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REVIEW

Co-morbidities of COPD in primary care: frequency, relation to COPD, and treatment consequences

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Abstract

Introduction: In the Western world, chronic obstructive pulmonary disease (COPD) is predominantly caused by long-term smoking, which results in pulmonary inflammation that is often associated with systemic inflammation. A number of co-morbid conditions, such as cardiovascular disease, muscle wasting, type 2 diabetes and asthma, may coexist with COPD; these and other co-morbidities not directly related to COPD are major causes of excess morbidity and mortality.

Aim: This review sets out to explore the most frequent co-morbidities in COPD and their implications for treatment.

Method: Review of the literature on co-morbidities of COPD.

Results: Co-morbidities are frequent, but often remain undiagnosed in the COPD patient. In order to provide the best possible care for people with COPD, the physician should be aware of all potential co-morbidities that may arise, and the critical role that effective management of these co-morbidities can play in improving patient outcomes.

Conclusions: Increased awareness of the potential co-morbidities of COPD, although potentially adding to the general practitioner's work burden, may provide insights into this difficult disease state and possibly improve each individual's prospects for effective management.

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Keywords COPD, diagnosis, co-morbidities, asthma, systemic inflammation

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation caused by noxious particles or gases, most commonly cigarette smoke in the Western world.[1] A recent population-based cohort study of elderly smokers and non-smokers indicated that 1 in 4 men and 1 in 6 women went on to develop pulmonary obstruction,[2] although it is unclear how many of these individuals subsequently developed a clinical diagnosis of COPD. Whilst at least 50% of smokers will develop some degree of airflow limitation,[3] the disease is not characterised by airflow limitation alone. Patients with COPD often suffer from bronchitis-like symptoms and most patients also have pathophysiological changes in the lung that are associated with emphysema.[4] The availability of several treatment guidelines has provided physicians with different definitions of COPD in which post-bronchodilator obstruction

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plays a pivotal role.[1,5] However, a clinical diagnosis of COPD also includes a history of smoking and/or exposure to risk factors such as pollutants or occupational dusts.[1,5] COPD sufferers tend to be elderly and are likely to have multiple chronic health conditions, which can further complicate diagnosis for the primary care clinician. As a result, COPD remains difficult to diagnose and manage.[6] Furthermore, diagnosis tends to occur at a late stage in the disease process, limiting the opportunity to prevent deterioration.[7]

In addition to COPD, smoking can also cause or influence the severity of many other diseases. Patients with COPD can therefore have multiple coexisting co-morbidities that extend beyond the lung. Although the initial diagnosis of COPD is often made on the basis of respiratory symptoms in combination with spirometry, general practitioners (GPs) need to be mindful of the presence of the common co-morbidities associated with COPD to ensure optimal patient care. Generally, patients seeking help for their respiratory symptoms in primary care are not in advanced stages of COPD, but may have an elevated risk of associated co-morbidities.[8] The consequences of these co-morbidities are different from those seen in tertiary care, where patients have more severe COPD with a greater number of, and

Table 1. Components of systemic inflammation in chronic obstructive pulmonary disease (COPD).[13]

Inflammatory marker	Details
Cytokines	
Interleukin-6	• Increased systemic circulation of patients with COPD, particularly during exacerbations • Induces release of acute phase proteins • Functional effects uncertain – evidence of skeletal muscle weakness
Tumour necrosis factor-α (TNF-α)	• Plasma TNF-α and its soluble receptor increased in COPD • Released from circulating cells in COPD patients with cachexia • Circulating TNF-α is related to hypoxaemia • Increased systemic TNF-α implicated in cachexia, skeletal muscle atrophy and weakness in COPD
Interleukin-1β (IL-1β)	• Although IL-1β has been linked to cachexia, increased plasma concentrations or decreased concentrations of its endogenous antagonist IL-1 receptor antagonist have not been seen in COPD • Association between COPD and an IL-1β gene polymorphism noted
Chemokines	• Roles in neutrophil and monocyte recruitment in COPD • Increased circulating concentrations of CXCL8 related to muscle weakness
Adipokines	• Leptin has an uncertain role in cachexia • Ghrelin is elevated in cachectic patients with COPD
Acute-phase proteins	
C-reactive protein	• Increased plasma levels seen in COPD, particularly during exacerbations • Increased levels correlate with health status, exercise capacity, body mass index and cardiovascular risk • May be involved in innate defence against *Streptococcus pneumoniae* • No correlation with progressive decline in FEV_1 (forced expiratory volume in 1 second)
Fibrinogen	• Increased plasma levels in patients with COPD with frequent exacerbations and are related to worse FEV_1 and increased risk of hospitalisation
Serum amyloid A	• Increased during exacerbations, levels correlate with exacerbation severity • Part of the innate defence mechanism against bacterial infections • Pro-inflammatory effects
Surfactant protein D	• Role in innate defence against microorganisms • Increased serum concentrations in COPD • Better related to disease severity and symptoms than C-reactive protein • Derives from lung tissue – evidence that lung inflammation leads to inflammatory changes in the systemic circulation
Circulating cells	
Monocytes	• Recruited to the lung by chemotactic factors, where they differentiate into the macrophages that drive COPD • Greater macrophage accumulation seen in the lungs of patients with COPD than in normal smokers
Neutrophils	• Inverse correlation between circulating neutrophil numbers and FEV_1 • Turnover may be increased in smokers • Enhanced production of reactive oxygen species in COPD • Increased chemotactic responsiveness and proteolytic activity in emphysema
Lymphocytes	• Changes in circulating lymphocytes difficult to interpret • Increased apoptosis of peripheral T-lymphocytes from COPD patients • Circulating γδ T-cells increased in normal smokers but not in COPD
Natural killer cells	• Reduced cytotoxic and phagocytic function in COPD – uncertain significance

more severe, co-morbidities.[9]

One of the most frequently reported co-morbidities of COPD is asthma.[1,10] Both COPD and asthma are major chronic obstructive airway diseases that involve underlying airway inflammation, but the type of inflammatory process differs;[11] the airway inflammation in asthma is typically reversible and is typically eosinophilic, whereas COPD is characterised by neutrophilic inflammation that does not respond well to standard asthma therapies.

Although the association between COPD and its systemic co-morbidities is not fully understood, it may involve the persistent, low-grade pulmonary and systemic inflammation seen in COPD.[12] This systemic inflammation is independent of cigarette smoking status, and persists after smoking cessation. The inflammatory markers that can be detected in COPD have been speculated to represent a 'spill over' from the lung (see Table 1).[13] However, these inflammatory components are also known to result from direct systemic exposure to particulate pollutants.

Since all coexisting diseases may influence the perceived severity of COPD and alter COPD treatment, this review sets out to explore the most frequent co-morbidities and their implications for treatment.

Prevalent co-morbidities of COPD seen in general practice

Patients with COPD are at increased risk of a range of co-morbid conditions, and a high baseline rate of these co-morbidities has been reported in newly diagnosed patients compared with matched controls.[14] These conditions may share a common pathophysiology with COPD (e.g. smoking-related diseases), a complicating co-morbidity (e.g. pulmonary hypertension), a coincidental co-morbidity that is unrelated to the pathogenesis of COPD (e.g. age-related disorders such as prostate cancer) or an intercurrent co-morbidity that has a greater impact in patients with COPD (e.g. upper respiratory tract infections).[1]

Patients with COPD may suffer from chronic cough and sputum for many years without seeking treatment, typically presenting symptoms to their GP only when they experience dyspnoea that interferes with their daily activities. In primary care, COPD may be diagnosed at any stage,[15] depending on the physician's experience and level of interest in COPD. Indeed, it has been suggested that patients with chronic cough and sputum production may define a specific phenotype at risk of COPD exacerbations.[16,17]

The co-morbidities of COPD are associated with increased morbidity and mortality; indeed, co-morbidities such as cardiovascular disease and lung cancer are a major cause of mortality in COPD, particularly in mild-to-moderate disease.[18] Table 2 presents an overview of the diagnostic techniques that can be used by the GP to verify the presence of co-morbidities in COPD. The physician should be aware that some of these conditions (such as low bone mass) may be asymptomatic, while depression and heart failure are the most disregarded co-morbidities of COPD in primary care.

A number of studies have investigated the types of co-morbidities observed in patients with COPD (see Table 3).[14,19,20] On the basis of these findings, the following chronic co-morbidities appear to be the most common. However, as highlighted by Soriano *et al.*, it is also important to remain aware of the potential for acute events, such as pneumonia, in these patients.[14]

Asthma

COPD and asthma are distinct diseases and, therefore, can coexist in the same patient.[21] Inflammation of the bronchial tree, although different in origin, can cause tissue injury in both diseases and structural abnormalities may develop. Although these structural abnormalities differ, with smooth

Table 2. Diagnostic techniques for the identification of co-morbidities in chronic obstructive pulmonary disease (COPD).

Co-morbidity	Diagnostic techniques/key issues and features
Asthma	Time of onset (<40 years), very frequent allergy, hyperresponsiveness, reversible symptoms
Cardiovascular disease	Atherosclerosis: physical examination, blood testing (cholesterol, blood sugar and low-density lipoprotein levels), electro- or echocardiography, radiography of the chest, CT scan, coronary angiography or ultrasonography, ankle/brachial index, exercise stress test or nuclear stress test Chronic heart failure (COPD patients with clinical deterioration): plasma B-type natriuretic peptide *Cor pulmonale*: physical examination
Depression and anxiety	Clinical COPD Questionnaire (CCQ), Primary Care Evaluation of Mental Disorders (PRIME-MD) patient health questionnaire, the Patient Health Questionnaire-9 (PHQ-9), the Zung Self-Rating Depression Scale, Hospital Anxiety and Depression Scale, the Depression and Anxiety Stress Scale and the Beck Anxiety Inventory
Body mass	Loss of fat-free mass
Osteoporosis	Dual-energy X-ray densitometry
Lung cancer	Work up according to guidelines

Table 3. Prevalence of common co-morbidities found in patients with chronic obstructive pulmonary disease (COPD).

Study		Prevalence rate (%)		Statistical data
		COPD patients	Controls*	
				Odds ratio
Sidney *et al*.[19]	Asthma	40.0	2.6	24.71
	Congestive heart failure	7.2	0.9	8.48
	Ventricular tachycardia/fibrillation or cardiac arrest	0.8	0.1	7.94
	Pulmonary embolism	0.3	0.1	4.69
	Myocardial infarction	1.8	0.4	4.42
	Atrial fibrillation	4.7	1.1	4.41
Sin & Man[20]**	Diabetes mellitus	17.2	13.0	
	Congestive heart failure	5.1	4.9	–
	Probable/possible prior myocardial infarction	22.7	14.6	–
				Relative risk
Soriano *et al*.[14]	Cardiac	22.6	–	4.01
	Respiratory, thoracic and mediastinal	29.0	–	3.14
	Hepatobliliary	1.0	–	2.89
	Infections and infestations	39.2	–	2.13
	Psychiatric	10.6	–	1.98
	Immune system	4.8	–	1.78

* If data available.
** Combined data from patients with mild, moderate, or severe airflow obstruction.

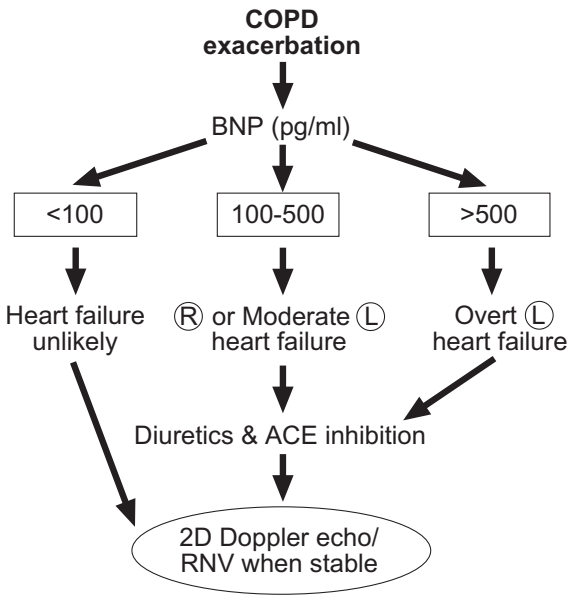
muscle proliferation seen in asthma and alveolar destruction in COPD, the net result of a decline in the forced expiratory volume in one second (FEV_1) is the same.[22]

The most practical features in distinguishing between asthma and COPD in general practice are age of onset (young in asthma, over 45 years in COPD), atopy (asthma), a relevant smoking history (COPD) and possibly a different symptom pattern.[23] In a Dutch analysis of GP patient lists, around 10% of patients using an inhaled medication had both COPD and asthma as assessed by an independent pulmonologist.[24] The combination of COPD and asthma can complicate both diagnosis and treatment.[25] In a Belgian survey of 26 GPs, 30% of patients with asthma and 38% with COPD had their diagnosis changed to the combination of asthma and COPD following re-examination.[26] This illustrates that, in general practice, asthma and COPD are frequent co-morbid conditions and that GPs have difficulty in diagnosing these conditions, particularly when they coexist. Indeed, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recognise that a clear distinction between chronic asthma and COPD cannot be made in all patients, and that some of these patients should be managed in a similar way to those with asthma.[1] In the same Belgian survey, it was found that GPs prescribe inhaled corticosteroids (ICS) in 80% of patients with asthma, 72% in patients with asthma and COPD and 63% in patients with COPD.[26] In many cases, GPs seem to be following the GOLD guidelines in this respect. Although there is very little evidence about the best treatment for patients with coexisting COPD and asthma, the best current strategy is to follow the guidelines and treat both diseases. The Dutch hypothesis states that airway obstruction – such as is found in COPD, asthma and emphysema – forms part of a single disease entity in which both endogenous and exogenous factors play a role in pathogenesis.[27] A British hypothesis was subsequently put forward stating that asthma and COPD were distinct diseases generated by different mechanisms.[28] Debate continues as to the true relationship between these diseases; whilst it is likely that there is some genetic basis to both asthma and COPD,[29] inhalation of noxious particles remains a key event in the development of COPD. Asthma is a risk factor for COPD,[1,30] and adults with asthma have a 12-fold higher risk of acquiring COPD than those without asthma, after adjusting for smoking status.[31] However, a number of asthma patients who smoke will develop irreversible obstruction, but may not exhibit the typical characteristics (cough, sputum and dyspnoea) of COPD.[32]

Cardiovascular disease

Cardiovascular disease is one of the most common co-morbidities associated with COPD, and chronic heart failure may remain undiagnosed in these patients as shortness of breath and fatigue are attributed to COPD.[33] Cardiovascular disease becomes more prevalent with increasing COPD severity, with a higher incidence of arrhythmia, ischaemic heart disease, angina and congestive heart failure found in patients with more severe COPD. These patients with more severe COPD are almost twice as likely to die of cardiovascular causes than those with less severe disease.[34] Four independent clinical variables for concomitant heart failure in COPD can be measured in the primary care setting: history of ischaemic heart disease, high body mass index (BMI), laterally displaced

Figure 1. Diagnostic utility of type B brain natriuretic peptide (BNP) in evaluating chronic heart failure in exacerbations of chronic obstructive pulmonary disease (COPD). Reproduced with permission from Le Jemtel *et al*.[33]



2D: 2-dimensional; ACE: angiotensin-converting enzyme; L: left-sided heart failure; R: right-sided heart failure; RNV: radionuclide ventriculography.

apex beat, and raised heart rate.[35] Additional measurement of N-terminal pro-brain natriuretic peptide (BNP) adds to the diagnostic value of these parameters (Figure 1).[33,35]

Patients with COPD are at risk of worse outcomes after myocardial infarction compared with those without COPD,[36] possibly because alterations in pulmonary vessel structure and function are prevalent in these patients and lead to lower survival rates and poorer clinical evolution. Mild-to-moderate pulmonary hypertension may be present in the later stages of COPD and can progress to right ventricular hypertrophy and *cor pulmonale*.[37,38] Transient increases in pulmonary artery pressure may also occur during exacerbations, exercise and sleep.[37,38]

COPD is also an important risk factor for atherosclerosis.[20] Given this association, it has been suggested that patients with COPD should be screened for the presence of atherosclerotic disease and vice versa.[13] However, studies have not reported a significant association between airway obstruction and ischaemic stroke.[39,40]

Depression

In stable COPD, clinical depression and anxiety are seen at prevalences of 10–42% and 10–19%, respectively, with higher rates seen in more severe disease and in patients recovering from an acute exacerbation.[41,42] Patients with COPD are at risk of depression related to their marked and progressive functional impairment, the systemic effects of tobacco smoking, and possibly the systemic inflammation associated with COPD.[12,23,43] In COPD, depression and anxiety are largely untreated and lack of effective treatment can affect compliance, which may lead to increases in primary care consultations and the frequency or length of hospitalisation.[41]

Depressive symptoms are also an independent prognostic factor for all-cause mortality in stable COPD.[44] Primary care physicians may use additional help in the management of these symptoms, but options for best treatment are unclear. As with general depression and anxiety, these symptoms in COPD are managed using pharmacotherapy[45] and cognitive behavioural therapy,[46] although mixed results have been obtained with these approaches. Interestingly, there is evidence that pulmonary rehabilitation can improve psychosocial morbidity in COPD, including depression.[47]

BMI

Body Mass Index (BMI) is an important factor in many chronic conditions and is a strong independent predictor for mortality.[48] Underweight patients are a minority in COPD, and many patients with chronic bronchitis have a high BMI. Patients with a low BMI are at greater risk of mortality in COPD, while a high BMI may partially reduce the risk of mortality; the loss of excess weight can improve health status, irrespective of underlying lung function. Around 14% of patients with COPD suffer from both loss of body weight and depletion of fat-free mass, though the latter may also occur in normal-weight patients.[49,50] Schols *et al*. found that such patients also exhibit decreased creatinine height index and suffer from physical impairment, suggesting that fat-free mass may be a better indicator of body mass depletion than body weight.[50] Loss of fat-free mass has an adverse effect on respiratory and peripheral muscle function, exercise capacity and health status in COPD,[51] and has been identified as an independent predictor of mortality, irrespective of fat mass.[50]

Diabetes mellitus type 2

The risk of developing type 2 diabetes is increased in patients with COPD,[52] even in those with mild disease.[53] Recent evidence suggests that elevated levels of pro-inflammatory molecules present in COPD, such as C-reactive protein, interleukin-6 and tumour necrosis factor-α (TNF-α), may contribute to an altered metabolic state and insulin resistance. Hotamisligil reported that TNF-α, a key inflammatory mediator in the process of muscle wasting, promotes cachexia by reducing peripheral insulin action.[54] Muscle loss and decreased fat oxidative capacity lead to further muscle loss and fat gain which, in turn, elevate TNF-α levels and so escalate insulin resistance and muscle loss.

Other co-morbidities

Patients with COPD are at increased risk of malignancy, particularly lung cancer, and the risk increases with decreasing FEV_1.[55,56] This association cannot be ascribed purely to the

Table 4. Potential drug interactions and adverse events in patients with co-morbid chronic obstructive pulmonary disease (COPD).

COPD drug	Potential complications
β_2-agonists	Pulmonary effects may be blocked by β-blockers in COPD, and may produce severe bronchospasm in patients with reversible obstructive airways disease. This may impact on treatment of chronic heart failure in patients with COPD β_2-agonists used in COPD may precipitate cardiac rhythm disturbances (rare)[69] Hypokalaemia may be seen when β_2-agonists are coadministered with thiazide diuretics or corticosteroids[75] Acute hypotension may be seen when salbutamol is coadministered with methyldopa,[61] and coadministration with salbutamol may reduce plasma concentrations of digoxin[64]
Theophylline/ aminophylline	Theophylline should be used with extreme caution in patients with cardiac arhythmias[69] Theophylline clearance is reduced in elderly patients (>60 years) and patients with congestive heart failure or cor pulmonale, and increased in elderly smokers[70,76]
Oral and inhaled corticosteroids	Use of oral and inhaled corticosteroids may be associated with a decrease in bone mineral density and an increased risk of pneumonia Oral corticosteroids may be associated with steroid myopathy, which contributes to muscle weakness, decreased functionality and respiratory failure, and with hyperglycaemia[65,71] The use of oral corticosteroids concomitant with a range of drugs that may be used in comorbid patients (e.g. high-dose aspirin,[68] diuretics, warfarin[67]) may be associated with drug–drug effects[62]
Anticholinergics	Reports of increased risk of cardiovascular death, myocardial infarction and stroke in patients with COPD[74]
Long-acting β_2-agonists/ inhaled corticosteroids (ICS) combination	Use with caution in patients with severe cardiovascular disorders, heart rhythm abnormalities, diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia, or those predisposed to low serum potassium levels (may cause cardiac arrhythmias, mild transient reduction in serum potassium, and increases in blood glucose levels).[63,66] Treatment with ICS, both alone or in combination with LABAs, may increase the likelihood of pneumonia[65,72]
Macrolide and quinolone antibiotics	May be associated with adverse cardiovascular events, such as QTc prolongation[73]

shared risk factor of tobacco smoking, as lung cancer is more common among never-smokers with COPD than non-smokers.[57]

COPD is associated with increased bone loss and risk of fracture, with 35–72% of patients estimated to have osteopenia and 36–60% osteoporosis.[58] Osteoporosis can be detected in mild COPD, and its prevalence increases with disease severity.[58,59] The increased prevalence of low bone mineral density in COPD may be associated with shared risk factors, including smoking, age, limited physical activity, oral corticosteroid use and malnutrition/low weight, but other pathophysiological factors such as chronic inflammation may also be involved.[59] As an osteoporotic fracture increases the risk of subsequent fractures,[60] and as fractures may further compromise lung function and decrease mobility,[58] the early identification of osteoporosis is important to avoid excess physical impairment in COPD.

In general, low physical activity is common in COPD patients and occurs as a result of several factors, including dyspnoea and obesity. Lack of exercise leads to further decline in lung function, health status and quality of life. Primary care physicians should encourage patients to become more active, as enhanced physical activity can be one of the most fruitful interventions in obese patients with COPD.[15]

Drug interactions in patients with COPD and associated co-morbidities

As elderly patients with COPD typically receive a number of drugs, there is the potential for drug interactions in these patients. Reducing the number or doses of drugs in patients with COPD is often not possible, even when symptom control has been achieved. Furthermore, the progressive decline in lung function, the identification of co-morbid conditions, and advancing age in elderly patients, typically necessitates the introduction of additional therapies.[1] Table 4 lists the possible drug interactions in patients receiving different types of therapy for COPD;[61-76] these should be borne in mind, particularly when treating elderly patients with multiple co-morbidities.

One potential interaction of particular interest is between selective β-blockers and β_2-agonists, which are often used together in patients with COPD. However, despite the theoretical counteractive effect of these drugs, there is little evidence of clinical problems arising from this combination. Indeed, a recent Dutch study of COPD patients undergoing major vascular surgery between 1990 and 2006 found that patients who did not receive cardioselective β-blockers were twice as likely to die within 30 days of surgery than treated patients.[77] During long-term follow-up, 67% of patients who did not receive β-blockers died, compared with 40% of COPD patients receiving these drugs.

Finally, although many patients with COPD use ICS, little is known about the local and systemic adverse effects of ICS in patients with COPD, and the patient factors (such as personality) that can affect the reporting of these adverse events.[78]

Conclusions

The routine screening of patients with COPD for the presence of all potential co-morbidities is not currently recommended in COPD management guidelines. However, GPs should be aware that multiple co-morbidities may coexist in their patients with COPD and that assessment of these patients should not end with the measurement of pulmonary function and health status. Increased vigilance is needed to ensure that co-morbidities are recognised and, where possible, managed appropriately.

Conflict of interest declarations

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