REVIEW

Patient-centred outcomes in primary care management of COPD — what do recent clinical trial data tell us?

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Tiotropium

Summary Traditionally, the severity of chronic obstructive pulmonary disease (COPD) and effectiveness of interventions have been determined using measures of lung function. However, a relatively small reduction or change in lung function — such as those observed in mild to moderate COPD — may not always reflect the impact of the disease or intervention on patients' physical and psychological well-being. This paper examines the utility of various outcome measures that can be used in primary care to monitor and manage COPD. In particular, it demonstrates the importance of measuring patient-centred outcomes, such as health-related quality of life and exacerbations, which may reflect more accurately the effects of the disease and treatment on patients' everyday lives. Recent large-scale clinical trials of budesonide/formoterol and fluticasone/salmeterol combination therapies and tiotropium have utilised these outcome measures to show the significant benefits these treatments bestow to patients in the presence of relatively modest gains in lung function.

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Introduction

Traditionally, clinical trials in patients with chronic obstructive pulmonary disease (COPD) have focused on changes in lung function, due to both regulatory requirements and the fact that this is a recognised, objective measure of disease progression. To most healthcare professionals, prevention of decline in lung function remains the “Holy Grail” of COPD management. However, it is increasingly evident that outcomes such as symptoms, exacerbations, exercise capacity and health-related quality of life (HRQL) are at least as important as changes in lung function. The importance of such patient-centred outcome measures has been acknowledged in the recently updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) management guidelines [1], which emphasise that the extent to which the goals of effective COPD management can be realised varies with each individual patient. Patient-centred outcome measures can be used by clinicians in conjunction with lung function measurements to optimise patient management strategies and to evaluate fully the effectiveness of therapeutic interventions.

Historically, COPD has been a relatively neglected disease area in primary care — particularly compared with asthma. Nevertheless, COPD is one of the most common conditions encountered in primary care among patients aged over 55 years, accounting for more consultations than angina [2]. Indeed, it has been estimated that COPD will be the third leading cause of death globally by 2020 [3]. Furthermore, although about 20–30% of elderly individuals have evidence of obstructive airways disease, some will not have received a formal diagnosis from their doctor and will consequently not be receiving specific therapy [4].

In this paper we explore the utility of various disease outcome measures in primary care, focusing in particular on patient-centred outcomes. The findings of recent, 1-year studies of three newly established COPD therapies — the long-acting, inhaled, anticholinergic bronchodilator tiotropium (Spiriva®, Boehringer Ingelheim) and the inhaled corticosteroid/long-acting β_2 -agonist

[ICS/LABA] combinations of budesonide/formoterol (Symbicort®, AstraZeneca) and fluticasone/salmeterol (Seretide®, GlaxoSmithKline) — are used to illustrate the value of these patient-centred measures in the clinical trial setting.

Outcome measures in COPD

Traditional measures of airflow limitation do not give a complete picture of the effect of COPD on the patient and therefore other outcome measures are required. Patient-centred outcomes are those that reflect the impact of the disease and/or treatment on patients’ everyday lives and include measures such as HRQL and exacerbations. To date, very few studies have been undertaken which assess the effects of therapy on such patient-centred endpoints. However, recent studies of tiotropium (18 μ g, once daily) and ICS/LABA combinations (budesonide/formoterol in a single inhaler [160/4.5 μ g, 2 inhalations twice daily] or fluticasone/salmeterol [500/50 μ g, twice daily]) have included these measures [5–13]. These studies were selected on the basis of being placebo-controlled clinical trials involving novel pharmacological therapies recently recommended in the GOLD guidelines for COPD [1], which reported patient-centred outcome measures and were of at least 1-year duration. The results of these studies indicate that important patient-centred benefits, including improvements in symptoms, exacerbations and HRQL, can be achieved with these new treatment options.

Lung function

Prognosis in COPD is directly related to post-bronchodilator forced expiratory volume in 1 second (FEV₁), making slowing or halting the decline in lung function central to improving prognosis. Smoking cessation is the single most critical intervention that can help achieve this [14,15]; the debate regarding the effects of long-term ICS on lung function decline continues [16].

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While measuring lung function can provide valuable information for prognosis, it may not accurately reflect patients' current day-to-day disability. Unlike dyspnoea, for example, FEV₁ does not predict physiological impairment [17] and symptoms of COPD may be present when there is relatively little or even no lung function abnormality [1]. Furthermore, only modest changes in lung function may be associated with clinically significant gains in health status and patient well-being, as observed, for example, in trials of salmeterol [18]. Consequently, while spirometric assessment undoubtedly provides an objective measure of lung function, it seems reasonable to suggest that it need not be performed more regularly than once every 1–3 years in routine clinical practice, although evidence regarding the optimal frequency of assessment is not available. The new UK General Medical Services contract recommends a period of 15 months between assessments. Furthermore, it does not appear to be needed to confirm the success of therapeutic intervention, provided patients are showing benefits with other less objective outcome measures.

Lung function parameters such as FEV₁ are widely measured in clinical trials. In new studies, ICS/LABA combination therapy has been shown to provide significant improvements in FEV₁ compared with monotherapy with either component alone and placebo (Table 1) [10–12]. Tiotropium has also been shown to provide significant improvements in FEV₁ compared with placebo [6,9].

Symptoms

Surveys of patients with COPD indicate that disease symptoms — which can be monitored using patient diaries — cause both significant disability and emotional and social disturbance, in addition to restricting normal daily activities [20–23]. However, with the exception of instruments that specifically measure dyspnoea, there is an overall lack of validated, objective measures of common COPD symptoms.

Chronic cough is usually the first symptom of COPD to manifest and can precede the development of airflow limitation by many years [1]. Sleep disturbance is more common among elderly patients with chronic airway diseases than in those with other chronic diseases and is independently correlated with depression [24]. Fatigue is another important — but commonly overlooked — symptom, with general fatigue (measured using the Multidimensional Fatigue Inventory) shown

to correlate with poor lung function, exercise intolerance, depression and reduced HRQL [25]. Nutritional abnormalities, weight loss, muscle wasting and tissue depletion, which are also common in chronic inflammatory conditions such as COPD, further increase the likelihood of tiredness or exhaustion [26,27]. All of these factors indicate that COPD is not just a disease of the lungs, and serve to emphasise its systemic nature. This, coupled with the likelihood of intercurrent illness, highlights the need for a holistic approach to disease management in order to optimise outcome for the individual patient.

Various subjective scoring systems have been used to examine symptoms in recent clinical trials of new COPD treatments. Total symptom score (Table 1), reliever medication use and night-time awakenings were found to be reduced with both ICS/LABA combination inhalers compared with placebo [10,11], with the effects of budesonide/formoterol on symptoms evident within the first week of treatment [13]. For patients using tiotropium, cough and chest tightness were not significantly improved, but less reliever medication was used compared with the placebo group at the end of the 12-month study period [6].

Dyspnoea and activity limitation

Dyspnoea is rated as the most important disabling symptom by many patients, limiting both their health status and activities of daily living [1,28–30]. When patients are inactive they experience fewer or no severe symptoms of breathlessness and this may cause them to adapt their behaviour accordingly. However, inactivity is not an acceptable way of managing patients with COPD. Instead, management strategies should enable patients to become more active, while maintaining control of their symptoms.

Several indices have been devised to quantify dyspnoea both cross-sectionally and longitudinally in response to treatment (Table 2) [37]. The Medical Research Council Dyspnoea Scale, which is recommended by the National Institute for Clinical Excellence (NICE), has good cross-sectional validity [32] but its lack of longitudinal validity means that it is relatively insensitive to change because of therapeutic intervention. Dyspnoea is an important predictor of exercise tolerance [38], and both factors have been shown to influence patients' health status at all levels of COPD severity [39–41]. All scales of the Respiratory Quality of Life Questionnaire have been shown to have a

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Table 1 Key clinical outcomes in 1-year placebo-controlled studies of ICS/LABA combination inhalers and tiotropium in COPD.

	Calverley et al. (2003) [11]				Szafranski et al. (2003) [13]				Calverley et al. (2003) [10]				Casaburi et al. (2002) [6]	
	Bud/Form (254)	Plac (256)	Bud (257)	Form (255)	Bud/Form (208)	Plac (205)	Bud (198)	Form (201)	Flu/Sal (358)	Plac (361)	Flu (374)	Sal (372)	Tio (550)	Plac (371)
FEV ₁ , L														
Baseline	0.98	0.98	0.99	1.00	0.96	0.98	1.01	1.00	1.31	1.27	1.26	1.25	1.04	1.00
Improvement vs. placebo (%)	14*	—	2*	8*	15*	—	5*	14*	NA	—	NA	NA	NA	—
Endpoint	NA	NA	NA	NA	NA	NA	NA	NA	1.40*	1.26	1.30*	1.32*	NA	NA
Improvement vs. placebo, L	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	NA	NA	0.12–0.15*	—
Total symptom score (0–16)														
Reduction vs. placebo	0.56*	—	0.30	0.54*	0.77*	—	0.07	0.50	NA	—	NA	NA	NA	—
Breathlessness score (0–4)														
Reduction vs. placebo	0.21*	—	0.09	0.21*	0.36*	—	0.10	0.25	NA	—	NA	NA	NA	—
Endpoint	NA	NA	NA	NA	NA	NA	NA	NA	1.47	1.66*	1.58*	1.59*	NA	—
Exacerbation definition	Medical intervention-based ^a				Medical intervention-based ^a				Medical intervention-based ^b				Symptom-based ^c	
Total exacerbations														
Rate/patient/year	1.38* [†]	1.80	1.60	1.85	1.42* [†]	1.87	1.59	1.84	0.97*	1.30	1.05*	1.04*	0.76*	0.95
Reduction vs. placebo (%)	24	—	12	–3	24	—	15	2	25	—	19	20	20	—
OCS subset														
Rate/patient/year	0.63* ^{†‡}	1.14	0.87*	0.91	0.74* [†]	1.07	0.76*	1.04	0.46*	0.76	0.50*	0.54*	NA	NA
Reduction vs. placebo (%)	45	—	23	20	31	—	29	3	39	—	34	29	NA	—
SGRQ score														
Reduction vs. placebo ^d	7.5* ^{†‡}	—	3.0*	4.1*	3.9*	—	1.9	3.6*	2.2* [‡]	—	0.8	1.1	2.7 ^{e*}	—

Abbreviations: Bud = budesonide; FEV₁ = forced expiratory volume in 1 second; Flu = fluticasone; Form = formoterol; NA = not available; OCS = exacerbations requiring oral corticosteroids; Plac = placebo; Sal = salmeterol; SGRQ = St George's Respiratory Questionnaire; Tio = tiotropium. *Statistically significant vs. placebo; †statistically significant vs. combination inhaler; ‡statistically significant vs. formoterol; †statistically significant vs. inhaled corticosteroid.

^a Requirement for antibiotics and/or oral corticosteroids and/or hospitalisation. Data are mean values over 12 months.

^b Requirement for antibiotics and/or oral corticosteroids. Data are mean values over 12 months.

^c A complex of respiratory events (cough, wheezing, dyspnoea, sputum production) lasting >3 days. Data are mean values at 12 months.

^d A reduction of 4 units in SGRQ total score represents a clinically important difference relevant to the patient (Jones, 2002 [19]).

^e Estimated from figure.

moderate to substantial association with indices of dyspnoea and exercise tolerance [40]. Validated instruments, such as the Transitional Dyspnoea Index (TDI) and the 6-minute walking test (6MWT), have also been shown to be responsive to changes in breathlessness [31,42] and exercise capacity [33,38], resulting from disease progression or therapeutic intervention. The 6MWT [43] and other indicators of exercise capacity such as the shuttle walking test [34] have also been shown to be useful outcome measures in pulmonary rehabilitation and clinical studies. However, time and space constraints limit their use in primary care settings.

Tiotropium has been shown to be associated with statistically significant improvements in dyspnoea on the TDI scale compared with placebo or salmeterol at 6 months [7]. Significant improvements in TDI score were also seen with tiotropium compared with placebo in a 1-year study (1.0 versus 0.0, respectively) [6]. Shortness of breath, measured using a subjective patient-rated scale, was also reduced with both ICS/LABA combination inhalers compared with placebo (Table 1) [10,11,13]. These results are encouraging, since even modest improvements in breathlessness are likely to lead to improved mobility and an increased level of physical activity — with associated improvements in HRQL.

Exacerbations

There is some discrepancy in the way exacerbations of COPD are defined in clinical trials, according to whether they are based on symptoms alone or on a requirement for specific medical intervention. Recently, medical intervention-based definitions have been used more frequently as they have objective endpoints that reflect more severe events likely to have a significant impact on patients, such as the need for oral corticosteroids (OCS) or hospitalisation [10,11,13,44,45]. Recent publications have highlighted the urgent need to improve our understanding of COPD exacerbations and to develop a standard definition for these [46]. One definition, developed by an international working party of experts, defines exacerbations as *‘a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD’* [47]. However, application of this definition is limited by the need for further definition and assessment of the term *‘sustained worsening’*. Furthermore, emerging data confirm that exacerbation is a term not easily understood by patients, who prefer to use simpler words such as *‘crisis’* [48].

Table 2 Tools for assessing breathlessness.

Measure	Comments	Reference
Baseline Dyspnoea Index (BDI)/ Transitional Dyspnoea Index (TDI)	Includes three domains: Functional Impairment; Magnitude of Task; and Maximal Effort. Too complex for everyday clinical use	Mahler et al. (1984) [31]
Medical Research Council (MRC) Dyspnoea Scale	Easy to use in practice with good cross-sectional validity, but less sensitive to change than BDI/TDI. Recommended by the National Institute for Clinical Excellence	Mahler and Wells (1988) [32]
6-minute walking test (6MWT)	Commonly used test to assess exercise tolerance and to detect a change following therapeutic intervention	Carter et al. (2003) [33]
Shuttle walking test	Fulfils basic criteria for an exercise test and is easy to use in practice and in the home	Singh et al. (1998) [34]
Oxygen Cost Diagram	Easy to use as patients mark off the grade of activity at which they get breathless on a scale. Patients may not actually relate to the activities listed on the scale	Mahler and Wells (1988) [32]
Borg Scale	Patients rate the degree of breathlessness during a particular task. Responsive to change, but intended to be completed whilst patient performs task and therefore practically limited in everyday clinical use	Burki (1987) [35]
Visual Analogue Scale	Patients mark their degree of breathlessness on a 10 cm scale	Nosedá et al. (1992) [36]

Prevention of exacerbations is one of the most important goals of COPD management [1]. Exacerbations have a significant impact on patients' daily activities and HRQL [49–51], with their effects lasting for several weeks or months [52]. Furthermore, frequent exacerbations lead to a poorer recovery in terms of improvement in health status [53]. COPD exacerbations have also been shown to have a dramatic impact on healthcare costs [54–56]. Hospital admissions and emergency care account for the greatest management cost in COPD. Prior admission to hospital for a COPD exacerbation is a key risk factor for subsequent readmissions, while higher than usual levels of physical activity may be an important protective factor against exacerbations requiring hospitalisation [57]. Reducing the number of exacerbations is also important for reducing use of OCS and the risk of systemic side effects associated with these agents.

Inhaled corticosteroids, while not appearing to alter the rate of decline in lung function in individual studies [45,58–60], have been shown to reduce the severity and frequency of exacerbations as well as increasing FEV₁ performance and improving HRQL [44,45,58]. More recently, a meta-analysis of eight studies involving over 3700 COPD patients with moderate to severe airflow limitation has suggested that treatment with ICS for at least 2 years significantly slows the rate of decline in FEV₁; this effect is greater in those patients receiving higher doses of ICS [16]. The current GOLD guidelines recommend ICS treatment for patients who have demonstrated a response to corticosteroids and for those with severe disease (FEV₁ < 50% predicted) with repeated exacerbations requiring antibiotics and/or OCS [1].

In recent trials of combination ICS/LABA therapies, budesonide/formoterol was the only

treatment which significantly prolonged the time to first exacerbation requiring medical intervention — defined as a need for antibiotics and/or OCS and/or hospitalisation due to respiratory symptoms — compared with placebo or either monocomponent (all $p < 0.05$) (Figure 1). This prolonged time to first exacerbation may delay the deterioration of the disease and help maintain health status and patient well-being [11]. The rate of exacerbations per patient per year was also reduced with budesonide/formoterol compared with formoterol or placebo (Table 1). In the trial of fluticasone/salmeterol, combination therapy was shown to reduce the rate of exacerbations requiring medical intervention — defined as a worsening of COPD symptoms that required treatment with antibiotics, OCS or both — versus placebo only (Table 1). Tiotropium was also shown to reduce the rate of exacerbations versus placebo; however, it should be noted that these trials used a more subjective symptom-based criterion to define exacerbations: a complex of respiratory events (cough, wheezing, dyspnoea, sputum production) lasting for more than 3 days (Table 1). In addition, patients were allowed concomitant ICS, OCS or theophylline throughout the studies, which makes interpretation of the results more difficult. Similar results were reported in a 6-month comparison of tiotropium, placebo and salmeterol in which tiotropium significantly reduced the exacerbation rate (symptom-based criteria) compared with placebo, but not salmeterol [61]. The rate of exacerbations requiring OCS was also reduced with budesonide/formoterol compared with placebo and either monocomponent alone [11], as well as with fluticasone/salmeterol compared with placebo [10] (Table 1), suggesting that decreasing the frequency of exacerbations may be important for reducing patients' overall systemic steroid load.

Figure 1 Budesonide/formoterol prolonged the time to first exacerbation requiring medical intervention compared with budesonide, formoterol and placebo in a 1-year, placebo-controlled COPD study (reproduced with permission from Calverley et al, 2003 [11]). Footnote: * $p < 0.05$ vs. placebo, $p = 0.037$ vs. budesonide, $p = 0.002$ vs. formoterol (log-rank test).

Health-related quality of life

Symptoms, exacerbations and lung function are all known to impact on HRQL [49,51]. Individuals with COPD recognise changes in HRQL [30,62], and any improvements may be meaningful if they enable patients to become more active in ways that are important to them (for example, walking to the local shops), thus allowing them to live more normal, independent lives. Recent data relating to exacerbations suggest that impact on daily life and level of medical care required (for example, hospitalisation) are the two most important factors for patients, and that these are more important even than simple symptoms

[63]. In addition to participation in daily activities, psychological/emotional status is also known to be an important determinant of HRQL [64]. Patient-centred goals leading towards improving HRQL are clearly important in the management of COPD, but data on this topic are currently lacking.

Validated instruments, such as the disease-specific St George's Respiratory Questionnaire (SGRQ) [21] and other measures [65] have been used effectively in clinical studies to quantify changes in HRQL, utility and productivity (Table 3), but are not easily employed in primary care settings. Indeed, primary care clinicians may find it easier to gauge patients' health status using shorter validated questionnaires such as the Short Form 12

Table 3 Tools for assessing health-related quality of life, utility and productivity outcomes in patients with COPD.

Measure	Comments	Reference
Short Form 36 (SF-36)	Generic HRQL questionnaire that includes 36 items in 8 domains. Two summary scores are used (Physical and Mental Component Summaries)	Brazier et al. (1992) [66]
Short Form 12 (SF-12)	A shortened version of the SF-36 that includes 12 items in 8 domains. Again, two summary scores are used (Physical and Mental Component Summaries)	Ware et al. (1996) [67]
St George's Respiratory Questionnaire (SGRQ)	Disease-specific HRQL questionnaire that includes 56 items across 3 domains (Symptoms, Activity and Impact)	Jones et al. (1992) [21]
Chronic Respiratory Disease Questionnaire (CRDQ)	Disease-specific HRQL questionnaire with four dimensions (dyspnoea, fatigue, emotional function and feeling of control over the disease), scored 0–16	Guyatt et al. (1987) [68]
Clinical COPD Questionnaire (CCQ)	Disease-specific HRQL questionnaire that includes 10 items in 3 domains (Symptoms, Functional and Mental state), scored 0–6. A short questionnaire that is easy to administer and responsive to change	van der Molen et al. (2003) [69]
Airways Questionnaire (AQ)	A concise HRQL questionnaire for COPD or asthma that exists as a shorter version with 20 items (AQ-20) and a longer version with 30 items (AQ-30). Highly correlated with the SGRQ but simpler to administer	Alemayehu et al. (2002) [70]
EuroQol-5D (EQ-5D)	Generic utility measure that evaluates subjective preferences on a linear scale (0–100)	Johnson et al. (1998) [71]
Health States-COPD (HS-COPD)	Disease-specific utility measure that evaluates subjective preferences on a linear scale (0–100). The instrument is still under development	Ståhl et al. (2003) [65]
Work Productivity and Activity Impairment Questionnaire for COPD (WPAI-COPD)	Disease-specific questionnaire that measures 7 items relating to the limitations that impact on work and daily activity	Ståhl et al. (2003) [65]

Abbreviations: COPD = chronic obstructive pulmonary disease; HRQL = health-related quality of life.

[67], Clinical COPD Questionnaire [69] and Airways Questionnaire 20 [72].

Trials of new COPD therapies have shown important HRQL benefits for patients. After 1 year of treatment, both ICS/LABA combination inhalers and tiotropium provided HRQL improvements versus placebo as demonstrated by change in SGRQ total score (Table 1). It is interesting to note that in all of these 1-year studies, only the improvements in SGRQ total score achieved with budesonide/formoterol versus placebo exceeded (-7.5 ; [11]) or approached (-3.9 ; [13]) the level that is considered noticeable to the patient, where a reduction of 4 units represents a clinically important difference [19]. A similar clinically relevant improvement in SGRQ score was observed in a 6-month study with tiotropium, but not with placebo or salmeterol [7]. Clinical studies using HRQL measures that are more easily applied in clinical practice are now warranted.

Psychological measures

Living with COPD can produce feelings of hopelessness combined with the fear of — often unpredictable — exacerbations [73,74]. Moreover, reduced interaction with friends and family because of the disease can lead to increased social isolation. Related to this is the fact that patients with severe COPD have a 2.5-times greater risk of depression than control subjects and about 25% of COPD sufferers will have comorbid depression [75]. Depression, which can be assessed relatively easily in primary care, appears to be related to the degree of physical impairment, respiratory symptoms, reversibility of lung function and living alone [75]. On a positive note, this does mean that these symptoms can be treated in their own right and, because of the overlap of symptoms of depression with those of COPD, this might have a beneficial effect on other patient-centred outcomes of COPD, such as perceived HRQL.

Mortality

Mortality is not often considered as an outcome measure in COPD, which may contribute to underestimation of the significance of the disease. Several prospective studies have shown that poor HRQL is a strong predictor of mortality in patients with COPD [76–78], with results of one study showing HRQL to be more closely correlated with mortality than FEV₁ [77]. Despite high mortality in COPD, death rates can be reduced with effective disease management. This may be at least in part due to the

prevention and treatment of exacerbations, which are known to be associated with excess mortality in COPD patients — mortality rates of 43% have been reported at 12 months following an exacerbation [79].

In an observational study, treatment with an ICS and/or LABA increased 3-year survival of COPD patients compared with individuals who regularly used other types of bronchodilators (78.6% versus 63.6%, respectively) [80]. Furthermore, use of an ICS/LABA combination inhaler increased survival by a greater extent than either therapy alone. These findings are supported by the results of another retrospective cohort analysis, which showed that risk of death or hospitalisation in the year following first hospitalisation for COPD was reduced by 41% in patients who received ICS/LABA combination therapy compared with a reference population using short-acting bronchodilators only [81]. This compares with a reduction in the risk of death or hospitalisation of 10% in patients who received LABA alone and 16% in those receiving ICS only. Recent controlled clinical trials of ICS/LABA combinations did not examine survival as an efficacy endpoint. However, results of these studies do indicate potential mortality benefits, with consistent reductions in exacerbation rates and improvements in observed lung function — with associated improvements in HRQL.

Safety

Both the safety and tolerability of drug therapy are of paramount importance in the treatment of COPD. Despite studies showing that OCS may slow the decline in lung function and reduce symptoms and exacerbations in patients with COPD [82,83], long-term treatment is not generally recommended because of the risk of systemic side effects such as bone loss and disturbance of adrenocorticoid function [84]. ICS are clearly associated with fewer systemic side effects [85]. In some studies, use of LABAs has been associated with a small increased risk of adverse cardiovascular effects, but these appear to be more important in patients with pre-existing cardiac arrhythmias [86,87].

Results of recent clinical studies show ICS/LABA combination inhalers to be generally well tolerated, with a safety profile similar to that of placebo [10,11,13]. No treatment-related patterns regarding the incidence of serious adverse events (SAEs) were reported. Indeed, in one study, the lowest number of SAEs was seen in patients receiving the budesonide/formoterol combination or placebo [11]. Given the long-term nature

of these studies, there was a surprisingly low incidence of SAEs; for example, 18% of patients receiving tiotropium compared with 21% receiving placebo [6]. The number of SAEs was not reported in the 1-year study of fluticasone/salmeterol.

Bone mineral density, although not examined in these studies, was not altered in a 3-year placebo-controlled study of the ICS budesonide at the same inhaled dose [85]. In the study of fluticasone/salmeterol, minor changes in cortisol secretion were observed with fluticasone alone or in

combination. This may have been due to the higher ICS dose used in this study [10], which is reflected in the licenses now available. No clinically significant cardiovascular side effects were associated with formoterol or salmeterol treatment. There was, however, an increased incidence of oral candidiasis in patients treated with fluticasone or combination fluticasone/salmeterol therapy. There were no reports of bruising with budesonide/formoterol [13], while this side effect was slightly elevated among patients receiving fluticasone or the

Table 4 Utility and ease of assessment of COPD outcomes in primary care.

Outcome	Tool	Author opinion
Lung function	Spirometry	Valuable for determining disease prognosis but does not accurately reflect day-to-day disability May not be easily accessible in all centres
Symptoms	Patient diaries, symptom scores	Very important patient-centred outcomes which can be assessed on an individual basis Lack of validated, objective measures of common COPD symptoms
Dyspnoea/activity limitation	BDI/TDI, MRC Dyspnoea Scale, Oxygen Cost Diagram, Borg Scale, Visual Analogue Scale, 6-minute walking scale, shuttle walking test	Rated as the most important and disabling symptom by patients Useful and accurate outcome measure in pulmonary rehabilitation and clinical studies Time and space constraints limit their utility in everyday practice
Exacerbations	Subjective assessment of individual patient	No standard definition Medical intervention-based definitions have the most objective endpoints that reflect the more severe events experienced by the patient
HRQL	SF-12, SF-36, SGRQ, CRDQ, CCQ, AQ, EQ-5D, HS-COPD, WPAI-COPD	Symptoms, exacerbations and lung function affect HRQL Individuals recognise and value improvements in HRQL Outcome measures are useful in clinical studies but are not easily employed in primary care. Shorter questionnaires may be more useful in this setting
Depression/anxiety	Clinical judgement, short scales such as BASDEC (recommended by the National Institute for Clinical Excellence) or Beck's Depression Inventory	Very common in patients with severe COPD. Symptoms of depression overlap with symptoms of COPD Relatively easy to assess

Abbreviations: AQ = Airways Questionnaire; BASDEC = Brief Assessment Schedule Depression Cards; BDI = Baseline Dyspnoea Index; CCQ = Clinical COPD Questionnaire; COPD = chronic obstructive pulmonary disease; CRDQ = Chronic Respiratory Disease Questionnaire; EQ-5D = EuroQol-5D; HRQL = health-related quality of life; HS-COPD = Health States-COPD; MRC Dyspnoea Scale = Medical Research Council Dyspnoea Scale; SF-12 = Short Form 12; SF-36 = Short Form 36; SGRQ = St George's Respiratory Questionnaire; TDI = Transitional Dyspnoea Index; WPAI-COPD = Work Productivity and Activity Impairment Questionnaire for COPD.

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combination inhaler compared with salmeterol or placebo [10]. Treatment with tiotropium was associated with almost a 6-fold greater incidence of dry mouth than placebo, but this common anticholinergic side effect was mild in most instances [6].

Implications for clinical practice

Primary care practitioners see most patients with COPD well before the symptoms or signs of moderate-to-severe disease are present [88]. As such, they are in a pivotal position to make a difference to the treatment and outcome of this under-recognised and undertreated disorder. Emerging data highlight the importance of focusing on patient-centred outcomes for optimal clinical management of COPD patients, with the potential to improve assessment of both the impact of the disease and the efficacy of therapeutic interventions in individual patients.

It is important that patients with COPD are monitored on a regular basis (perhaps annually) to allow disease progression to be reviewed more accurately. In addition to assessment of lung function, the most relevant patient-centred outcomes to consider include symptoms, dyspnoea and associated activity limitation, exacerbations and HRQL. Of the assessments that have been discussed in this paper, an overview of those easily performed in primary care settings is given in Table 4. Further development of simple and meaningful tools to enable clinicians and patients to consistently assess these outcomes in clinical practice and at home is clearly required. While data on this topic are lacking, individual patient goals are important to measure the effectiveness of interventions for each patient. Key activities such as climbing 10 steps matter to patients and can be readily assessed.

Although smoking cessation remains the most important intervention that can slow the decline in lung function associated with COPD, emerging data confirm that newer therapies — such as anticholinergic bronchodilators and ICS/LABA combination therapies — have beneficial effects on patient-centred outcomes, including exacerbations requiring medical intervention, symptoms and HRQL. Any improvement in these outcomes, particularly exacerbations which are serious events for patients, should allow patients to become more active in their daily lives and thereby help to relieve the physical, psychological, social and economic burden of their disease.

Summary

Treatment studies are looking beyond the more traditional endpoints (for example, effects on lung function) to consider outcomes that matter most in patients' daily lives. These studies show that treatments are available which have a meaningful impact on patient-perceived outcomes, including symptoms, exacerbations requiring medical intervention and HRQL.

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