



## Review Article

# Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life



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## ABSTRACT

Exacerbations of chronic obstructive pulmonary disease (COPD) represent a significant clinical problem, and are associated with decreased lung function, worsening quality of life and decreased physical activity levels, with even a single exacerbation having detrimental effects. The occurrence of COPD exacerbations can also have a considerable impact on healthcare costs and mortality rates, with over one-fifth of patients hospitalized for a COPD exacerbation for the first time dying within one year of discharge. This highlights the need for COPD exacerbations to be a major focus in clinical practice. Furthermore, the substantial effect that COPD exacerbations can have on patient mental health should not be underestimated. Despite their clinical importance, COPD exacerbations are poorly recognized and reported by patients, and improving patient understanding and reporting of exacerbations to ensure prompt treatment may minimize their deleterious effects. Renewed focus on improving current clinical practice with support from evidence-based guidelines is required. This also raises a challenge to payors, healthcare systems and government policies to do more to tackle the considerable outstanding burden of COPD exacerbations.

## 1. Introduction

Chronic obstructive pulmonary disease (COPD) was the third leading cause of mortality in 2016 and was responsible for an estimated 3 million deaths worldwide that year, representing a vast global problem [1]. COPD exacerbations are responsible for the majority of the substantial burden that COPD places on healthcare systems [2,3]. In the USA, the annual cost of COPD management has been shown to increase proportionally with the number of COPD exacerbations, with COPD-related costs, including pharmacy claims for COPD treatments, more than six times higher in patients experiencing frequent ( $\geq 2$ /year) exacerbations (\$4361) compared with those who had none (\$644) [4].

The prevalence of COPD exacerbations is high, with over 50% of patients with COPD experiencing exacerbations in multiple long-term studies that lasted 3 years or more [5]. Furthermore, patients can experience

multiple COPD exacerbations per year: 23% of patients with a spirometry-confirmed diagnosis of COPD experienced  $\geq 2$  moderate/severe exacerbations per year, and 14% of patients experienced  $\geq 3$  exacerbations per year [6,7].

Additionally, exacerbations and hospitalization due to exacerbations were the outcomes that patients with COPD considered to be the most important [8]; therefore, COPD exacerbations should be a major focus in clinical practice. This review will focus on the definition, triggers, reporting and impact of COPD exacerbations.

## 2. Search methods

Relevant articles for this non-systematic, narrative literature review were identified via PubMed searches and from author knowledge. Only articles published in English were included.

*Abbreviations:* COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease

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### 3. Definition

The definitions for COPD exacerbations vary, but the most commonly used definitions are either symptom-based or event-driven [9]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report defines COPD exacerbations as acute worsenings of respiratory symptoms that require additional treatment, with dyspnea recognized as the key symptom [3]. Other characteristics may include increased airway inflammation, mucus production, gas trapping, sputum purulence and volume, cough and wheeze [3]. Since no diagnostic test is available in routine clinical practice, a COPD exacerbation is diagnosed when other causes of symptom changes in patients with COPD have been excluded [3,10].

The severity of COPD exacerbations can be defined as mild, moderate, or severe based on the treatment required and on whether hospitalization is needed [3]. A mild COPD exacerbation is a worsening of symptoms that can be managed by treatment with short-acting bronchodilators only, although some definitions do not include a requirement for treatment [3,11]. Moderate COPD exacerbations require treatment with antibiotics and/or oral corticosteroids [3]. Severe COPD exacerbations require hospitalization or emergency room visits, and patients may also have acute respiratory failure, which can be life-threatening [3]. The definition of COPD exacerbation severity should not be confused with the definition of COPD severity, which is classed as mild-to-very severe based on airflow limitation [3]. Although the classification of exacerbation severity is useful for clinical studies, the severity of a patient's illness in clinical practice should represent a composite of the severity of the underlying disease, the severity and frequency of exacerbations, and any comorbidities. There are also other limitations to these definitions; for example, there are inherent difficulties in validating patient-reported symptoms, patient access to healthcare, the social and financial situation of patients, and the presence of differential diagnoses in patients with COPD, which may mimic an exacerbation [12].

### 4. Differential diagnosis

Differential diagnoses of COPD exacerbations include pneumonia, pneumothorax, pleural effusion, pulmonary embolism, cardiac arrhythmias, and cardiac-related pulmonary edema [3].

Difficulties in distinguishing between a COPD exacerbation and pneumonia can occur, since symptoms overlap [3,13], and a history of COPD exacerbations is significantly associated with the occurrence of pneumonia in patients with COPD [14]. Additionally, short- and long-term outcomes in hospitalized patients with COPD who have pneumonia and those who have COPD exacerbations are similar [15]. Pneumonia is frequently underdiagnosed in patients hospitalized with a COPD exacerbation [13,16], and conversely, experience from external adjudication committees, which are often used in clinical trials, has shown that pneumonia can be overdiagnosed (i.e., not confirmed) in patients with COPD. Importantly, findings indicate that patients with COPD who also have pneumonia should potentially be treated differently than those experiencing an exacerbation [13,17].

Systematic reviews and meta-analyses highlighted that up to one quarter of patients hospitalized with a suspected COPD exacerbation have a pulmonary embolism [18,19], with similar symptoms observed between patients who did and did not have a pulmonary embolism [18]. Additionally, many patients with COPD exacerbations have cardiac arrhythmias [20], and the presence of heart failure alongside COPD is common, resulting in diagnostic challenges in these patients since the symptoms for exacerbations of both diseases overlap [21–23].

Therefore, misdiagnosis of COPD exacerbations is a potential risk, which could result in inappropriate treatment. With COPD diagnosis, as is true for all medical conditions, it is important to be aware of the relevant differential diagnoses, and to decide which should be further investigated, depending on their importance and likelihood.

### 5. Triggers

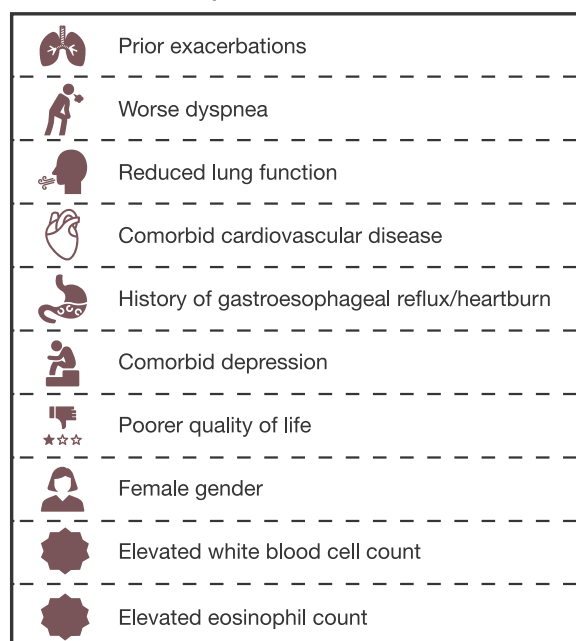
COPD exacerbations can be triggered by a variety of factors, including respiratory infections (bacteria, fungi and, most importantly, viruses), variations in outdoor temperature and air pollution [24]. Consequently, a patient's exacerbation frequency can vary from year to year [25], and also seasonally. The incidence of exacerbations is ~2-fold higher in the winter versus the summer [26,27], potentially due to an increased prevalence of respiratory viral infections [26,28]. Furthermore, exacerbations that occur in the winter, when respiratory viruses are more prevalent in the community, are associated with slow symptom recovery [29]. In the UK, the presence of pneumonic infiltrates during an exacerbation was more common in winter than in summer, and was associated with increased systemic inflammation [30].

Additional independent risk factors for patients experiencing frequent exacerbations ( $\geq 2$  per year) have been reported; these include: (i) demographic characteristics (such as being female); (ii) disease characteristics (increased dyspnea, reduced lung function, poorer quality of life, and prior exacerbations [strongest association]); (iii) comorbidities (such as cardiovascular events, depression, and a history of gastroesophageal reflux or heartburn); and (iv) potential biomarkers such as an elevated white blood cell count (Fig. 1) [7,31,32].

In addition, high blood eosinophil counts are an independent risk factor for the occurrence of future exacerbations [33], and pulmonary artery enlargement (i.e., a ratio of the diameter of the pulmonary artery to the diameter of the aorta of  $> 1$ , a marker of pulmonary hypertension) has been significantly associated with an increased risk of future severe exacerbations [34]. However, no plasma or serum protein biomarker has been shown to be independently predictive of the occurrence of COPD exacerbations across different patient cohorts [35].

COPD exacerbations are more common in patients with higher severity of airflow limitation, a higher symptom burden and a higher frequency of previous exacerbations. Annual exacerbation rates have been reported to at least double between patients with mild-to-moderate airflow limitation and those with very severe airflow limitation [6,36]. Moreover, in another study, annual exacerbation rates increased ~3-fold between patients with a low symptom burden and exacerbation

**Risk factors for frequent exacerbations include:**



**Fig. 1.** Independent risk factors associated with frequent exacerbations [7,31–33].

risk and those with a high symptom burden and exacerbation risk [37].

## 6. Under-recognition and under-reporting

Exacerbation recognition and reporting by patients is generally poor. Almost three-quarters of patients have difficulties with understanding the term ‘exacerbation’ [38], and ~40% of patients do not immediately take action (e.g., contacting their healthcare provider; increasing their medication dose, or taking a different medication; resting; or reducing or stopping smoking) when they experience an exacerbation [39].

Factors that have the potential to influence exacerbation reporting include access to healthcare, distance from the clinic, availability of personal and public transport, the ability to travel to a clinic (for example, if the patient is on oxygen therapy), and limited resources that may prevent general practitioners from making home visits. Unreported COPD exacerbations are associated with slower recovery [40], and prompt recognition, reporting, and treatment of COPD exacerbations reduces the duration of symptoms [41]. Patients who do not report COPD exacerbations remain untreated with maintenance or preventive therapies, highlighting the fact that defining exacerbations based on the treatment provided may not provide a complete picture. Furthermore, exacerbations may not be recognized in patients with undiagnosed COPD; for example, a smoker who receives antibiotics or oral corticosteroids for the treatment of bronchitis may be experiencing a COPD exacerbation.

## 7. Effect on symptom duration

Even a single COPD exacerbation has the potential to result in a significant decrease in lung function [42] and an increase in the risk of further exacerbations [43]. Data collected during a randomized controlled trial showed that patients who had experienced  $\geq 1$  exacerbation of any severity since their last study visit had a significantly reduced quality of life, compared with those who had not experienced an exacerbation [44]. Additionally, in the 2–3 months following a severe exacerbation, patients were at their greatest risk of suffering from another exacerbation [43]. Each exacerbation further increased the risk of experiencing another event; compared with a first severe exacerbation, the risk of a subsequent severe exacerbation was increased 3-fold following a second severe exacerbation and 24-fold following a tenth severe exacerbation [43]. The duration of an exacerbation is also linked to an increased risk of further exacerbations and poorer health status in patients with COPD exacerbations [45]. Exacerbations in which lung function did not recover were associated with viral infection symptoms and an accelerated lung function decline [45]. Together, these findings show that even one exacerbation can have harmful effects on the patient and highlight the importance of recognizing COPD exacerbations, as prompt treatment may decrease symptoms and lung function decline. A key aim in clinical practice should be to minimize the rate of exacerbations experienced by patients with COPD.

## 8. Effect on lung function

Many studies have reported the detrimental impact of COPD exacerbations on lung function. COPD exacerbations are associated with accelerated lung function loss, particularly in patients with mild airflow limitation and severe exacerbations [46]. Additionally, patients who have frequent COPD exacerbations are generally the most symptomatic and have the largest decline in lung function [47,48].

Recovery of lung function following an exacerbation can be prolonged, with findings showing that for 25% of exacerbations, lung function does not return to the patients’ pre-exacerbation levels 5 weeks after the event, and that for 7% of exacerbations, lung function does not return to the patients’ pre-exacerbation levels after 3 months [49]. Therefore, patients should be monitored until they have fully recovered

from their COPD exacerbation [49]. While a long symptom duration during a COPD exacerbation was associated with an increased risk of further exacerbations [45], a fast recovery in lung function following treatment has been shown to be significantly associated with a lower risk for COPD exacerbations [50].

## 9. Effect on quality of life and physical activity

COPD exacerbations affect many different factors relating to patient quality of life. As expected, patients who experienced frequent exacerbations ( $\geq 3$ /year) had a significantly reduced quality of life compared with patients who experienced less frequent exacerbations ( $< 3$ /year) [51]. Furthermore, the severity of a COPD exacerbation has been shown to correlate with quality of life. Patients who had a recent severe COPD exacerbation had higher levels of activity impairment and reduced health-related quality of life when compared with those who had a recent moderate COPD exacerbation [52]. However, even a mild COPD exacerbation can adversely impact patient health-related quality of life [53]. Conversely, a better health-related quality of life has been associated with a lower risk for COPD exacerbations [50].

A global patient survey revealed that the majority of patients with COPD felt that exacerbations prevented them from making plans for the future and impacted daily activities such as walking, sleeping, and speaking [39]. Consistent with this, increased daytime sleepiness, decreased total sleep time, decreased sleep efficiency, and levels of fatigue have been reported during an exacerbation [54,55]. In addition, COPD has previously been associated with sexual dysfunction in males, particularly erectile dysfunction, with most patients dissatisfied with their current and expected sexual function [56,57]. How COPD exacerbations affect sexual functioning has not yet been fully elucidated, but sex hormone levels have been shown to be markedly altered during a COPD exacerbation [58], which may have resulted in sexual dysfunction.

Hospitalization due to a COPD exacerbation has been shown to result in physical and functional impairment in patients, which deteriorates further between discharge from hospital and 1 month following the exacerbation [59]. Exercise capacity and muscle strength were found to decrease when patients suffered even a moderate COPD exacerbation [60] and reduced physical activity levels were associated with an increased risk of further exacerbations and mortality [61]. Additionally, patients with COPD exacerbations may have balance impairments that are associated with increased dyspnea and reduced muscle strength, which may contribute to the high incidence of falls experienced by these patients following hospitalization [62].

Hence, a decrease in physical activity levels following a COPD exacerbation can lead to reduced muscle strength, resulting in further physical impairment in patients. The link between COPD exacerbations, physical activity and depression is discussed further on in this review.

## 10. Mortality

COPD exacerbations have a major impact on mortality [43,63]. Mortality after a severe exacerbation has been found to peak in the first week following hospitalization [43], and a UK national audit in 2014 determined an inpatient mortality rate of 4.3% in patients hospitalized for a COPD exacerbation [64]. Furthermore, a meta-analysis of studies that followed patients for at least 1.5 years after hospital admission reported a predicted case fatality rate of 16%, defined as the ‘excess mortality that results from a COPD exacerbation’ [65]. In patients with COPD hospitalized for an exacerbation for the first time, more than one in five died within 1 year of discharge [63] and only one-half of patients were alive within 3.6 years [43]. Moderate and severe exacerbations were associated with an increased mortality risk, which increased with exacerbation frequency [66,67].

## 11. Impact on mental health

In one study, COPD exacerbations were associated with moderate-to-severe depression in nearly half of patients who had experienced exacerbation episodes in the previous year, moderate-to-severe anxiety in more than two-thirds of patients, and post-traumatic stress symptoms in one-third of patients [68]. Symptoms of anxiety, depression, and post-traumatic stress have been more commonly reported in patients with frequent COPD exacerbations ( $\geq 2$ ) versus patients with  $\leq 1$  COPD exacerbation in the previous year [47,68]. However, a study comparing the results of patient interviews with physician assessments found that physicians may underestimate the psychological impact of exacerbations on patients [69], highlighting the importance of raising physician awareness of these comorbid mental health issues.

Depression and anxiety are also associated with a decrease in physical activity and worsening health-related quality of life, and with increased respiratory symptoms and risk of hospitalization, mortality, and further exacerbations [70–72]. Decreases in physical activity have also been associated with higher levels of depression in patients with a moderate COPD exacerbation [60]. These findings suggest that, for some patients, decreased physical activity after a COPD exacerbation may result in them becoming housebound, which may, in turn, increase patient depression, thereby creating a vicious cycle, which could lead to further impairments in physical activity for the patient (Fig. 2).

Prescription data in hospice patients with end-stage COPD – who most likely have severe or very severe airflow limitation, a high symptom burden, and a high risk of exacerbations – have shown that 58.5% were prescribed anxiolytics, 42.4% were prescribed antipsychotics, 19.1% were prescribed antidepressants, and 3.1% were prescribed nonbenzodiazepine hypnotics [73]. These data indicate that mental health issues may be prevalent in hospice patients with end-stage COPD who are at high risk of COPD exacerbations. However, it has been proposed that time-limited anxiety and depression symptoms that occur during COPD exacerbations do not require treatment [74], since the exacerbation may be resolved by the time these treatments exert their effects.

COPD not only affects the mental health of patients with COPD; almost two-thirds of people caring for patients with COPD reported anxiety symptoms and approximately one-third reported depression

symptoms [75]. Perceived caregiver burden and patient activity limitation were identified as predictors of anxiety and depression symptoms in caregivers [75].

## 12. Association with other comorbidities

COPD exacerbations have been linked to many different comorbidities, with the presence and number of comorbidities significantly associated with the length and cost of hospitalization [76]. Additionally, patients with two mild or one severe comorbidity are at an increased risk of exacerbation recurrence [77].

Alongside mental health comorbidities, physical comorbidities such as hypertension, diabetes mellitus, chronic heart failure, ischemic heart disease, anemia, and dyslipidemia are common in patients hospitalized for a COPD exacerbation [77]. COPD exacerbations have been found to increase the risk of cardiovascular disease, including myocardial infarction and stroke [78–80].

Additionally, heart failure, visual impairment, lung cancer, depression, prostate disorders, asthma, osteoporosis, diabetes, gastroesophageal reflux, and peripheral vascular disease are significantly associated with frequent ( $\geq 2$  per year) exacerbations [32,81]. Coexisting asthma has also been shown to significantly increase the frequency of severe exacerbations [82].

## 13. Discussion and conclusion

In conclusion, COPD exacerbations represent a significant clinical problem, with deleterious effects on many aspects of patient health status, such as lung function, quality of life, comorbidities, and mortality. Furthermore, patients may take several weeks to recover following a COPD exacerbation.

Improving physician and patient recognition, and increasing awareness of the impact of COPD exacerbations, are key to minimizing detrimental effects. Patient education initiatives are needed to increase their understanding and reporting of COPD exacerbations, allowing swift identification and treatment.

The occurrence of a COPD exacerbation increases the risk of further exacerbations and can result in a progressive cycle of patient decline. Therefore, understanding the predictors of an increased exacerbation risk and prevention of COPD exacerbations should be a key focus of COPD clinical research. Although current treatment options for the prevention and treatment of COPD exacerbations are outlined in the GOLD 2020 report [3], further research is required on approaches to better predict and, therefore, prevent COPD exacerbations. To reduce the significant burden of COPD, a concerted effort from healthcare providers, payors, and policymakers is needed to drive early identification of those at risk, improve reporting and increase preventative care.

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### Declaration of Competing Interest

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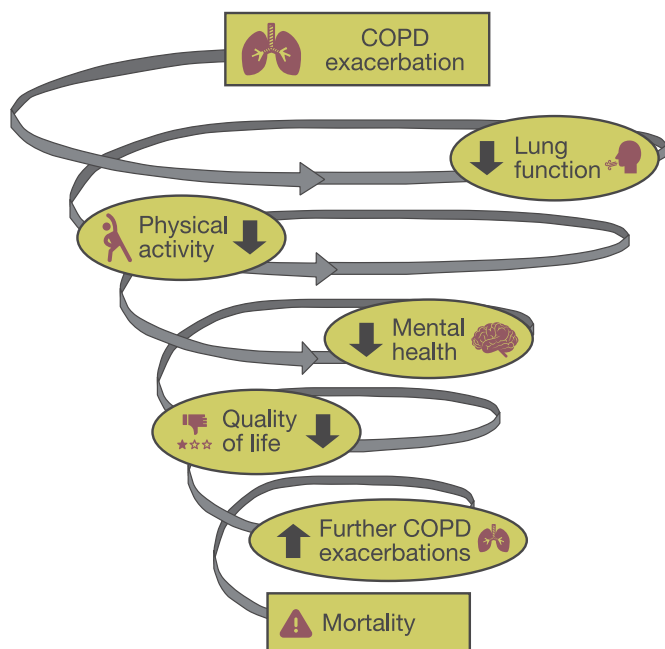


Fig. 2. Downward spiral of COPD exacerbations. COPD, chronic obstructive pulmonary disease.

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