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ORIGINAL RESEARCH

Defining COPD exacerbations: impact on estimation of incidence and burden in primary care

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Summary
Aims: To investigate the impact of definition on the incidence of chronic obstructive pulmonary disease (COPD) exacerbations in primary care.
Methods: In a one year prospective, observational study, data from diary cards were used to determine the incidence of symptom- and healthcare-defined exacerbations. One hundred and twenty seven patients completed ≥80% of days in the diary card and were included in the analysis.
Results: Incidence of COPD exacerbation varied according to definition. Mean yearly rates were 2.3 for symptom- and 2.8 for healthcare-defined exacerbations. Although patients with $FEV_1 < 50\%$ had a higher mean yearly rate of healthcare-defined exacerbations than those with $FEV_1 \geq 50\%$ (3.2 vs 2.3; $p = 0.003$), patients with less severe disease reported recurrent exacerbations. There was limited agreement between symptom- and healthcare-defined exacerbations.
Conclusion: Lung function does not appear to be a valid criterion for assigning COPD management directed at patients with recurrent exacerbation.

Introduction

Exacerbation of chronic obstructive pulmonary disease (COPD) indicates a worsening of symptoms, with frequency and severity considered largely a feature of moderate-to-severe disease [1,2]. Reported COPD exacerbation rates vary considerably but generally range from 1.1 to 2.5 per patient per year [3—6]. Frequencies as low as 0.8 per patient per year have been reported [7], and at least one study reported a median exacerbation frequency as high as 4 per patient per year [8].

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These wide variations may stem from a lack of global consensus on a definition of COPD exacerbation. Anthonisen et al. [4] described three levels of exacerbation based on patients' symptoms [4] and provided the basis of subsequent criteria [4,9]. Although symptom-based definitions are commonly adopted, medical event-based definitions, including change of therapy (antibiotics and/or oral corticosteroids) or management (Emergency Room (ER) attendance or hospital admission), have been increasingly used to circumvent the problems in identifying and defining symptoms [9]. Calverley et al. [10] suggested that most clinicians assume that these approaches are broadly comparable. However, one study found that as many as 50% of exacerbations, defined according to modified Anthonisen criteria, may not be reported by patients [3].

Exacerbations are strongly associated with increased healthcare resource use [11,12], with an excess cost of £44.9 million per year in England and Wales [13]. Although the cost of managing exacerbations rises with exacerbation severity [14], less costly mild/moderate exacerbations are more frequent so total direct costs from these exacerbations can be considerable [14,15]. In the first prospective follow-up study in Spain, the mean yearly direct cost for the management of COPD patients was $1760, (range $1484 to $2211) [16]. The group had a mean of 1.9 exacerbations, with a mean cost of $59 (initial visit and treatment of exacerbation). Another observational economic study of 1097 patients with chronic bronchitis or COPD in primary healthcare in Spain estimated the cost of the initial treatment of the exacerbation plus the cost of treatment failure evaluated over a period of 30 days as €119 (95% CI = €92—145) [17].

The high healthcare costs associated with COPD exacerbations highlight a need for early recognition and treatment of exacerbations, and the identification of patients at risk from frequent exacerbations. Due to the considerable economic and health status burden of exacerbations [3,18] and the effect on lung function decline [19], international guidelines have stated that reducing the frequency of exacerbations should be a primary target in the management of COPD [20—22].

Most studies have reported on the frequency of COPD exacerbations in hospital or clinical trial settings. This 'real-life' study is the first to describe the frequency and direct healthcare cost of treating COPD exacerbations, using different definitions of the term 'exacerbation', in patients managed routinely in primary care, and it investigates the impact of the definition on the incidence of exacerbations.

Methods

Study subjects

Patients eligible for inclusion were those registered with the Wyre Primary Care Trust (PCT), North West England, with a diagnosis of COPD, as previously described [23]. All patients who consented to take part were included in the All Patients Sample (APS). Baseline characteristics of each patient were obtained at the time of recruitment.

Study design

This was a prospective, 12-month observational study in a primary care setting. All study documentation was reviewed and approved by the Local Research Ethics Committee of the PCT. All data were collected by postal survey and were anonymous. Patients completed sequential 5-week diary cards, each sent out before the return of previous cards to ensure complete daily data capture. Primary healthcare practitioners of consenting patients were informed.

Patients without a diagnosis of COPD, holiday-makers, and those patients unable to complete the data collection activities required, were excluded from the study.

Data collection

Information on symptoms, quality of life and use of healthcare services was recorded to identify symptom- and healthcare-defined exacerbations using patient-completed diary cards (Figure 1). The participating patients were asked not to change their usual behaviour in response to perceived symptoms. Lung function was not measured but the most recent recorded value was used for patient classification.

Definitions of exacerbations

Symptom-defined exacerbations

An increase in major and minor symptoms was recorded by the patient each day using the diary card. Exacerbations were defined as a symptom score of at least 2 for two consecutive days, with no score for at least two of these symptoms in the preceding five days. The time of onset was taken as the first day of these symptoms. The baseline period was defined as between eight and 14 days prior to the onset of the exacerbation, inclusive. Baseline symptom score was the mean of the scores over the baseline period. In accordance with the definitions described by Seemungal et al. [24],

	COMPLETE EACH EVENING The score system can be found on the back of the example card. **Date** (please add to each day): DD/MM/YY	Monday Day 1 / /	Tuesday Day 2 / /	Wednesday Day 3 / /	Thursday Day 4 / /	Friday Day 5 / /	Saturday Day 6 / /	Sunday Day 7 / /
	SECTION ONE: Symptoms							
	MAJOR SYMPTOMS							
1	Have you been more breathless than usual due to chest problems? ***Tick if yes***							
2	Has your sputum been a darker color than usual due to chest problems? ***Tick if yes***							
3	Have you produced more sputum than usual due to chest problems? ***Tick if yes***							
	MINOR SYMPTOMS							
4	Have you any of these other symptoms i.e. nasal discharge/congestion, wheeze, sore throat, cough? ***Tick if yes***							
	SECTION TWO: Quality of Life							
5	Have you found it more difficult to perform activities of daily living due to an increase in chest problems? e.g. dressing, washing yourself. ***Enter appropriate score (0-2)***							
6	Have you found it more difficult to perform physical activities you are usually capable of completing due to an increase in chest problems? e.g. climbing stairs, hurrying. ***Enter appropriate score (0-2)***							
7	Have you found it more difficult to take part in your usual social activities due to an increase in chest problems? e.g. being with friends, visiting friends/relatives, talking. ***Enter appropriate score (0-2)***							
8	Have you missed time from work or usual activities due to an increase in chest problems? ***(Circle NONE or HALF DAY or FULL DAY)***	None Half day Full day	None Half day Full day	None Half day Full day	None Half day Full day	None Half day Full day	None Half day Full day	None Half day Full day
	SECTION THREE: Use of Health Care Services							
9	How many extra times did you use your short acting 'relief' inhaler? e.g. Ventolin inhaler. ***(please write times not puffs e.g. 1 time = 2 puffs taken together***							
10	Have you spoken on the telephone to a GP for advice because of worsening chest symptoms? ***Tick if yes. If more than once in a day record number of times***							
11	Have you spoken on the telephone to a nurse at the practice for advice because of worsening chest symptoms? ***Tick if yes. If more than once in a day record number of times***							
12	Have you visited the GP because of worsening chest symptoms? ***Tick if yes. If more than once in a day record number of times***							
13	Have you visited the nurse at the practice because of worsening chest symptoms? ***Tick if yes. If more than once in a day record number of times***							
14	Have you had a home visit by the GP during the day? ***Tick if yes. If more than once in a day record number of times***							
15	Have you had a home visit by the GP out of hours/at night? ***Tick if yes. If more than once in a day record number of times***							
16	Are you taking a course of antibiotics for chest problems? ***(Circle YES or NO). If YES, write details of the course on the last page of this diary card***	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
17	Are you taking a course of steroid tablets for chest problems? ***(Circle YES or NO). If YES, write details of the course on the last page of this diary card***	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
18	Have you attended A&E, but not been admitted to hospital? ***Tick if yes***							

Figure 1 Diary Card.

exacerbations were defined as having ended once symptom scores returned to baseline or less, as calculated from a three-day rolling mean. The last day of the exacerbation was defined as the third day of this period.

Healthcare-defined exacerbations

Exacerbations were defined as the need to take antibiotics and/or oral corticosteroids (OCS) for chest problems. Onset was defined as the day prior to starting medication, and the last day of the exacerbation was defined as the last day of taking medication. If less than seven days elapsed between the completion of one course and the start of a further course of medication, this was classified as a continuation of the first exacerbation. To identify healthcare-defined exacerbations, patients recorded in the

diary cards the medication taken for chest problems and any use of healthcare resources, including visits/telephone calls to their physician or nurse.

Statistical analysis

Data from the study were stored on a Microsoft Access database. The 12-month cumulative incidence of exacerbations was determined from the diary card data. The cost of each exacerbation comprised: the cost of the associated drug treatment (OCS and antibiotics) and healthcare resource use; telephone call to the general practitioner (GP) or nurse; consultation with a GP or nurse; home visit by GP (day or night); Accident & Emergency attendance; and inpatient stay in hospital. Cost data were taken from the Personal Social Services Research Unit (PSSRU) [25] and British National Formulary (BNF) [26]. A Poisson regression model was fitted, with time in study as an offset variable, to obtain a yearly exacerbation rate.

Results

Patients

In total, 848 patients with a diagnosis of COPD were invited to take part. Of these, 309 (36%) consented and were included in the APS. Twenty-seven (9%) of eligible patients discontinued the study generally due to research fatigue. Four patients (1%) died during the study with cause of death not noted.

Baseline characteristics of the APS are summarised in Table 1. Overall, 201 patients (65%) in the APS completed at least one diary card during the study and were included in the Diary Card Sample (DCS). Of these, 127 (63%) completed diary cards covering at least 80% of the year and this patient group is termed the 80% DCS.

Baseline characteristics of patients in the DCS and the 80% DCS are similar to those of the APS, indicating that the 80% DCS was representative of the DCS and the APS for this analysis (Table 1).

Exacerbation incidence

Symptom-defined exacerbations

A total of 296 symptom-defined exacerbations were experienced in the 80% DCS by 77% of the patients (Table 2). The mean yearly rate of exacerbations was 2.3 (95% confidence interval (CI) 2.1—2.6). One-third ($n = 42$) of patients experienced ≥ 3 exacerbations and 23% (29) experienced none. The median duration of exacerbations was seven days.

When patients were grouped according to lung function, the mean yearly rates were similar for both groups, with 2.5 (95% CI 2.1—2.9) exacerbations for patients with a Forced Expiratory

Table 1 Exacerbation incidence and patient characteristics at baseline

Parameter	All Patients Sample	Any diary card (DCS)	80% Diary Card Sample
Patient characteristics	($n = 309$)	($n = 201$)	($n = 127$)
Male/Female (%)	56/44	61/39	63/37
Age (mean ± SD [years])	69.71 ± 8.85	69.30 ± 8.44	69.44 ± 8.24
Current smoker (%)/Ex-smoker (%)	30/64	27/65	20/70
Lung function	($n = 299$)	($n = 198$)	($n = 126$)
FEV_1 % predicted ± SD	50.13 ± 18.71	49.70 ± 19.20	49.70 ± 18.64
FEV_1 < 50% predicted ± SD	36.1 ± 8.8	35.7 ± 9.0	35.9. ± 8.2
$FEV_1 \geq 50\%$ predicted ± SD	65.4 ± 14.1	65.6 ± 14.7	66.4 ± 13.2
COPD severity — *GOLD, n* (%)			
Stage 0/1	12 (4)	7 (5)	6 (4)
Stage II	131 (44)	86 (43)	51 (40)
Stage III	123 (41)	79 (40)	54 (43)
Stage IV	33 (11)	26 (13)	15 (12)
Exacerbation incidence in previous 12 months	($n = 306$)	($n = 201$)	($n = 127$)
Total exacerbations, n (%)			
0	108 (35)	64 (32)	48 (38)
1 or 2	117 (38)	82 (41)	50 (39)
3+	81 (26)	55 (27)	29 (23)

SD = standard deviation; FEV_1 = Forced expiratory volume in one second; GOLD = Global Initiative for Chronic Obstructive Pulmonary Disease.

Table 2 Summary of exacerbations (80% Diary Card Sample; $n = 127$)

	Type of exacerbation dependent on definition	
	Symptom-defined	Healthcare-defined
Total number of exacerbations experienced	296	351
Mean yearly rate of exacerbations	2.3 (95% CI: 2.1—2.6)	2.8 (95% CI: 2.5—3.1)
Patients experiencing 0 exacerbations, *n* (%)	29 (23)	29 (23)
Patients experiencing 1—2 exacerbations, *n* (%)	56 (44)	41 (32)
Patients experiencing 3 or more exacerbations, *n* (%)	42 (33)	57 (45)
Median duration of exacerbations (days)	(exacerbations = 275) 7	(exacerbations = 336) 8

Volume in one second (FEV_1) < 50%, and 2.2 (95% CI 1.9—2.7) ($p = 0.36$) for patients with $FEV_1 \geq 50\%$ (Table 3). The majority of patients with $FEV_1 < 50\%$, or $FEV_1 \geq 50\%$ (74% and 82% respectively) reported suffering ≥1 exacerbation. The percentage of patients experiencing 0, 1—2 or ≥3 exacerbations was similar for both groups. The median duration remained similar at seven days, for both groups. A review of the defining symptom profile for exacerbations in both groups showed that breathlessness was one of the defining symptoms for those with $FEV_1 < 50\%$, and $FEV_1 \geq 50\%$ in approximately three-quarters of exacerbations (74%—125/170 and 79%—99/126, respectively). However, amongst patients with $FEV_1 < 50\%$, notably more patients with exacerbation had darker sputum as a defining symptom, 49% (83/170) compared with 39% (31/126) amongst those with $FEV_1 \geq 50\%$. Amongst patients with $FEV_1 \geq 50\%$ notably more patients with exacerbation had minor symptoms as a defining symptom, 56% (70/126) compared with 39% (67/170) amongst those with $FEV_1 < 50\%$.

Healthcare-defined exacerbations

The total number of healthcare-defined exacerbations was 351, reported by 77% of the patients (Table 2). The mean yearly exacerbation rate was 2.8 (95% CI: 2.5—3.1), with a median duration of eight days. Forty-five percent ($n = 57$) of patients experienced ≥3 exacerbations compared with 32% ($n = 41$) who experienced 1—2, and 23% ($n = 29$) who experienced none.

Table 3 Summary of exacerbations by FEV_1 % predicted (80% Diary Card Sample; $n = 126$[†])

	Type of exacerbation dependent on definition			
	Symptom-defined		Healthcare-defined	
Total number of exacerbations experienced	296		351	
FEV_1 % predicted (no. of patients)	**<50% (*n* = 69)**	**≥50% (*n* = 57)**	**<50% (*n* = 69)**	**≥50% (*n* = 57)**
Number of exacerbations experienced	170	126	220	131
Mean yearly rate of exacerbations	2.5 (95% CI: 2.1—2.9)	2.2 (95% CI: 1.9—2.7)[*]	3.2 (95% CI: 2.8—3.7)	2.3 (95% CI: 2.0—2.8)[**]
Patients experiencing 0 exacerbations, *n* (%)	18 (26)	10 (18)	11 (16)	17 (30)
Patients experiencing 1—2 exacerbations, *n* (%)	28 (41)	28 (49)	22 (32)	19 (33)
Patients recording 1 or more exacerbations, *n* (%)	51 (74%)	47 (82%)	58 (84%)	40 (70%)
Patients experiencing 3 or more exacerbations, *n* (%)	23 (33)	19 (33)	36 (52)	21 (37)
Median duration of exacerbations (days)	(exacerbations = 158) 7	(exacerbations = 117) 7	(exacerbations = 209) 8	(exacerbations = 127) 8

[†] One patient did not have an FEV1 % predicted, and is excluded from the table; for FEV_1 % predicted <50% vs ≥50%: [*] $p = 0.36$; [**] $p = 0.003$; FEV_1 = Forced expiratory volume in one second.

When the results were grouped according to lung function, the mean yearly rate was 3.2 (95% CI 2.8—3.7) exacerbations for patients with $FEV_1 < 50\%$, and 2.3 (95% CI 2.0—2.8) ($p = 0.003$) for patients with an $FEV_1 \geq 50\%$ (Table 3). The majority of patients with an $FEV_1 < 50\%$ or $\geq 50\%$ (84% and 70% respectively) reported suffering ≥ 1 exacerbation. The median duration remained similar at eight days for both groups. The proportion of patients reporting ≥ 3 exacerbations was greater amongst patients with FEV_1 <50%. Nearly one-third (30%) of patients with $FEV_1 \geq 50\%$ reported no exacerbations compared with only 16% patients with $FEV_1 < 50\%$. A review of the prescribed medication to treat a healthcare defined exacerbations showed that more exacerbations where patients had an $FEV_1 < 50\%$ (66%—146/220) were associated with taking both antibiotics and oral corticosteroids compared with those with an $FEV_1 \geq 50\%$ (53%—70/131); more exacerbations for those with $FEV_1 \geq 50\%$ (39%—51/131) were associated with taking antibiotics alone compared with those with FEV_1 <50% (28%—62/220).

Overlap between symptom- and healthcare-defined exacerbations

There were 336 healthcare-defined exacerbations with a stop date, of which 138 (41%) were also identified using the symptom definition. Of the 275 symptom-defined exacerbations with a stop date, 149 (54%) were also identified using the healthcare definition. Forty-five (28%) showed a pattern of increased symptoms before starting the treatment for an exacerbation, which tailed off as the week progressed. For the remaining patients, the pattern of recording symptoms was variable.

Healthcare resource use associated with exacerbation

Few patients made health-care contact during an exacerbation. Eighty-two percent ($n = 225$) of symptom-defined exacerbations, and 67% ($n = 225$) of healthcare-defined exacerbations, were not associated with a physician visit. Seventy-two percent of patients ($n = 92$) received treatment with antibiotics for chest problems during the study. Of the 351 healthcare-defined exacerbations, 22 (6%) were associated with OCS treatment; 113 (32%) were associated with antibiotic treatment, and 216 (62%) were associated with both OCS and antibiotics. The mean total cost of a healthcare-defined exacerbation was £30.69 (±111.40), almost double that of a symptom-defined exacerbation, £15.77 (±34.72).

Discussion

This one year prospective observational study directly compares the number of exacerbations using different definitions, and is the first to describe the incidence of exacerbations in primary care using the two definitions. Mean yearly rates ranged from 1.7—5.2, depending on the definition used and FEV_1 % predicted. The mean yearly exacerbation rate was similar, at more than 2 per year, using either definition in patients with FEV_1 % predicted above or below 50%.

The data suggest that the previously reported range of exacerbation rates may be conservative [3—6]. The range may reflect the variation in exacerbation definitions currently used. In this study less than half of the healthcare-defined exacerbations were also identified as symptom-defined exacerbations, and only just over half of the symptom-defined exacerbations were also identified as healthcare-defined exacerbations. Calverley et al. [10] have also reported that individual symptom-based episodes showed only limited agreement with episodes when patients sought medical help, and that combining symptoms worsened the degree of agreement between definitions. As Calverley et al. discussed, the limited overlap may be due to incomplete or retrospective diary card completion over the year by some patients, possibly due to research fatigue. Alternatively, the perception and interpretation of symptoms by an individual patient is likely to be variable such that their recording of symptoms may be inconsistent in the diary cards. If some patients are under-reporting symptoms this could lead to fewer exacerbation overlaps.

These previous studies also relied on patient reporting of exacerbations or physician-recorded prescribing during an exacerbation. This study confirms that most patients do not inform their physician or seek medical intervention during an exacerbation. This may reflect self-treatment by patients with pre-prescribed 'emergency' courses of antibiotics and/or steroids [26] or low expectations for treatment [27]. Therefore, healthcare professionals are likely to underestimate the number of exacerbations. Effective management requires patients to understand the importance of increased symptoms, and be encouraged to seek help [28].

Direct costs of COPD management in primary care were similar to those in a previous study in which a successfully treated exacerbation was estimated to cost $59 [16]. However, in the

Miravittles study [16] greater costs were associated with hospitalisation (44% of total costs). In our study, there were no hospitalisations so the costs calculated may underestimate the total cost burden of exacerbations.

This study investigates an important but difficult subject, and despite the challenges to research design, offers insight into 'real life' impact on the healthcare system. Patients were recruited via a register of diagnosed patients [23]. Just over a third consented to participate and only diary card data from patients completing $\geq$80% were included in the analysis, potentially limiting the external validity of the findings. The data may be limited by patient completion of diary cards and the subjective nature of these. Nevertheless, patient discontinuation rates were low and diary card completion rates were high. Furthermore the patient characteristics of the 309 patients who consented, the 201 patients who completed at least one diary, and the sample analysed (127), were all similar.

Current guidelines state that patients should be considered for preventative therapy for exacerbations using inhaled steroids only if they experience 'at least one exacerbation requiring OCS or antibiotics within the previous 12 months, and have an $FEV_1 < 50\%$ predicted' [21], or if they experience 'repeated exacerbations and have an $FEV_1 < 50\%$ predicted' [20]. Therefore patients who experience ≥ 1 exacerbation but have $FEV_1 \geq 50\%$ predicted would not qualify for interventional therapy other than a bronchodilator. Data from this study show that FEV_1 % predicted is not an accurate discriminator for exacerbations, with the majority of patients with $FEV_1 \geq 50\%$ reporting ≥ 1 exacerbation. Furthermore, one-third of patients with $FEV_1 \geq 50\%$ suffered ≥ 3 exacerbations. Interestingly, although breathlessness was a dominant defining symptom for the symptom-defined exacerbations in both groups, there were other differences in their profiles. Similarly, the pattern of medication taken for healthcare-defined exacerbations varied for both groups. Confirmation and the rationale and implications of these findings require further research.

The lung-function based criteria for the management of COPD patients with recurrent exacerbations should be re-evaluated in the light of these data.

Conflicts of interest

Angela Williams and Leanne Rice are employees of GlaxoSmithKline. Dr O' Reilly has received support to attend medical conferences, and speaker fees from Altana Pharmaceuticals Astrazeneca, Boehringes Ingelheim, and GlaxoSmithKline.

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