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Does COPD stand for “COmorbidity with Pulmonary Disease”?

Lowie E.G.W. Vanfleteren

Affiliation: CIRO+, Research and Development, Horn, The Netherlands.

Correspondence: Lowie E.G.W. Vanfleteren, CIRO+, Hornerheide 1, Horn, 6085NM, The Netherlands. E-mail: lowievanfleteren@ciro-horn.nl



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COPD is part of a multimorbid disease network in which chronic diseases develop in response to common risk factors <http://ow.ly/AYt2Y>

Treating chronic obstructive pulmonary disease (COPD) as a pulmonologist may lead to existential questions. What's in the name “COPD” when it is only a disease label of a complex and heterogeneous group of patients who merely have persistent airflow limitation in common? What can I do as a “pulmonologist” when my patient with COPD suffers from multiple other diseases treated with numerous drugs that all together impact on his or her well-being? For those who deliver COPD care, it is time to zoom out and get an overview of the organism after a detailed focus on the organ. This without forgetting the human involved [1].

The complexity of COPD needs to be addressed, including specific phenotypes, such as α_1 -antitrypsin deficiency and suppletion [2], (endoscopic) lung volume reduction in severe hyperinflation [3], noninvasive ventilation in chronic respiratory failure [4], and optimal exacerbation prevention in frequent exacerbators [5]. In addition, we also need to realise that a COPD phenotype is not limited to the expression of the pulmonary disease itself. Other physical manifestations and the presence of chronic noncommunicable diseases need to be appreciated in our approach to characterising the patient with COPD.

There is an increased awareness that healthcare and social systems are progressively confronted with coincidental chronic diseases and that this so-called multimorbidity is one of the major challenges facing healthcare systems in the next decades [6]. Nevertheless, we do not always need to disentangle the different morbidities into single diseases and treatments. Rather, we want to increase our understanding of the coexistence of these morbidities with their treatments and impact in our patients. Today, there is very little evidence that one chronic disease dominates or is the cause of the other chronic disorders. It is more likely that various chronic diseases develop at different speeds in response to common risk factors, such as smoking, alcohol, diet, pollution and physical inactivity [7]. All contribute, to some extent, to a process of early development of different disorders, which has been referred to as accelerated ageing [8]. In subjects with COPD, multiple morbidities co-exist and patterns can be recognised, which also suggest common pathophysiological pathways (fig. 1). Moreover, the beneficial cross-effects of certain treatments for different morbidities are food for thought for the understanding of the coexistence of morbidities. For example, the potential beneficial effects of β -blockers [10], thrombocyte aggregation inhibitors [11], angiotensin-converting enzyme inhibitors [12] and metformin [13] in subjects with COPD.

In the context of COPD within complex multimorbidity, the study by GERSHON *et al.* [14] in this issue of the *European Respiratory Journal* highlights an important dimension of real-life COPD healthcare. Using a 4-year, longitudinal, Canadian, health-administrative databank of >7 million adults, they found that the 13% of subjects with COPD were responsible for a fifth of all psychiatric, musculoskeletal or diabetic, a third of all lower respiratory tract infection and cardiovascular disease, and over half of all lung cancer

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	Renal impairment %	Anaemia %	Hypertension %	Obesity %	Underweight %	Muscle wasting %	Hyperglycaemia %	Dyslipidaemia %	Osteoporosis %	Anxiety %	Depression %	Atherosclerosis %	Myocardial infarction %
Renal impairment (n=47)		6	49	9	32	45	43	36	38	13	11	47	11
Anaemia (n=11)	27		45	36	9	18	64	18	36	18	18	73	0
Hypertension (n=103)	22	5		27	12	23	58	35	26	20	16	62	12
Obesity (n=50)	8	8	56		0	0	72	42	18	12	18	72	4
Underweight (n=30)	50	3	40	0		93	37	27	57	21	4	17	3
Muscle wasting (n=60)	35	3	40	0	47		42	22	55	33	14	29	9
Hyperglycaemia (n=116)	17	6	52	31	10	22		41	29	22	20	55	12
Dyslipidaemia (n=77)	22	3	47	27	10	17	62		20	14	18	63	11
Osteoporosis (n=66)	27	6	41	14	26	50	52	23		29	23	49	13
Anxiety (n=43)	14	5	47	14	14	44	58	26	42		40	46	12
Depression (n=33)	15	6	49	27	3	24	67	42	42	52		70	19
Atherosclerosis (n=106)	20	8	57	31	5	15	57	43	28	17	21		14
Myocardial infarction (n=19)	26	0	63	11	5	26	68	42	42	29	35	75	

FIGURE 1 The frequencies of objectively identified comorbidities in chronic obstructive pulmonary disease (COPD) patients with each of 13 selected specific comorbidities. VANFLETEREN *et al.* [9] actively searched for comorbidities in patients with COPD and found that specific comorbidities tended to cluster together. For example, osteoporosis and low muscle mass are highly prevalent in subjects with a low body mass index (BMI) but almost absent in obese subjects. Hyperglycaemia, dyslipidaemia and atherosclerosis are highly prevalent in obese subjects with COPD but less so in those with low BMI. These findings emphasise that comorbidity is more the rule than the exception and that there are patterns in the coexistence of different morbidities that might be helpful to consider specific morbidities when another is present. Reproduced and modified from [9] with permission from the publisher.

ambulatory care visits, emergency department visits and hospitalisations. People with COPD had more health service claims for comorbid disease than for COPD itself. However, there are several issues with these so-called real-world data and they need to be interpreted cautiously: this was a retrospective analysis; the diagnosis of COPD did not include spirometry; the diagnosis of all other comorbidities was also based on physician-reported International Classification of Disease (10th edition) coding; and multiple diagnoses were pooled together. Nevertheless, these data emphasise that subjects with COPD place a significant burden on the healthcare system through the management of comorbidities. It has been shown previously that subjects with COPD are at increased risk of hospitalisation and mortality when comorbidity is present. MANNINO *et al.* [15] reported that COPD patients with hypertension, diabetes or cardiovascular disease had increased risk of hospitalisation or mortality compared with subjects with similar lung function impairment without comorbidity. DIVO *et al.* [16] observed that 12 specific comorbidities were significantly associated with an increased risk of death in patients with COPD.

COPD, as a component of multimorbidity, seems to be an important indicator of the disease burden individually and for our society. It is likely that COPD, in itself, influences the amount of health services used for other diseases, as, for example, subjects with heart failure or lung cancer have increased frailty and less physical or pulmonary reserves to tolerate disease expressions, and consequently require earlier medical attention. This is corroborated by the presence of COPD in >60% of the hospitalisations for lung cancer and >40% of the hospitalisations for cardiovascular disease in the study by GERSHON *et al.* [14]. Previously, it was

also shown that subjects with ST-elevation myocardial infarction and concomitant COPD are at greater risk of death and hospital readmission due to cardiovascular causes than patients without COPD [17].

Similarly, COPD was found in 47% of male veterans with hip fractures, and was associated with increased risk of death and complications. Moreover, osteoporosis was known pre-fracture in only 3% [18]. In that study, general anaesthesia and delays to surgery were significant modifiable risk factors [18].

In addition, it is well known that smoking rates among people with mental health diagnoses are disproportionately high, ranging from 40% to 50% for diagnoses of depressive and anxiety disorders, to around and above 70% for diagnoses among people with schizophrenia [19, 20]. As a consequence smoking-related diseases, including COPD, constitute a considerable cause of morbidity and excess mortality in the severely mentally ill. Heavy smoking among these people is recognised as a threat of a widening health gap and a call for awareness has been published [19]. Many mental health professionals regard smoking as a phenomenon that belongs, somehow, to the “other side”, namely the area of physical health, occupying a space outside the direct spectrum of their influence and responsibility [19].

Patients with comorbid COPD are at a much higher risk of morbidity and mortality and, thus, require special attention. Therefore, it is of utmost importance that other physicians with other areas of interest have also knowledge of the disease COPD and its consequences. It is important to recognise a potential COPD case, intervene on smoking and refer the patient for further evaluation. It is also important, when subjects with COPD are hospitalised for other reasons, to recognise COPD exacerbations, to continue inhalers, to know the consequences of oxygen therapy and to start early mobilisation.

Respiratory-orientated care providers need to realise first what are the most important, undiagnosed and impactful morbidities in patients with COPD, and secondly, to know how should we manage them appropriately. We need to realise that those morbidities are highly prevalent in subjects with COPD but are mostly undiagnosed. Indeed, the presence of COPD may throw sand in our eyes because of similar symptomatology or due to the physician, who may feel assured of a diagnosis that can presumably explain the symptoms. Echocardiographic abnormalities are highly prevalent and often unknown in patients with COPD [21], and up to one in five patients has unknown ventricular dysfunction that impacts on survival [22]. A simple diagnostic tool, such as a resting ECG, might show evidence of old ischaemia that was previously undiagnosed [23]. All patients with COPD should receive a minimal cardiovascular check-up (e.g. blood pressure, (exercise) ECG, N-terminal pro-brain natriuretic peptide, and echocardiography when clinically indicated). In addition, many COPD exacerbations are accompanied by cardiac ischaemia [24]. The differential diagnosis of increased symptoms in a patient with COPD is broader than the diagnostic spinal reflex of a COPD exacerbation [25]. Fasting-state blood analysis is an easy-to-perform test that can reveal multiple relevant comorbidities like dyslipidaemia, hyperglycaemia, anaemia and impaired renal function [9]. In subjects with COPD and low body weight, osteoporosis is highly prevalent and should be investigated [9, 26], which may improve diagnosis and treatment of osteoporosis, and in turn, could reduce the incidence of hip fractures and vertebral compression fractures. As COPD is a major risk factor for developing lung cancer, these patients legitimately deserve low-dose computed tomography for screening [27]. The treatment of sleep apnoea in COPD affects survival [28]. There is a risk of under-treatment of depression in patients with COPD, as depressive symptoms, including suicidal tendencies, can erroneously be conceptualised as an understandable reaction to COPD and not as signs of an independent depressive disorder [29].

In conclusion, it is of utmost importance to increase awareness amongst healthcare professionals regarding comorbidity in COPD but also regarding COPD as a comorbidity in other prevalent chronic diseases. Indeed, the importance of comorbidities in patients with COPD is emphasised by its incorporation in the latest COPD definition [30]. This directly involves that COPD care is not limited to the prescription of bronchodilators and the treatment and prevention of COPD exacerbations, but is a comprehensive and holistic approach considering the rigorous diagnosis and treatment of COPD-related systemic manifestations and comorbidity. We are not treating a single disease but a patient with (undiagnosed and untreated) multiple other noncommunicable chronic diseases. We now need to talk to each other across the borders of our disciplines and think about how we can improve the care of our patients. We need to integrate our skills and treatment options between disciplines for optimal management in order to look for the synergistic effect of our efforts in contrast with the potential harmful effect of pharmacological interactions, polypharmacy and certain disease-specific interventions. The single disease centred clinical guidelines do not consider the reality of care for a patient with multiple chronic conditions [31].

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