15 hours a day) increases survival duration in patients who are severely hypoxaemic due to COPD (odds ratio for five-year survival versus no oxygen therapy 0.42, 95% CI 0.18 to 0.98).[29] However, there is no proven effect of long term oxygen therapy in preventing COPD exacerbations, although hypoxaemic patients who do not receive long term oxygen therapy are more likely to be admitted to hospital.[30] Similarly, there is no robust evidence to suggest that domiciliary non-invasive positive pressure ventilation for patients with COPD reduces exacerbation frequency.

Other interventions

Pulmonary rehabilitation

Pulmonary rehabilitation programmes, which comprise graded exercise training, education and psychological/behavioural interventions (including smoking reduction strategies), have several benefits in COPD, including reduction of symptoms and improvement of quality of life.[31] However, such programmes are not universally available to UK patients. A Cochrane systematic review of randomised controlled trials comparing pulmonary rehabilitation of any duration after exacerbation of COPD with conventional care identified six trials (involving a total of 219 patients).[32] The authors concluded that the evidence (small studies of moderate methodological quality) suggested that pulmonary rehabilitation was a highly effective and safe intervention for reducing hospital admissions (NNT 3, 95% CI 2 to 4) and mortality (NNT 6, 95% CI 5 to 30) and improving health related quality of life. In a subsequently published trial involving 60 patients with COPD who had been admitted to hospital because of an exacerbation, fewer of those randomised to outpatient acute pulmonary rehabilitation (within a week of hospital discharge) were readmitted to receive treatment for an exacerbation within the following 3 months (7% *v* 33% of those given usual care, P=0.02).[33]

Patient education

Several controlled trials have examined the effects of education programmes aimed to teach self-medication, guide health behaviour change, and provide emotional support for patients with COPD. Data from these studies suggest that such programmes reduce the likelihood of hospital admission but there is insufficient evidence to formulate clear recommendations about the form and content of self-management education programmes.[34-36]

Disease management programmes

A systematic review of nine randomised controlled trials (total number of patients not included in the report) failed to find any consistent benefits of nurse led disease management for patients with stable COPD.[37] In a subsequently published trial, 155 patients who had been admitted to hospital for a COPD exacerbation were randomised to either integrated care (consisting of a comprehensive assessment, self-management support, an individual care plan and enhanced accessibility to healthcare professionals through a call centre and video conferencing) or usual care.[38] Patients receiving integrated care had fewer hospital admissions during one year (1.5 *v* 2.1, P=0.033) and more avoided re-admissions (49% *v* 31%, P=0.03).

In a randomised controlled study, 122 patients with moderate to severe COPD admitted to hospital with an acute exacerbation received a nurse led care package incorporating initial pulmonary rehabilitation and self-management education, a written COPD action plan, monthly telephone calls and three-monthly home visits over 24 months of follow-up.[39] Compared to patients receiving usual care, those receiving the nurse led intervention were more likely to start self-medication with antibacterials or corticosteroids during exacerbations and required fewer unscheduled primary care consultations than those receiving usual care. There were also significantly fewer COPD related deaths in the intervention group (one *v* eight), although rates of hospitalisation were similar. This was the first study to demonstrate a mortality benefit resulting from an integrated care intervention in COPD. As with other studies, it is unclear which element(s) of the programme were the most important, but it is likely that prompt self-medication mitigated the severity of exacerbations and accounted for the fewer COPD related deaths.

NICE advice

The updated National Institute for Health and Clinical Excellence (NICE) guideline on managing COPD[8] makes the following recommendations.

- All patients with COPD still smoking, regardless of age, should be encouraged to stop, and offered help to do so, at every opportunity
- People with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required should be offered (if FEV_1 is 50% or more of predicted) either a long-acting beta-2 agonist (LABA) or long-acting antimuscarinic as maintenance therapy; or (if FEV_1 is below 50% of predicted) either a LABA plus an inhaled corticosteroid in a combination inhaler or a LABA plus a long-acting antimuscarinic;
- People with COPD who remain breathless or have exacerbations despite taking a LABA plus inhaled corticosteroid, should be offered a long-acting antimuscarinic in addition, irrespective of their FEV_1

- Pulmonary rehabilitation should be available to all appropriate patients with COPD, including those who have had a recent hospitalisation for an acute exacerbation.

Conclusion

Exacerbations of chronic obstructive pulmonary disease (COPD) cause significant morbidity and mortality, and have a huge impact on healthcare services in terms of activity and costs.

The most effective intervention for patients with COPD is stopping smoking, which can reduce the decline in lung function and improve survival rate. Drugs can help to reduce the frequency of exacerbations, although their overall effect is modest. In general, the stepwise approach to using medicines recommended in the updated guideline from NICE on COPD seems reasonable on current evidence. However, there is insufficient evidence to show that any further benefit is gained from triple therapy, one of NICE's recommendations (a long-acting beta agonist plus a long-acting antimuscarinic plus an inhaled corticosteroid). Decisions about drug treatment should take into consideration the frequency of exacerbations in the particular patient and the possibility of unwanted effects of treatment (including a risk of pneumonia with inhaled corticosteroids). Pulmonary rehabilitation appears highly effective in reducing hospital admissions and mortality and should be available to all patients with moderate to severe COPD, which is currently not the case in all areas of the UK.

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