Current Drug Treatment, Chronic and Acute

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KEYWORDS

• Bronchodilators • Inhaled corticosteroids • COPD and exacerbations

KEY POINTS

- Increasing the dose or number of bronchodilators together with a short course of oral corticosteroids reduces the severity of chronic obstructive pulmonary disease (COPD) exacerbation.
- Supplementary methylxanthine treatment adds nothing to exacerbation management except risk for patients.
- Long-acting antimuscarinics should be given once daily as a first-line treatment of COPD, although new once daily long-acting beta-agonists may prove equally effective.
- Adding inhaled corticosteroids to a long-acting beta-agonist prevents exacerbations in severe disease and seems to be effective in some once daily combination treatments.
- Pneumonia is seen with all treatments containing fluticasone-related drugs, but appears to be less evident with budesonide. Once-daily tiotropium seems safe when given as a dry power, but there are concerns about its use when inhaled from a soft mist system.

INTRODUCTION

The appropriate management of chronic obstructive pulmonary disease (COPD) involves more than taking prescription medicines. The key components have been set out in detail in many treatment guidelines, both national and international.[1–3] They include the avoidance of identified risk factors, especially tobacco smoking, and the optimization of daily physical activity, topics covered elsewhere in this volume.

For a few patients with severe disease, noninvasive ventilation can be a lifesaving treatment in the acute episode,[4] although not all patients benefit.[5] There is a role for long-term domiciliary oxygen treatment, which is widely used in the United States and can reduce mortality and even improve exercise performance.[6,7] However, the effectiveness of ambulatory oxygen has been challenged[8]; the use of oxygen to relieve breathlessness after exercise having been shown to be ineffective when compared with room air.[9] These considerations do not seem to have dented the popularity of this treatment, with patients and their physicians indicating the limits of evidence-based clinical practice. However for many patients with COPD, a key part of their care remains the drugs their doctors prescribe and in recent years both the choice of treatment and the evidence for its effectiveness has improved.

This article reviews the key components of the pharmacologic treatment of COPD, both acute and chronic, with an emphasis on those recent studies, which are likely to change practice in the next few years.

DRUG TREATMENT IN ACUTE EXACERBATIONS

Acute exacerbations of COPD drive the morbidity and cost associated with this disease and the markers of an increased risk of dying, especially after the patients have been hospitalized.[10] In patients with more severe COPD and those attending

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the emergency department, breathlessness is the dominant symptom; there are good data showing that this results from a mixture of static and dynamic hyperinflation and consequent restriction on tidal volume.[11,12] Worsening lung mechanics leads to the deterioration in ventilation-perfusion matching and an increase in dead space, producing hypoxemia with or without hyperpnoea. Hence, the management of the acute episode focuses on reversing or limiting these physiologic abnormalities. The distress and ill health of the hospitalized patient makes the conduct of randomized control trials difficult or risky and so we have almost no clinical trial data to support the use of oxygen to either reduce breathlessness or improve outcomes in COPD. We do know that oxygen-induced hypercapnia can be dangerous,[13] but for physicians to take the opposite view and not prescribe oxygen to critically ill patients would seem to be perverse.

Similar considerations apply to drug treatment, but here there is at least some direct physiologic evidence of benefit resulting from studies conducted over the last decade.

Inhaled bronchodilators are the key components of management. For good practical reasons related to the speed of onset of action and the risk of adverse effects, the inhaled route is preferred for both acute and chronic treatment, and the main drug classes are beta-agonists (BA) and antimuscarinic (MA), which are also known as anticholinergic drugs.

There is little evidence for a dose-response effect with either BA or MA in COPD, although some data for unstable disease suggest a potential benefit of high doses of ipratropium.[14] However, many physicians prescribe nebulized BA, usually salbutamol in doses of 2.5 to 5.0 mg or MA such as ipratropium 250 to 500 mcg alone, or in combination with each other, to reduce symptoms in hospitalized patients with exacerbations. Adding ipratropium to salbutamol did not change the rate of recovery of forced expiratory volume in the first second of expiration (FEV_1) in one small UK study,[15] which did not examine other markers of lung mechanics or symptoms. However, there is evidence that even at high doses of BA, adding another drug of a different class can produce physiologically important reductions in end expiratory lung volumes,[16] changes similar to those observed after combination bronchodilators in acutely ill patients with COPD.[12]

There are no good studies to indicate when this high-dose treatment should be discontinued; this decision is usually an empiric one, made by the attending physician. Patients often think high-dose nebulized drugs during an exacerbation should be continued during their chronic care; but the evidence for this is lacking and is confused by the facial cooling effects of the nebulized mist, which can decrease acute breathlessness.[17] Other considerations related to the reimbursement of nebulized drugs may also be potent reasons why these agents are considered. The most common adverse events are tachycardia and palpitations with high doses of BA while hypokalemia is not a problem in normal clinical practice. MA drugs are well tolerated, although there is a risk of inducing glaucoma if mist from a facial mask enters the eyes of susceptible patients.

Intravenous aminophylline was used as the primary treatment of hospitalized acute COPD exacerbations long before safer inhaled bronchodilators were available, and it is still often added to the treatment of patients with severe breathlessness caused by acute COPD. However, xanthenes are weak bronchodilators and only effective at near-toxic doses.[18] Data from Rice and colleagues[19] suggested that it was ineffective when used acutely. This finding was confirmed in a large randomized controlled trial that showed that aminophylline reduced arterial carbon dioxide slightly but made no difference to the rate of recover, symptoms, lung function, or to the time spent in hospital.[20] Given the toxicity of this therapy, it should not be used in hospitalized patients with COPD. A trial of the acute effects of the phosphodiesterase IV inhibitor roflumilast in acute exacerbations of COPD is currently being conducted; but until these data are available, this drug is not recommended for acute use.

Acute exacerbations are characterized by an increase in inflammation,[21] triggered by infections and/or environmental insults, which produce the acute deterioration in lung mechanics noted earlier. Two therapies have been applied to reduce inflammation and shorten the acute episode.

High-dose enteral or parenteral corticosteroids have been tested in a limited number of studies. With one exception, patients were recruited from the emergency department (ED) or had been hospitalized; in these settings, corticosteroid treatment delayed the time to relapse (including relapses occurring within 30 days of an ED visit), reduced the number of treatment failures related to the primary event, and accelerated the rate at which lung function improved (**Fig. 1**), thereby reducing the hospital stay.[22–24] Lower doses of oral prednisolone (approximately 30 mg/d) were as effective as large doses of methylprednisolone. Although the large trials gave treatment for 10 to 14 days, most of the benefit accrues in the first week; one small study has shown that 10 days of treatment is better than 3 days.[25]

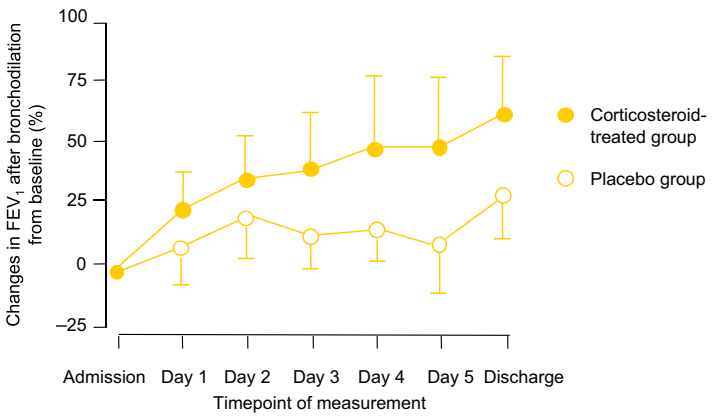

Fig. 1. Rate of recovery of FEV_1 in hospitalized patients with COPD treated with oral corticosteroids (*closed circles*) or placebo (*open circles*). (*Adapted from* Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet 1999;354(9177):456–60; with permission.)

Data on ambulatory output patient events are very limited, but arterial oxygen tension improved more rapidly in those patients given prednisolone.[26] This treatment is widely prescribed for exacerbations of COPD in the community, particularly in Western Europe. Hyperglycemia is somewhat more common in corticosteroid-treated COPD exacerbations, but the degree is as likely to be a marker of the severity of the insult as the use of short courses of corticosteroids per see. The major risk of oral corticosteroid treatment is that it is sustained and converted into chronic oral therapy, which is hazardous to patients, producing a host of undesirable complications, including marked muscle weakness and immobility.[27]

The alternative and potentially complementary method of modifying exacerbation-related inflammation is the prescription of antibiotics with courses normally lasting 5 to 7 days. The choice of treatment is best determined by local sensitivity patterns to *Haemophilus influenzae* and *Streptococcus pneumoniae*, the dominant causes of these episodes.[28] In practice, coverage of other pathogens likely to cause pneumonia is also sensible, given the difficulties of distinguishing pneumonias from COPD exacerbations.[29] Only a few studies have compared antibiotics with placebo in COPD exacerbations, most trials having been comparator studies of microbiological cure rates. However, one community-based randomized controlled trial in Dutch patients all treated with oral prednisolone is instructive. This study showed that patients who had a history of cough, sputum production, and breathlessness recovered more rapidly when randomized to antibiotic treatment than with placebo,[30] a finding that confirmed the observations by Anthonisen and colleagues[31] some 25 years earlier.[32] There is database evidence that patients in intensive care unit (ICU) with COPD exacerbations who receive antibiotics have better outcomes,[32] and so the threshold for prescription in hospitalized patients should probably be lower than in the community at large.

Table 1 summarizes the current approaches to drug treatment and the management of acute exacerbations of COPD.

DRUG TREATMENT IN CHRONIC MANAGEMENT

Management approaches to stable COPD still rely heavily on drug treatment, but the way in which patients are evaluated and in which treatments are used have recently changed. **Box 1** summarizes the principal goals of medical treatment, whereas **Figs. 2** and **3** illustrate the preferred management approaches advocated by the Global Initiative in Obstructive Lung Disease (GOLD) and by the evidence-based UK National Institute of Health and Clinical Excellence's (NICE) guidelines.[33,34] Drug therapy is based on the use of long-acting inhaled bronchodilators, whereas shorter-acting inhaled treatments for rapid onset, usually salbutamol, are reserved for rescue treatment, when symptoms increase unexpectedly (eg, after exercise or during exacerbations). The efficacy of short-acting beta-agonists (SABA) treatment in reducing symptoms like this is not well established. Bronchodilators and phosphodiesterase 4 (PDE4) antagonists are considered in detail elsewhere; but before examining how these treatments are deployed, it is worth considering the current evidence for the use of inhaled corticosteroids (ICS) alone or in combination with other drugs.

ICS AND COPD

ICS have revolutionized the management of bronchial asthma for the first-line treatment of patients with persistent symptoms.[35] They decrease eosinophilic inflammation dramatically but have little, if

Table 1
Pharmacologic management of COPD exacerbations

Drug	Setting	Route	Dose	Comment
Bronchodilator (SABA/SAMA)	OP	Inhaled	2 puffs 3–4/h	Frequency of use should decrease over 48 h or seek help
	IP	Inhaled	Salbutamol 2.5 or 5 mg and Ipratropium 500 mcg 6/h	Nebulized till symptoms resolve
Corticosteroids	OP and IP	Oral	Prednisolone 30 mg	Give for 7–10 d and stop
Antibiotics	OP	Oral	Drug with appropriate sensitivity	Give for 5–7 d in patients with worse cough and sputum and dyspnea
	IP	Oral	Drug with appropriate sensitivity	Give for 5–7 d if one or more of the aforementioned; parenteral route seldom needed

To be used with appropriate supportive care and subsequent preventive management.
Abbreviations: IP, hospitalized in-patient or ED attendee; OP, outpatient; SABA, short-acting beta-agonist; SAMA, short-acting anti-muscarinic agents.

any, effect on inflammation and COPD, at least over 6 weeks to 3 months of treatment,[36,37] although some effects, in some patients, have been reported over longer periods.[38] Given the observed benefits of high-dose corticosteroids during exacerbations, it was reasonable to assess whether ICS had any effects in stable patients with COPD.

After 10 years, the general consensus can be summarized as follows:

- ICS have no effect on the rate of decline of lung function in lung disease in patients with GOLD grade 1 and 2 disease who smoke and in patients with severe COPD.[39–42] The different views derived from post hoc meta-analysis[43] and patient level meta-analysis[44] about whether these conclusions are correct, are likely to say more about the methodology than the effect of ICS.
- Small but consistent increases in FEV_1 are observed, the degree differing with the initial severity of airflow obstruction. This finding likely reflects the patients studied because improvement with short-acting bronchodilators is greater in patients with moderate severity disease than those with severe problems.[45] At any given GOLD grade, the change in postbronchodilator lung function with ICS is similar to that seen with roflumilast.[46,47]
- There is a reduction in the number of exacerbations defined by the need for medical treatment in patients treated with ICS.[42,48] This reduction seems to be especially true for episodes treated with oral corticosteroids, even though the doctor is blind to the background preventative medication.[49]
- ICS is not associated with any change in mortality as compared with placebo, but neither is mortality likely to be reduced.[50] This finding is contrary to the initial impression based on the result of the database analysis whereby confounding by disease severity may have played a role.[51] By contrast, combining a long-acting beta-agonist (LABA) with an ICS produced a trend to improvement mortality relative to placebo and a significantly better mortality than what was seen with ICS alone in the TORCH (TOwards a Revolution in COPD Health) trial.[50]
- ICS have not been conclusively shown to increase the risk of osteoporosis or cataracts, at least over a 3-year study in a randomized controlled trial. The background frequency with which these occur in patients with COPD makes it difficult to detect a small effect.[52] However, pneumonia, reported by physicians and subsequently confirmed radiologically, is more common in ICS-treated patients with COPD.[53] This effect is shown most clearly for fluticasone[49] and more

Box 1
Goals of COPD Management

- Improve lung function
- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat exacerbations
- Prevent and treat complications
- Reduce mortality
- Minimize side effects from treatment

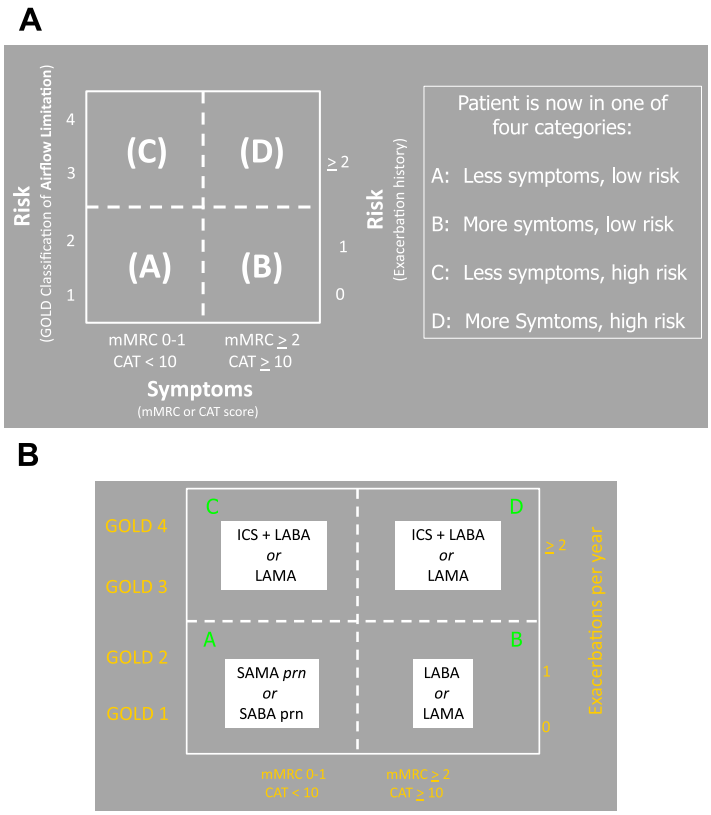

Fig. 2. Assessment by symptom severity and future risk as proposed by Vestbo and colleagues.[33] (*A*) Indicates groups in nonproportional quadrants, and (*B*) indicates the suggested initial treatment of patients in each quadrant. CAT, COPD Assessment Test; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting anti-muscarinic agents; mMRC, modified Medical Research council breathlessness scale; prn, as needed; SABA, short-acting beta-agonist; SAMA, short-acting anti-muscarinic agents.

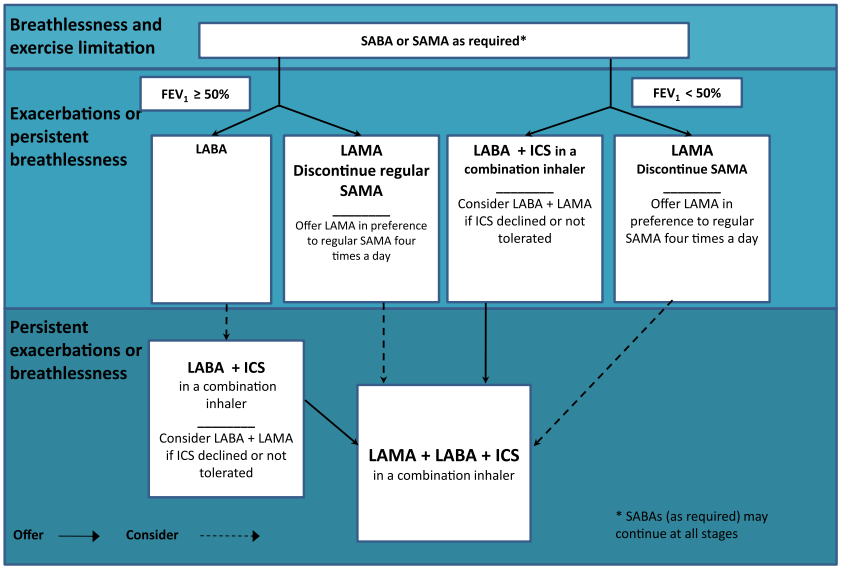

Fig. 3. Evidence-based treatment recommendations for patients with COPD as suggested by the UK National Institute for Clinical Excellence. ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting anti-muscarinic agents; SABA, short-acting beta-agonist; SAMA, short-acting anti-muscarinic agents. (*Adapted from* O'Reilly J, Jones MM, Parnham J, et al. Management of stable chronic obstructive pulmonary disease in primary and secondary care: summary of updated NICE guidance. BMJ 2010;340:c3134; with permission.)

recently for fluticasone furoate[54]; the signal with budesonide was smaller and did not reach statistical significance.[55] In the Investigating New Standards for Prophylaxis in Reduction of Exacerbations (INSPIRE) study, the excess of pneumonia events in patients treated with an ICS/LABA combination treatment was mainly caused by exacerbations that failed to resolve.[29] Patients treated with ICS have a higher airway bacterial load,[56] although whether this is a causal association and relates to the greater number of pneumonia events remains to be determined.

Based on these findings, there is consensus that ICS should not be used as the only regular treatment of COPD or combined with regular short-acting bronchodilators. Their role together with LABA is considered further later.

EVIDENCE-BASED THERAPY

The movement toward evidence-based therapy is both logical and desirable. Identifying areas where there is good evidence from randomized controlled trials (RCT) and other areas where practice is supported mainly by professional consensus is clinically helpful. However, some unintended consequences have arisen and effect the guidance in COPD care. Careful analysis of data, according to prespecified questions, with either systematic review or formal data pooling in a meta-analysis has become the preeminent way of determining the value of treatment. This method has reached its most sophisticated form in the GRADE (Grading Recommendations Assessment, Development and Evaluation) guideline methodology, which weighs data by the strength of the studies assessed on technical grounds and offers nuanced terms in support of an eventual recommendation for treatment.

There are limitations to this approach. Pooling underpowered studies to produce a conclusion can produce the disconcerting effect of a firm recommendation being overturned with a better-powered RCT report. Subtle differences in the a priori event rate of discontinuous variables, like exacerbations, can modify the conclusions drawn or at least the strength of the recommendations supporting them. Differential drop out in patients randomized to placebo treatment, a recurrent feature in recent COPD studies,[57,58] means that the study quality is penalized while the distorting effect and the loss of the sicker patients who drop out while using placebo decreases the chance of a positive outcome.[59] Most importantly, the questions answered by the guidelines are shrunk to ones for which sufficient RCT data are available; this often means that they focus on drug treatment and its use rather than considering the wider aspects relevant to the care of patients with COPD.

Two recent contrasting approaches illustrate these issues. The GOLD guidelines have, for the past decade, drawn on an expert panel of changing composition to review new data about COPD management, expanding the recommendations in its original report, by applying a standard methodology to consider important new data.[2] The 2011 version of the GOLD document changed its focus because the task of analyzing all of the recommendations using a grade approach has become prohibitively expensive.[33] Similar concerns have inhibited a full review of the previous American Thoracic Society/European Respiratory Society's (ATS/ERS) COPD guidelines. Instead, the new version of GOLD offers a management strategy with some preferred options for treatment. This version allows it to escape criticism as a guideline but means that its recommendations are less clearly evidenced based than in the past.

By contrast, the greater resources available to the American College of Physicians (ACP) (working jointly with the ERS and ATS) and to the UK government have allowed them to ask specific grade-based questions, producing focused recommendations.[34,60] The UK NICE updated a previous expert group approach and discovered a wider range of questions than did the ACP. Even so, many specific issues remain unanswered, particularly relating how long to continue with the specific treatment before it is changed, how best to assess the success of therapy, and how strong the evidence is in favor of one treatment rather than another.

As examples of these different approaches, the remainder of this review focuses on the similarities and differences brought up by these well-written, authoritative documents.

EVALUATING PATIENTS

For the last decade, there has been a strong emphasis on the need to monitor spirometry, preferably after a bronchodilator, to determine the disease severity in COPD. Treatment guidance has been closely anchored to this, by both the ATS/ERS' guidelines and in the NICE COPD revision. The current spirometric severity grades advocated by GOLD are as follows:

1. FEV_1 greater than 80% predicted: mild
2. FEV_1 79% to 50% predicted: moderate
3. FEV_1 49% to 30% predicted: severe
4. FEV_1 less than 30% predicted: very severe

Clinical trials have been aligned with these criteria and, hence, data on new drugs can be evaluated relative to their predecessors. However, patient well-being, expressed as either symptoms or health status, is only poorly related to FEV_1[61] and is significantly influenced by the number of COPD exacerbations.[62] To capture this component and make patient evaluation more clinically relevant, the 2011 GOLD revision separated patients into those with mild/moderate disease (GOLD grades 1 and 2) and severe/very severe disease (GOLD grades 3 and 4). In addition, the presence of symptoms evaluated by either an Medical Research Council (MRC) breathlessness score of 2 or greater or a COPD assessment test score of 10 or more was used to further subdivide patient groups.[63,64] FEV_1 was considered a marker of future risk, as was the number of exacerbations, with patients with a history of frequent exacerbations with 2 or more exacerbations forming a distinct phenotype[65] that predicted more future problems. The resulting matrix displayed in **Fig. 2** gives rise to 4 possible groups, A to D, each with a potentially different treatment approach.

The NICE approach also stratified patients with a cutoff point of an FEV_1 of 50% predicted and based initial treatment recommendations on the responses of patient groups defined spirometrically. However, they did consider the possibility that symptoms might be persistent or associated with recurrent exacerbations, despite treatment; therefore, they offered a follow-up treatment option for patients who had already received the first-line therapy but continued to have problems. This approach is somewhat closer to the one that operates in outpatient clinics and is helpful when spirometry is readily available. For many clinicians, the GOLD approach is attractive because it stresses not only spirometry but also the importance of symptoms and exacerbations.

The exact size of the patient population contained within each of the GOLD quadrants is open to debate and seems to depend on whether hospital-based or population-based cohorts are studied.[66] Impaired spirometry rather than simply high numbers of exacerbation seemed to determine the patients in groups C and D. There is some uncertainty about the equivalence of the MRC and the COPD Assessment Test (CAT) cut points, and it is hoped that this will be resolved.[67]

Ultimately, the GOLD proposal needs to be tested prospectively, both for its robustness and its clinical utility. Nonetheless, this new classification represents an important step forward in the way that patients with COPD are managed and treatment choices are evaluated.

INITIAL DRUG THERAPY

The preferred initial choices of drug treatment are shown in **Figs. 2**B and **3** and are remarkably similar in both the GOLD and NICE approaches. Patients with well-preserved lung function and relatively few symptoms, which would equate to a CAT score of less than 10, can be tried on short-acting bronchodilators, with no clear preference between SABA or short-acting anti-muscarinic agents (SAMA). How effective such an approach might be has never been studied, and this recommendation remains largely consensus based.

If patients have an FEV_1 of more than 50% predicted, are more symptomatic, but have no exacerbation history, then either a long-acting anti-muscarinic agents (LAMA) or a long-acting beta-agonists (LABA) should be tried. Since the NICE evidence review, Vogelmeier and colleagues[68] have published convincing evidence that using once-daily tiotropium is more effective than twice-daily salmeterol in preventing COPD exacerbations, regardless of the background use of ICS. Whether the same would be true for once-daily LABA, such as indacaterol, is still to be established. Several studies have suggested that these drugs are at least equivalent in terms of their lung function and health status changes[69,70]; but to date, a direct comparison based on exacerbation frequency has not been presented.

For patients with more severe disease spirometrically, the first-line options are either an LAMA or an LABA/ICS combination. There are clear data to show that LABA/ICS is more effective than its components in reducing exacerbations, improving health status and lung function, and in exercise capacity.[50] Patients who would be included in the GOLD C group because of increased exacerbations rather than poor lung function (a small number in secondary care practice) also benefit from LABA/ICS treatment.[71] However, most patients with more substantial reductions in FEV_1 will also be symptomatic and have an exacerbation history; here the NICE data review suggests that either LAMA or a combination can be given with a slight preference for the combination based on data about secondary end points, such as hospitalization, study drop out, and health status, described in the INSPIRE study.[49] However, the primary outcome of that study was to show equivalence between the treatments in terms of preventing exacerbations.

ALTERNATIVE THERAPIES

Unlike GOLD, NICE makes explicit evidence-based recommendations for treatment when exacerbations remain frequent and/or

breathlessness cannot be reduced to acceptable levels. For patients in GOLD grades 1 and 2, the suggestion is to add another long-acting bronchodilator of a different class to that used initially. Until recently, there has been only limited evidence of efficacy from this approach, with most of the data coming from the Canadian Optimal trial, with combination drugs performing disappointingly, relative to tiotropium therapy.[72] However, a recent 6-month study comparing once-daily indacaterol with the LAMA glycopyrronium in a combination inhaler showed that the combination was superior to either component alone in terms of improving lung function over 3 months. The changes in health status were rather more equivocal and no exacerbation data were presented.[73] However, the well-conducted SPARK study has shown in more severe disease a small but significant reduction in COPD exacerbation rates when these 2 bronchodilators are given compared with either agent alone, lending stronger support to the value of dual bronchodilator therapy.[74]

The next option for these patients with less severe spirometric impairment and the preferred second-line option for those with an FEV_1 of less than 50% predicted is to use the combination of LABA/LAMA and ICS. There are data to show that this triple therapy can reduce exacerbation and improve morning symptoms, at least then the budesonide-formoterol combination is used.[75] In practice, such a combined regimen has been widely adopted in patients with COPD or those at risk of hospitalization. This approach is supported by the GOLD guideline and may be a first-line choice for some patients.

The GOLD system also offers data about the PDE4 inhibitor roflumilast, which has been shown to prevent corticosteroid-treated exacerbations, in patients with a history of these events, who also have chronic bronchitis and an FEV_1 of less than 50% predicted.[76] It seems effective in patients who use ICS (but not LABA)[77] or those who use either LABA or LAMA (but not ICS).[47] It is most effective when the background exacerbation rate is high[78] and converts frequent exacerbators to infrequent exacerbators. Further studies investigating the effect of roflumilast on top of either LABA/ICS or triple therapy are currently ongoing.[79] However, the most common side effects seen with roflumilast are a pharmacologically predictable increase in nausea, diarrhea, and, more surprisingly, weight loss, which are likely to limit its use in some patients.

A range of other alternative treatments is suggested by GOLD, although not necessarily in any preferred order of use. Again, this represents expert preference because specific studies defining clinical effectiveness in comparable groups are lacking. GOLD also offers some options for cheaper treatment for more cash-limited health care systems, although the comparability of studies conducted when there is almost no background therapy, even with short-acting bronchodilators to trials whereby other effective agents were already deployed, is difficult to evaluate.[80]

EMERGING ISSUES

All of the aforementioned treatments have the potential for adverse effects as well as beneficial ones. As noted in the acute episodes, beta-agonists can produce troublesome tremor and palpitations, particularly in older patients, although the metabolic effects, including hypokalemia, are not troublesome. Patients with coexisting cardiac disease are common in COPD, although the evidence to date suggests that the use of beta-agonists alone or in combination with ICS is not associated with an increased mortality and may actually be beneficial.[81] LAMA drugs, such as tiotropium, are absorbed somewhat more readily than ipratropium; the use of these agents seems to be associated with more cases of urinary retention.[82,83] Dry mouth is not a major side effect and is reported less frequently with tiotropium than ipratropium. The twice-daily anticholinergic aclinidium does not seem to have this side effect.[84]

Initial concerns about an excess recurrence of cardiac deaths with LAMA treatments have been allayed by data from the follow-up of patients in the large randomized controlled Understanding the Potential Long term Improvement in Function with Tiotropium (UPLIFT) trial whereby overall fewer patients died if randomized to tiotropium treatment.[85] Recently, anxieties have been raised about the use of a soft-mist aerosol form of tiotropium, which is available in Western Europe. Greater numbers of deaths were reported on patients randomized to this treatment in the regulatory studies, which were not primarily designed to assess mortality risk.[86,87] This finding has led some to call for this delivery system to be discontinued and is unlikely to become available in the United States until these issues are resolved. Important information about this problem will come from the TIOtropium Safety and Performance in Respimat (TIOSPIR) study of more than 17,000 patients who are receiving either 2 different doses of tiotropium from the soft-mist inhaler or conventional tiotropium from the dry power device.[88]

A range of new drugs belonging to the LABA and LAMA classes given once or twice daily alone or in combination with each other or inhaled corticosteroids are in the process of

development and registration. One such combination of the LABA vilanterol and the inhaled corticosteroid fluticasone furoate has received a favorable assessment at a Food and Drug Administration advisory panel.

At present, no new twice-daily LABA drugs have been evaluated; but twice-daily aclidinium bromide has been licensed for use in the United States and Western Europe, and studies combining this with formoterol are ongoing. Once-daily inhaled indacaterol has been combined with glycopyrronium, as noted earlier,[73,74] and is also being studied together with mometasone furoate, an ICS that can prove effective when given once daily.[89]

A new LABA, olodaterol, is being combined with tiotropium; but these studies have used the soft-mist delivery system discussed earlier, and their outcome will be influenced by the results of TIOSPIR. The vilanterol/fluticasone furoate combination has been investigated in several doses[90] and in replicate 1-year studies.[54] The inhaled steroid adds relatively little to the bronchodilator effect, but this is associated with fewer exacerbations than is seen with the LABA alone (**Fig. 4**). As with other fluticasone preparations, pneumonia was more common when the ICS was used; but overall, the combination of 25 mcg vilanterol and 200 mcg fluticasone furoate gave the most favorable benefit/risk profile.

Ultimately, the plethora of newer chemically and clinically similar entities will need a clear-sighted appraisal of the cost-effectiveness of treatment before these agents can be recommended in future treatment guidelines. The next generation of clinical trials will need to define not just whether the treatment works relative to a placebo comparator (an approach which seems to be increasingly unethical, given the established effects of treatment) but also how much benefit such treatment provides for the patients and payer. Defining when it is appropriate to add treatment to existing regimens or replace components of a current therapy will be our next challenge.

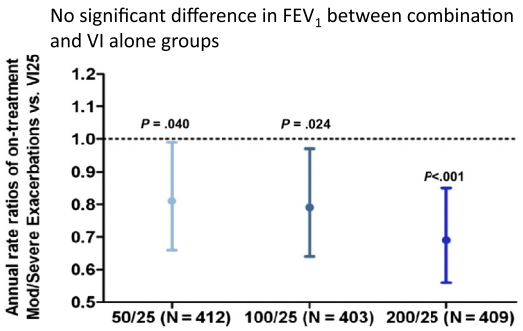

Fig. 4. Effect on exacerbation rate of adding the once-daily inhaled corticosteroid fluticasone furoate to the long-acting inhaled beta-agonist vilanterol (VI) in a 1-year clinical trial. Note the improvement in exacerbation rate with the corticosteroid in the absence of significant differences in FEV_1. Mod, moderate. (*Adapted from* Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol vs vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. Lancet Respir Med 2013;1:210–23; with permission.)

SUMMARY

Choosing the optimal drug therapy is a key component of the management of COPD. Acute exacerbation treatment, whether in the community or hospital, has changed little in recent years and involves increasing the frequency and/or dose of inhaled bronchodilators, giving a short (up to 10 days) course of oral prednisolone, having a low threshold for starting antibiotics of an appropriate spectrum to cover likely pathogens, and avoiding the use of methylxanthines.

Chronic treatment choices are influenced by baseline lung function, symptom intensity, and how often patients have exacerbated in the past. Short-acting reliever treatment with beta-agonists or antimuscarinics may be appropriate for patients with few symptoms and preserved lung function; but at present, long-acting antimuscarinic treatment is the first-line option when managing patients whose FEV_1 is more than 50% predicted. Those with more severe disease spirometrically and/or a history of 2 or more exacerbations per year gain benefits from either long-acting antimuscarinics but especially from combinations of LABA and ICS. These 3 treatment approaches can be combined if there are persistent problems, especially in patients who exacerbate often.

Other agents, such as PDE4 inhibitor roflumilast, can be considered as an alternative to ICS and may prove helpful in disease that is difficult to manage with triple treatment, although this has yet to be definitely established. Many other options exist, with once-daily combinations of bronchodilators and bronchodilator corticosteroids becoming available in the near future.

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