

REVIEW

Earlier diagnosis and earlier treatment of COPD in primary care

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Abstract

Chronic obstructive pulmonary disease (COPD) is a progressive disease that begins many years before a diagnosis is usually made. The need for an early and confirmed diagnosis of COPD is increasingly appreciated by primary care physicians in whose hands the ability to make improvements in early diagnosis largely rests. Case-finding of patients with symptoms of lifestyle limitation is probably the most practical way to achieve early diagnosis. Evidence suggests a burden of early COPD on afflicted people and their families. Early encouragement of smoking cessation, in conjunction with management of symptoms and treating activity limitation and exacerbations by appropriate non-pharmacologic and pharmacologic management at the earliest possible stage, could positively affect the impact and progression of the disease.

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Introduction

Chronic obstructive pulmonary disease (COPD) progressively debilitates patients, resulting in increasing disability and worsening impact of exacerbations.¹ Many patients with COPD

remain undiagnosed and potentially unknown to healthcare providers until the more advanced stages of the disease.¹ Delayed diagnosis results in patients suffering symptoms and limitations that could otherwise be alleviated by treatment. Moreover, potential opportunities to disrupt the progressive nature of COPD may be forfeited.

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Recent evidence from Spain suggests that a large majority of COPD patients remain undiagnosed; when these undiagnosed patients were identified, nearly 95% of the patients had early COPD of mild and moderate severity (56.4% and 38.3% for Global initiative for chronic Obstructive Lung Disease [GOLD] Stage I and II, respectively).² In the UK, a study of adults aged over 35 years suggests that more than 80% of those meeting GOLD spirometric criteria for COPD reported having no respiratory diagnosis.³ Even among those with severe or very severe airflow obstruction, less than half were diagnosed.³

Despite being distinct conditions, COPD is often misdiagnosed as asthma due to the overlap of symptoms.^{4,5} In the UK- and US-based study by Tinkelman and colleagues,⁴ 1 in 4 patients previously diagnosed with asthma were diagnosed during the study as having COPD.

Many countries are developing methods to assist with identifying and confirming early COPD.⁶ Campaigns are in place to increase public awareness of the disease and promote the presentation of COPD symptoms by patients to their doctors. These efforts may be having an impact given recent evidence that the percentage of patients diagnosed with GOLD Stage I may be increasing.⁷ This article discusses the issues of early stage COPD, including its burden, the challenges of diagnosis, the need to identify COPD patients earlier in the course of their disease, and highlights how patients with early COPD could benefit from non-pharmacologic and maintenance pharmacologic treatment.

Early COPD and its burden

Early COPD, with symptoms that may or may not be recognised, may express itself in many ways. Regardless of the expression, it can be characterised by variable damage to lung tissue and/or airway inflammation,⁸ all or one of which can lead to spirometry changes.⁹⁻¹¹

The GOLD guidelines define the severity of COPD primarily in terms of airflow obstruction, such as forced expiratory volume in one second (FEV₁) and other spirometry parameters.¹ While these are undoubtedly useful for staging the disease, a degree of airway obstruction is not the beginning of COPD. In this article, 'early COPD' refers to the initial, insidious stages of the disease through to moderate airflow limitation (GOLD Stage II) – i.e., the earliest stage at which many patients typically first seek medical attention. Furthermore, 'earlier diagnosis' refers to identifying and diagnosing COPD before airflow limitation is so great that patients seek medical attention for that reason.

COPD at an early stage may be expressed in different ways. Some patients may appear to be asymptomatic; however, probably more accurately, asymptomatic individuals are affected in ways that are difficult to perceive or measure, and which can easily be dismissed as being attributed to

ageing. Undiagnosed GOLD stage I COPD may already show signs of impaired daily activities and health-related quality of life (HRQoL).² Undetected activity limitation leads to changes in lifestyle, deconditioning and an increased risk of social isolation and depression.^{12,13} Conversely, patients with pathological processes that may lead to COPD may be overtly symptomatic, yet show no outward signs of airway obstruction. Their symptoms may include a persistent cough (associated with an increased risk of COPD development),¹⁴ excessive sputum production or recurring chest infections, none of which are specific for COPD, thereby adding to the challenge of correct diagnosis, especially if spirometry is not used.^{15,16}

COPD exacerbations occur regularly in patients with more severe disease; however, they occur in patients with milder COPD as well.¹⁷ Patients experiencing frequent exacerbations have an accelerated loss of lung function, more rapid disease progression and decreased quality of life, compared with infrequent exacerbators.^{18,19} Exacerbations may be especially surprising and debilitating among patients with mild COPD, and substantially impact on work productivity and health resource use. Thus, the clinical, social and economic importance of COPD exacerbations cannot be underestimated and focus should be given to their prevention.^{20,21} Furthermore, the incidence of exacerbations in the early stages of COPD may be much higher than expected, since many exacerbations in milder COPD patients are likely to be unreported.^{17,22}

Predicting progression of COPD

The pioneering work of Fletcher and Peto demonstrated that the progressive and rapid decline in FEV₁ is the hallmark of COPD progression.²³ In this landmark study of working men in England, mean rates of decline in FEV₁ within the population were dependent on whether patients continued to smoke. More recent studies confirmed and extended these findings; for example, the Lung Health Study and others showed the average linear rate of FEV₁ decline in COPD is approximately 60 mL/year,²⁴⁻²⁷ which is double the rate of decline in non-COPD subjects.²⁴

While the Fletcher and Peto study suggested that the rate of FEV₁ decline becomes more rapid as COPD patients age,²³ recent evidence suggests that the rate of FEV₁ decline is greater in patients with less severe disease than those with more severe disease. Data in the appendices from the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT®) trial²⁸ suggest a more rapid rate of decline in post-bronchodilator FEV₁ in patients with GOLD Stage II versus GOLD Stages III and IV.²⁹ A similar pattern was shown in a secondary analysis from the TOwards a Revolution in COPD Health (TORCH) study of patients sub-grouped by baseline FEV₁.^{30,31}

Linking the rate of FEV₁ decline and progression of COPD to symptom severity is a rational and attractive construct for practitioners. Supporting evidence comes from recent studies demonstrating that symptomatic GOLD Stage I COPD patients exhibit a faster rate of FEV₁ decline than asymptomatic GOLD Stage I patients in whom the decline in FEV₁ is no greater than a 'normal' reference group.³² Caution must be used because often the rate of FEV₁ decline or the severity of FEV₁ limitations is an imperfect predictor of symptoms.^{24,33} The converse is also true; hence, progression of COPD in terms of symptoms may be more complex than decline in FEV₁ alone. For example, exercise tolerance³⁴ and HRQoL³⁵ are known to decline with only a weak association to FEV₁ over time.

Challenges of early diagnosis of COPD

As identified above, several key challenges hinder the early diagnosis of COPD. A first challenge is to encourage patients to recognise and present their symptoms (such as coughing, decreasing physical activity/exertion, mild breathlessness) rather than dismiss them as the result of normal physiological changes (e.g., ageing or gaining weight). Another challenge is for the physician to be attuned to the propensity to dismiss early COPD symptoms and focus solely on the acutely vexing symptoms with which patients present. A third challenge is to discern early COPD from asthma or other conditions with similar symptoms.

Finding patients with COPD earlier

Many patients are diagnosed after considerable damage has occurred to the lungs. This damage occurs slowly and the associated symptoms are typically only recognised at more severe stages (GOLD Stages III to IV). Even at this stage, COPD diagnosis may not be a first or second consideration. This has been recognised by COPD awareness initiatives such as GOLD and the US COPD Coalition,^{1,6} which attempt to raise awareness of COPD among the general public as well as medical professionals. Additionally, strategies within primary care such as active case-finding (e.g., targeting of smokers over 40 years of age with case-finding questionnaires) may have an important impact.³⁶⁻³⁸

Worldwide efforts to identify patients with COPD are providing encouraging results. The Detection, Interaction and Monitoring of COPD and Asthma project (DIMCA), being conducted in The Netherlands, screens the general adult population for COPD³⁹ as well as asthma, whilst the 'Know the Age of Your Lung' project in Poland is more targeted to at-risk populations and screens current and former smokers aged above 40 years.⁴⁰ Awareness programmes may be limited by cost; for example, the estimated cost per detected case in 'Know the Age of Your Lung' is between \$500 and \$1000, depending on the screening method.⁴¹ However, no indications of increased costs, above those of average care plus screening, are observed in the DIMCA project.⁴¹ Moreover, in the UK, opportunistic case finding in primary

care, using spirometry linked to smoking cessation, is shown to be cost effective.⁴²

Methods for early detection of COPD

Spirometry is the most reliable detection method for COPD. Case identification spirometry may improve early detection and management (including aggressive smoking cessation) by excluding patients with normal lung function and identifying patients who may require further evaluation using diagnostic spirometry.³⁶⁻³⁸ The International Primary Care Respiratory Group (IPCRG) currently recommends case identification spirometry in all patients over 35 years who present with respiratory symptoms and risk factors, such as prior or current smoking history.³⁸

Diagnostic spirometry using more stringent criteria (post-bronchodilator FEV₁/forced vital capacity (FVC) ratio of <0.7¹ versus FEV₁/FVC ≤0.8 for case-finding spirometry³⁸) should be offered to patients in whom the possibility of COPD cannot be excluded.

Despite its importance in identifying patients with COPD,^{39,43} many primary care physicians decide not to incur

Table 1. COPD questionnaire, to be used in patients presenting with a history suggestive of COPD and who are not suspected of having asthma.⁵²

		Points
What is your age?	40-49 years	0
	50-59 years	4
	60-69 years	8
	70 years or older	10
What is your height in metres? What is your weight in kilograms?	Calculated BMI <25.4	5
	Calculated BMI 25.4-29.7	1
	Calculated BMI >29.7	0
How many pack-years of cigarettes have you smoked?	0-14 pack years	0
	15-24 pack years	2
	25-49 pack years	3
	50+ pack years	7
Does the weather affect your cough?	Yes	3
	No	0
Do you ever cough up phlegm (sputum) from your chest when you don't have a cold?	Yes	3
	No	0
Do you usually cough up phlegm (sputum) from your chest first thing in the morning?	Yes	0
	No	3
How frequently do you wheeze?	Never	0
	Occasionally or more often	4
Do you have or have you had any allergies?	Yes	0
	No	3
Scoring system: Add up the total number of points based on the patient's response.		
● 16 or fewer points suggests a diagnosis other than COPD, probably asthma		
● 17 or more points suggests a diagnosis of COPD		

Table 2. Differential diagnosis of COPD.*

Diagnosis	Suggestive features
COPD	<ul style="list-style-type: none"> Onset in mid-life Symptoms slowly progressing Dyspnoea during exercise Largely irreversible airflow limitation
Asthma	<ul style="list-style-type: none"> Onset early in life (often childhood) Symptoms vary from day to day Symptoms at night/early morning Allergy, rhinitis and/or eczema also present Family history of asthma Largely irreversible airflow limitation
Congestive heart failure	<ul style="list-style-type: none"> Fine basilar crackles on auscultation Chest X-ray shows dilated heart, pulmonary oedema Pulmonary function tests indicate volume restriction, not airflow limitation
Bronchiectasis	<ul style="list-style-type: none"> Large volumes of purulent sputum Commonly associated with bacterial infection Coarse crackles/clubbing on auscultation Chest X-ray/CT shows bronchial dilation, bronchial wall thickening
Tuberculosis	<ul style="list-style-type: none"> Onset all ages Chest X-ray shows lung infiltrate Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	<ul style="list-style-type: none"> Onset in younger age, non-smokers May have history of rheumatoid arthritis or fume exposure CT on expiration shows hypodense areas
Diffuse pan-bronchiolitis	<ul style="list-style-type: none"> Most patients are male and non-smokers Almost all have chronic sinusitis Chest X-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation
<p>* These features tend to be characteristic of the respective diseases but do not occur in every case. For example, a person who has never smoked may develop COPD (especially in the developing world where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even elderly patients.</p> <p>CT = Computerised tomography; HRCT = High resolution computed tomography.</p>	

the cost of spirometry equipment; others may be intimidated by the complexity of the technology, the meaning of the results and interpretation to the patients, or may lack time and motivation.^{2,44,45} Patient questionnaires are an effective alternative, or add-on, case-finding tool for discriminating between persons with and without COPD.^{36,38,46-49} Questions include items on age, body mass index (BMI), smoking intensity, cough, phlegm, dyspnoea on exertion and wheeze, as well as prior diagnosis consistent with asthma or COPD.^{50,51} Questions on all these factors, other than dyspnoea, are included in the COPD questionnaire recommended in the IPCR guidelines³⁸ for diagnosis of respiratory diseases in primary care (Table 1).⁵² Individuals considered at risk of having early stage COPD, by either method, should be

Table 3. Differential diagnosis questionnaire to determine between COPD and asthma.^{38,56}

	Response choices	Points
What is your age?	40-49 years	0
	50-59 years	5
	60-69 years	9
How many pack years of cigarettes have you smoked?	0-14 pack years	0
	15-24 pack years	3
	25-49 pack years	7
	50+ pack years	9
Have you coughed more in the last few years?	Yes	0
	No	1
During the past 3 years, have you had any breathing problems that have kept you off work, indoors, at home or in bed?	Yes	0
	No	3
Have you ever been admitted to hospital with breathing problems?	Yes	6
	No	0
Have you been short of breath more often in the past few years?	Yes	1
	No	0
On average, how much phlegm (sputum) do you cough up most days?	None or less than 1 tablespoon (15 mL or 1/2 oz) per day	0
	1 tablespoon (15 mL or 1/2 oz) or more per day	4
If you get a cold, does it usually go to your chest?	Yes	4
	No	0
Are you taking any treatment to help your breathing?	Yes	5
	No	0
Scoring system: Add up the total number of points based on the patient's response.		
<ul style="list-style-type: none"> 18 or fewer points suggests a diagnosis of asthma 19 or more points suggests a diagnosis of COPD 		

referred for diagnostic assessment, which may require referral to specialist spirometry services.

Confirming the COPD diagnosis

The differential diagnosis for COPD can be complex. Several disorders may present with similar symptoms, signs and spirometry results (Table 2), including asthma, bronchiectasis and carcinoma of the bronchus.^{1,42} Furthermore, many of these conditions can co-exist with COPD, particularly those associated with cigarette smoking. A chest x-ray is recommended by most guidelines to assist in excluding some of these differential diagnoses (see Table 2).^{1,42,53,54}

Asthma remains the most common differential diagnosis and is difficult to distinguish from the early stages of COPD. Differentiation of asthma from COPD is confirmed through an FEV₁/FVC ratio after inhalation of a bronchodilator.^{1,42} As described above, a post-bronchodilator FEV₁/FVC ratio of less than 0.70 is indicative of COPD.¹ Bronchodilation with a short-acting β_2 -agonist is important since the prevalence of COPD

may be over-estimated by 27% if spirometry is used without bronchodilation.⁵⁵ Features from the history and examination should be used to assist in distinguishing COPD from asthma wherever possible, such as with the questionnaire for differential diagnosis of obstructive lung disease recommended in the IPCRG guidelines (Table 3).^{38,56}

Current recommendation for treating early COPD

Evidence-based guidelines recommend a step-wise approach to the treatment of COPD, involving the use of both non-pharmacologic and pharmacologic therapies.^{1,42,53,54}

Non-pharmacologic treatment

Non-pharmacologic therapies that are paramount to initial treatment success include the education of patients and the avoidance of risk factors; however, this is inconsistently provided to patients with early disease.⁵⁷ Vaccination against pneumococcal and influenza viruses is recommended for all patients.^{1,42,53,54}

Chief among non-pharmacological interventions is smoking cessation, which is essential in reducing lung function decline and has been shown to be beneficial even among the heaviest of smokers.^{24,33} The benefits of smoking cessation, notably on survival and disease progression, may be less evident in patients with more established disease, and may instead be restricted to milder, asymptomatic patients with measurable lung function impairment.⁵⁸ This was demonstrated in the 30-year follow-up data from a population cohort from the Seven Countries study,⁵⁹ in which significant reductions in mortality were observed in men aged 40-59 with impaired lung function who gave up smoking. The study demonstrated the likely changes that patients may experience following smoking cessation; however, it is possible that these benefits may not extend to all patients and some may not experience any change, regardless of their COPD stage.

All guidelines recommend that patients increase their physical activity levels.^{1,42,53,54} Structured exercise programmes improve exercise potential in more severe patients⁶⁰ through reduced hyperinflation and muscle conditioning; when initiated in early stage disease, exercise is likely to improve future disability.⁶¹ Nevertheless, the value of physical activity may be poorly communicated and/or underappreciated by prescribing physicians, or be forgotten by some patients, since only a minority of patients report receiving this advice.⁵⁷ Interventions in early COPD need to assist in changing a patient's attitudes to smoking and exercise. Performance enhancement through exercise may improve a patient's sense of health and initiate a positive cycle of activity and well-being that would otherwise be a cycle of decline.

Pharmacologic treatment

Pharmacologic therapy is crucial to the success of COPD management. Short-acting bronchodilators, as required, are recommended for breathlessness or reduced exercise capacity,

regardless of airway obstruction.^{1,42,53,54} Maintenance therapy with long-acting bronchodilators (defined as medication taken regularly when symptoms are more than just intermittent) is recommended to manage chronic airflow limitation and symptoms.^{1,42,53,54} Exacerbations, if they occur during the course of maintenance therapy with one or more long-acting bronchodilators, may be additionally prevented by regular administration of inhaled corticosteroids.^{1,42,53,54}

Potential advantages/disadvantages of maintenance treatment in early COPD

Much of the data supporting guidelines on pharmacologic interventions are derived from studies at least three years old and most often comprised of patients with severe COPD. However, recent investigations suggest greater benefits of identifying and treating COPD earlier rather than later.^{29,31,62}

Multiple reports demonstrating improvements in lung function, dyspnoea and quality of life, reduced risk of exacerbations, and possibly decreased rate of lung function decline through earlier pharmacologic intervention, make it difficult to uphold the traditional pessimistic view that COPD is a disease that responds poorly to treatment.⁶³ This seems particularly true in patients with early COPD. Maintenance bronchodilator treatment in patients with FEV₁ ≥50% predicted (GOLD Stage II) clearly improves lung function (FEV₁) to an extent greater than placebo,^{62,64} which also extends to patients with an FEV₁ of ≥60% predicted.⁶⁵ A reduction in the frequency of exacerbations in patients with milder COPD is also suggested.^{62,64,66}

Subanalyses from the UPLIFT® study demonstrate similar findings. For example, FEV₁ improvements were greater in patients with GOLD Stage II COPD²⁹ than the overall study population.²⁸ These results were similar to those observed in the TORCH study in which greater improvements in FEV₁ in response to chronic maintenance therapy were observed in GOLD Stage II patients compared with GOLD Stage III or IV.³¹ Improvements in lung function yielded greater improvements in the risk of exacerbations,²⁹ the number of exacerbations per year,^{29,31} and hospitalisations resulting from exacerbations²⁹ than similarly treated patients with either GOLD Stage III or IV. Maintenance pharmacologic therapies, given in the early stages of COPD may also improve the rate of FEV₁ decline.²⁸⁻³¹ Other secondary analyses of UPLIFT® suggest greater improvements in FEV₁, rate of decline in post-bronchodilator FEV₁, and symptoms, in COPD patients less than 50 years old,⁶⁷ as well as those in which tiotropium was administered as first-line maintenance treatment of COPD.⁶⁸

Considerations for future investigation of early maintenance treatment

Although interest in maintenance treatment in earlier COPD is

increasing, much work is required before evidence-based guidelines are able to assess its potential adequately. Future trials could rigorously investigate the combined effects of maintenance pharmacotherapy, education and exercise management programmes in patients who have mild COPD. Furthermore, there is a requirement for additional studies in symptomatic GOLD Stage I patients with respect to quality of life, activity limitation, and response to management. Investigations in patients 'at risk' of COPD could follow patients longitudinally over a number of years so that progression of COPD can be re-assessed in the context of recent longitudinal investigations designed with different purposes.

COPD is frequently associated with several co-morbidities, including vascular disease, osteoporosis, metabolic imbalances and depression.⁶⁹ While the causal relationship between COPD and co-morbidities is not entirely clear, inactivity and systemic inflammation have been suggested as part of the mechanism for the co-morbidities associated with COPD and may relate to the natural course of the disease.^{14,69-73} For example, the incidence of early vascular disease is increased in people with COPD compared with smokers without COPD or non-smokers.⁷⁴ Investigations that focus on the link between early COPD and the development of co-morbid conditions may be of considerable clinical value. Finally, another important question for study may be to determine the impact of the use of maintenance treatment on patient behaviours such as exercise and smoking.

Conclusions

Mounting evidence suggests that early detection, diagnosis, and maintenance treatment of COPD, alongside smoking cessation and exercise, may help provide the best symptom control, disease progression (whether spirometric or symptomatic) and outcomes in COPD. Specific, rigorous, clinical investigations testing this hypothesis should now be conducted to solidify the existing evidence. Early diagnosis of COPD should be viewed as an essential component of COPD care; primary care is the most pragmatic clinical setting in which this can be achieved. Case identification of patients with COPD risk factors and symptoms may be the most practical way to achieve early diagnosis. This requires changing attitudes of both physicians and patients, and raising awareness of COPD. Recognition of COPD symptoms, including mild limitations of physical activity, as well as others which are overlooked in early disease, needs to be at the forefront of physicians' minds when examining patients at risk of COPD, who often present for other ailments.

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