Utility of the COPD Assessment Test™ (CAT) to evaluate severity of COPD exacerbations

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Utility of the COPD Assessment Test™ (CAT) to evaluate severity of COPD exacerbations

Alex J Mackay1 * MBBS MRCP, Gavin C Donaldson1 PhD, Anant RC Patel1 MB BS MRCP, Paul W Jones2 PhD FRCP, John R Hurst1 PhD FRCP, Jadwiga A Wedzicha1 MD FRCP

1 Academic Unit of Respiratory Medicine  2 Division of Clinical Science
University College London Medical School  St George’s University of London
Royal Free Campus  Cranmer Terrace
Rowland Hill Street  London
London  SW17 0RE
NW3 2PF  UK
UK

E-mail addresses: alexander.mackay@ucl.ac.uk (*corresponding author)
g.donaldson@ucl.ac.uk
anant.patel@ucl.ac.uk
pjones@sgul.ac.uk
j.hurst@ucl.ac.uk
j.wedzicha@ucl.ac.uk

Tel: +44 (0)20 7317 7517
Fax: +44 (0)20 7472 6141
**Author Contributions:** Study idea and design: AJM, GD, JW. Analysis and interpretation of results: AJM, GD, AP, PJ, JH, JW. Manuscript drafting/ revision: AJM, GD, AP, PJ, JH, JW.

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**At a Glance Commentary**

What is the current scientific knowledge on the subject?

Currently there is no standardized, objective method for assessing symptom severity at exacerbation that has been universally accepted and available for use in both routine clinical practice and clinical trials.

What does this study add to the field?

The CAT provides a reliable score of exacerbation severity and its incorporation into assessment strategies may aid health care professionals to determine the severity of exacerbations and potentially assist management. The CAT may also prove useful in clinical trials to objectively assess the ability of novel interventions to reduce exacerbation severity.
Abstract (Word Count=244)

Rationale: The COPD Assessment Test™ (CAT) is an 8-item questionnaire designed to assess and quantify the impact of COPD symptoms on health status. COPD exacerbations impair quality of life and are characterized by worsening respiratory symptoms from the stable state. We hypothesized that CAT scores at exacerbation relate to exacerbation severity as measured by exacerbation duration, lung function impairment and systemic inflammation.

Objectives: To evaluate the utility of the CAT to assess exacerbation severity.

Methods: 161 patients enrolled in the London COPD cohort completed the CAT at baseline (stable state), exacerbation and during recovery between April 2010 and June 2011.

Measurements and Main Results: Frequent exacerbators had significantly higher baseline CAT scores than infrequent exacerbators (19.5±6.6 vs. 16.8±8.0, p=0.025). In 152 exacerbations, CAT scores rose from an average baseline value of 19.4±6.8 to 24.1±7.3 (p<0.001) at exacerbation. Change in CAT score from baseline to exacerbation onset was significantly but weakly related to change in CRP (rho=0.26; p=0.008) but not to change in fibrinogen (rho=0.09, p=0.351) from baseline to exacerbation. At exacerbation, rises in CAT score were significantly associated with falls in FEV₁ (rho=-0.20, p=0.032). Median recovery time as judged by symptom diary cards was significantly related to the time taken for the CAT score to return to baseline (rho=0.42; p=0.012).

Conclusions: The CAT provides a reliable score of exacerbation severity. Baseline CAT scores are elevated in frequent exacerbators. CAT scores increase at exacerbation and reflect severity as determined by lung function and exacerbation duration.

Key Words: COPD, Exacerbations, Severity, Patient-Reported Outcomes, Symptoms
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory airway condition associated with episodes of acute deterioration termed exacerbations (1). Exacerbations are amongst the commonest causes of medical admission to hospital (2) and the rate at which they occur appears to reflect an independent susceptibility phenotype (3). They are also important events in the natural history of COPD that drive lung function decline (4, 5), increase risk of cardiovascular events (6) and are responsible for much of the morbidity (7) and mortality (8) associated with this highly prevalent condition.

COPD exacerbations are characterized by a worsening of respiratory symptoms from the usual stable state, especially dyspnea, increased sputum volume and purulence. Changes in exacerbation symptoms relate to exacerbation recovery time (9), which is an index of exacerbation severity. In addition to exacerbation length, exacerbation severity influences acute treatment (9), drives hospital admission and also mortality (8).

Patient diary cards are direct measures of exacerbation symptoms that provide accurate information regarding the commencement and resolution of exacerbations (9). They can detect exacerbations that are both reported and unreported to health care professionals thus allowing accurate determination of exacerbation frequency (7). However, currently there is no standardized, objective method for assessing symptom severity at exacerbation that has been universally accepted and available for use in both routine clinical practice and clinical trials.
The COPD Assessment Test™ (CAT) is a validated 8-item questionnaire designed to assess and quantify the impact of COPD symptoms on patient health status (Figure 1). It has excellent measurement properties (10) and is short and simple for patients to complete, providing a score out of 40 to indicate disease impact, without the need for complex calculation. Initial studies have shown that the CAT correlates closely with health-related quality of life as measured by the St. George’s Respiratory Questionnaire (SGRQ) when patients are stable (10), and is responsive to pulmonary rehabilitation (11).

We hypothesized that elevated CAT scores at COPD exacerbation relate to exacerbation severity as measured by exacerbation length, lung function impairment and systemic inflammation. Furthermore, we hypothesized that CAT scores can be used to model recovery. Therefore, well characterized patients were prospectively assessed using the CAT in the baseline stable state, at exacerbation presentation and thereafter for five weeks during the recovery period.

**METHODS**

*Patient recruitment*

This study involved 161 COPD patients enrolled in the London COPD cohort between 1st January 2009 and 1st June 2011. The patients form part of a rolling cohort used to prospectively investigate the mechanisms of COPD exacerbations. Patients were included if the post-bronchodilator forced expiratory volume in 1 second (FEV₁) was ≤80% predicted from age, height, and sex and FEV₁/forced vital capacity (FVC) ratio was <0.7 (12). Patients with a history of any other significant respiratory diseases were excluded, as were those unable to complete daily diary cards.
At annual review or recruitment, a full medical and smoking history was obtained, a clinical examination performed and the SGRQ (13) completed. Comorbid diagnoses were established using clinical history and examination findings during a stable state visit, supported where appropriate with a review of available medical records. FEV₁ and FVC were measured with a Vitalograph Gold Standard spirometer (Vitalograph Ltd, Maids Moreton, UK). Oxygen saturations were also measured (PureSAT®, Nonin Medical Inc, Plymouth, MN, USA). Body mass index (BMI) was calculated from height and weight.

Ethical approval for the study was granted from the Royal Free Hospital research ethics committee and all patients gave written informed consent. Permission to use the CAT questionnaire was obtained from GlaxoSmithKline. The recruitment and monitoring of these patients has been previously described and the cohort has been the subject of previous publications (7, 9, 14-16), but the current study is entirely novel and has not been reported before.

**Monitoring and Definition of Exacerbations**

Patients were asked to record daily peak expiratory flow rate (PEFR) measured with a mini-Wright meter (Clement-Clark International, Harlow, UK), hours spent outside the home and any increase in respiratory symptoms on diary cards. An exacerbation was defined as an increase for two consecutive days in respiratory symptoms, with at least one major symptom (dyspnea, sputum purulence or sputum volume) plus either another major or a minor symptom (wheeze, cold, sore throat, and cough), the first of which was defined as the day of onset of the exacerbation. Symptom counts were obtained by summatmg each increased respiratory symptom recorded on diary cards per day.
Exacerbation duration was defined as the number of days after onset that worsening symptoms persisted. The last day of recorded worsening symptoms before two consecutive symptom-free days defined the end of the exacerbation. Exacerbation recovery was not determinable if patients failed to record diary card symptoms or continuously recorded symptoms for more than 99 days after onset. Exacerbation frequency was calculated for each patient using diary card data obtained between January 2009 and June 2011. For recently recruited patients with less than one year diary data, exacerbation frequency was based on the number of exacerbations the patient recalled for the year prior to recruitment. Previous work has shown a good correlation between the number of exacerbations recorded on diary cards and the number of exacerbations remembered by the patient over the same 1 year period (17) and has shown that exacerbation frequency represents a stable patient phenotype (3).

**Exacerbation Assessment**

Exacerbations were treated according to the prevailing guidelines and clinical judgment with increased inhaled therapy, antibiotics and/or oral steroids. Neither the magnitude of exacerbation CAT score nor the diary card symptom score played any role in treatment decisions. When patients attended for an exacerbation, venous blood samples were taken and spirometry performed prior to commencing exacerbation treatment. Serum C-reactive protein (CRP) was measured using Modular Analytics E 170 Module (Roche, Burgess Hill, UK) and plasma fibrinogen using the Clauss method (IL ACL Top Coagulation Analyzer, Lexington, MA, USA).

**CAT administration**

Patients completed the CAT at least once under supervision in clinic and then at home, based
on their symptoms experienced on the day of completion. Patients completed at least one CAT questionnaire in the stable, baseline state. Baseline occurred more than 35 days post- and 21 days pre- exacerbation onset. If unavailable pre-index exacerbation, CAT scores during periods of stability post-exacerbation were used to provide a baseline. No differences were seen between baseline scores obtained pre-index exacerbation and baseline scores post-exacerbation. Repeat scores were averaged to give a baseline CAT score. CAT questionnaires were also administered during exacerbation between April 2010 and June 2011. The exacerbation CAT score took place within 7 days of the symptomatic onset of the exacerbation as judged by diary cards, was completed prior to starting therapy and was recorded on the day treatment commenced. These were mandatory study criteria.

A subgroup of patients also completed CAT scores on a daily basis during their recovery. For the recovery subgroup, the first exacerbation was selected for analysis provided the patient had fully completed the questionnaire on at least 21 of 35 days post onset. CAT Recovery was the time taken from exacerbation onset for the CAT score to return to baseline value (Figure E1).

Statistical analysis

Data were analyzed with STATA 8.2 (Stata Corporation, Texas, USA). Normally distributed data were expressed as mean and standard deviation (SD) and skewed data as median and interquartile range (IQR). Comparisons were made by paired Student t-test or Wilcoxon signed-rank test. The relationship between exacerbation frequency and baseline CAT scores was examined with a negative binomial regression model, whilst Poisson regression was used to model exacerbation recovery and CAT scores. Cross-sectional regression models were
used to analyze the relationship between inflammatory markers during exacerbation and CAT score as allowance could be made for repeated measures on the same patient.

RESULTS

Patient Characteristics

161 COPD patients completed at least one CAT questionnaire when stable (exacerbation free). Their baseline characteristics are reported in Table 1 alongside 75 patients who were assessed using the CAT at exacerbation and the 52 of these who completed the CAT questionnaire daily during exacerbation recovery. The patients had moderate to severe disease with a mean FEV₁ % predicted of 50.3% (range 14.0-79.7%). Patients in whom CAT was assessed at exacerbation had significantly higher exacerbation frequencies (p<0.001) but differed in no other respect.

Patients completed the CAT successfully when stable and when acutely unwell during an exacerbation. In total, 6404 out of 6514 questionnaires (98.3%) were completed fully. There was no significant difference in the percentages fully completed at baseline, 3496 of 3561 (98.2%) compared to those at exacerbation onset and during recovery, 2908 of 2953 (98.5%; p=0.35).

Use of CAT at Baseline

Baseline CAT and exacerbation frequency

The 161 patients had a mean baseline CAT score of 18.1 (SD 7.45). Frequent exacerbators
(≥2 exacerbations per year, n=80) had a mean CAT score of 19.5 (SD 6.6) compared to infrequent exacerbators (<2 exacerbations per year, n=81) whose mean CAT score was 16.8 (SD 8.0; p=0.025, Figure 2). Thus, there was an average 2.7 point difference in CAT score between the frequent and infrequent exacerbators.

Relationship between CAT score and systemic inflammatory markers in the baseline state

At baseline, serum CRP was measured on the same day as a CAT was completed in 318 blood samples obtained from 150 separate patients and plasma fibrinogen in 282 blood samples from 144 patients. There was a significant relationship between systemic inflammation, as measured by log_{10} fibrinogen, and CAT score on the day of baseline sampling, regression coefficient= 0.0014 (95% CI 0.0001-0.0027; p=0.035, Figure 3), R^2=0.024 using random-effects GLS regression. However, there was no statistically significant relationship between log_{10} CRP and CAT scores, regression coefficient = 0.0059 (95% CI -0.0016-0.0133; p=0.122).

No difference in baseline CAT scores was seen between patients with or without potentially confounding comorbidities (congestive heart failure, renal failure, obesity or sleep disordered breathing, Table 2), confirming previous work that CAT scores appear unaffected by low levels of comorbidity (18).

Use of CAT at exacerbation

The CAT was completed at 152 treated exacerbations by 75 patients. The median interval from diary card exacerbation onset to the day of treatment was 2 days (IQR 1-4). Figure 4
shows that the CAT score rose from an average baseline value of 19.4 (SD 6.8) to 24.1 (SD 7.3; p<0.001) at exacerbation.

The magnitude in rise of CAT score from baseline to exacerbation was not affected by patient baseline characteristics. Patients whose change in CAT score at exacerbation was on average greater or equal to 2 units displayed no significant difference in age (73.2 vs 70.3 years; p=0.13), FEV₁% predicted (47.6 vs 47.3 %; p=0.94) or exacerbation frequency (2.73 vs 2.48; p=0.586) from those with smaller changes in CAT score.

The symptomatic characteristics of exacerbations did not significantly affect the magnitude of CAT rise at exacerbation (see online supplement). Whilst patients within the London COPD cohort complete daily symptom diary cards which allows detection of exacerbations that are unreported to healthcare professionals and untreated with extra medication (7), all 152 exacerbations included in the analyses were treated. The vast majority of exacerbations were treated with systemic treatment following clinical review by a member of the research team; 103 exacerbations were treated with antibiotics and oral corticosteroids, 22 with antibiotics alone, and 7 with oral steroids alone. Just 20 patients increased inhaled therapy (bronchodilators and/or inhaled corticosteroids) alone without systemic treatment. Increases of more than 2 units in CAT score were associated with a greater likelihood of treatment with antibiotics (88.7% vs 70.4%; p=0.004) but not oral steroids (75.5% vs 66.7%; p=0.243).

The main analysis was repeated using a strict health care utilisation (HCU) definition of an exacerbation, based on physician review and increased systemic treatment. 132 exacerbations
fitted this criterion. The mean change in CAT score from baseline to HCU exacerbation was 5.2 units (SD 6.7, n=132). Mean change in CAT score from baseline to exacerbation for patients who received increased inhaled therapy alone was 2.0 (4.9), although this was based on just 20 exacerbations. Further work is required to further explore the relationships between changes in CAT at exacerbation and choice of exacerbation treatment.

**Relationship between CAT score and systemic inflammatory markers at exacerbation**

CAT scores at exacerbation were significantly related to concurrent levels of systemic inflammatory markers. At exacerbation, serum CRP was measured on the same day as a CAT was completed in 114 exacerbations and plasma fibrinogen in 111 exacerbations. After log_{10} transformation, both inflammatory markers were significantly related to the CAT score recorded at exacerbation, and with allowance for repeated measures in the same patient, log_{10}CRP increased by 0.028 (95% CI 0.013-0.043; p<0.001) and log_{10}fibrinogen by 0.003 (95% CI 0.001-0.005; p=0.015), per unit increase in CAT score. Change in CAT score from baseline to exacerbation onset was significantly related to change in CRP (rho=0.26; p=0.008) but not to change in fibrinogen (rho=0.09, p=0.351) from baseline to exacerbation.

**Lung function changes and CAT scores at exacerbation**

CAT scores were significantly related to contemporaneous spirometry, as measured by FEV$_1$. At exacerbation, spirometry was performed on the same day as a CAT was completed in 112 exacerbations. Mean paired FEV$_1$ measured at baseline was 1.12 L (SD 0.44) and 1.01 L at exacerbation (SD 0.44) (p<0.001). Rises in the CAT score recorded at exacerbation were significantly associated with falls in FEV$_1$ at exacerbation (rho=-0.20, p=0.032).
**Time Course of CAT scores during exacerbation recovery**

52 different patients completed the CAT questionnaire on at least 21 of 35 days during the recovery phase following an exacerbation. All of these 52 exacerbations were treated; 41 with antibiotics and oral steroids, 5 with antibiotics alone, 3 with oral steroids alone, and 3 were treated with increased inhaled therapy alone. **Figure 5** shows the time course of the CAT scores, PEFR and diary card symptom counts (further details are available in the online supplement).

**Relationship between CAT score and symptom recovery**

CAT scores reflected symptomatic recovery following exacerbations. Amongst the 52 episodes, the median recovery time as judged by symptom diary cards was 12 days (IQR 9-23, n=47) and this was significantly related (rho=0.42; p=0.012) to the time taken for the CAT score to return to baseline (median 11 days, IQR 4.5-17, n=40).
DISCUSSION

This novel study prospectively assessed the utility of the CAT to evaluate exacerbation severity in COPD patients. At exacerbation, CAT scores were significantly elevated from paired baseline values and we have uniquely demonstrated that CAT scores reflect exacerbation severity as measured by exacerbation length and reduction in lung function. A weak relationship was also found between systemic inflammatory markers and CAT scores at exacerbation. Furthermore, we have shown that baseline CAT scores are significantly elevated in stable COPD patients with a history of frequent exacerbations.

The CAT is a validated health status questionnaire that is free to use and can be administered without prior permission for research purposes and by individual practitioners (http://www.catestonline.org). Previous studies have shown that the instrument can be successfully administered in both primary (18) and secondary care settings (11), and is responsive to a course of pulmonary rehabilitation and able to distinguish different levels of response (11). Additionally, CAT scores exhibit little variability across countries; they are not influenced by age or sex but reflect disease severity in the stable state as determined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric staging, MRC dyspnea score, SGRQ and clinician-judged severity (10, 18).

Our study complements this existing work by demonstrating that the CAT can be used as a score of the multi-dimensional nature of COPD exacerbation severity. At present the assessment of symptom severity at exacerbation and during recovery is subjective in nature, with no established scoring system in clinical practice. Exacerbation therapy is currently
determined by a subjective physician assessment of exacerbation severity and so an objective tool to determine exacerbation severity will fulfill an important unmet need. This has particular relevance as patients are increasingly seen by healthcare professionals in the community, often within their own homes, without the benefit of objective measures of exacerbation severity such as accurate spirometry or systemic inflammatory markers. PEFR is a cheap, reliable and easy way for patients to assess lung function on a daily basis. We have shown in previous studies that PEFR decreases to a small extent but significantly at exacerbation onset and can be a useful tool to indicate exacerbation recovery in population studies. However the changes are not large enough to use PEFR at an individual level for exacerbation detection and monitoring (9).

An objective, validated exacerbation severity score is also required for use in clinical trials. Treatments to prevent exacerbations may also reduce exacerbation severity in addition to exacerbation frequency but at present tools to determine efficacy of this are limited and only exacerbation rates are usually recorded in clinical studies (19, 20). Most clinical trials to date have used therapy and hospitalization rates to assess exacerbation severity and thus an objective symptom severity score will enable the ability of novel interventions to reduce exacerbation severity to be assessed and compared across studies (21). Therapies involving either exacerbation prevention or management of the acute exacerbations may reduce exacerbation CAT scores or the time taken for scores to recover to baseline. Further evaluation of the CAT in clinical trials is now required.

The CAT provides an objective quantification of the impact of symptoms that is acceptable to patients and can be easily completed at exacerbation and during recovery. We have previously shown that systemic inflammation, as measured by plasma fibrinogen and serum
CRP increases at exacerbation (22-24), and in this study we have demonstrated a weak relationship between CAT scores at exacerbation and systemic inflammatory markers. Inflammatory changes at COPD exacerbations are also related to clinical non-recovery and recurrent exacerbations within 50 days (15). Recovery time is an index of exacerbation severity (9) and for the first time this study has evaluated use of the CAT during exacerbation recovery. We have demonstrated that CAT scores reflect recovery following exacerbations; the time taken for scores to return to baseline being significantly related to recovery time as judged by symptom diary cards. Additionally, at exacerbation, CAT scores are significantly but modestly related to contemporaneous lung function impairment, as measured by FEV₁, consistent with previous data examining the relationship between baseline CAT scores and FEV₁ (18). Thus CAT scores provide an easily quantifiable, overall score of exacerbation severity and may be useful in studies evaluating interventions for the management of acute exacerbations.

When measured in the stable state CAT scores are highly correlated to concurrent SGRQ measurements (10). However, this study has shown a divergence between the behavior of the CAT and SGRQ during exacerbation recovery. Following a study of exacerbations of chronic bronchitis, whilst an early improvement is seen in SGRQ scores when measured 4 weeks after an index event, improvements can also slowly continue for several months (25). In this study we found that CAT scores have returned to baseline levels more rapidly. This may be a result of the daily use of the instrument in this study and the response system in the CAT, which is based on categories of difference between two extreme statements about the same COPD impact. In contrast, the SGRQ has predominantly dichotomous yes/no responses and is administered at intervals. Thus, although we have demonstrated that the CAT can
reliably assess exacerbation severity, daily CAT readings may over-estimate the speed of recovery of health status post-exacerbation.

This study has also added to previous data examining the use of the CAT in the baseline stable state by examining the relationship between baseline CAT scores and exacerbation frequency. Patients with a history of frequent exacerbations have worse quality of life (7), increased risk of hospitalization (26) and greater mortality (8). Frequent exacerbators also exhibit faster decline in lung function (4) and may have worse functional status, as measured by time outdoors (16). In this study we have shown that baseline CAT scores relate to exacerbation frequency. When used in the stable state, scores were significantly elevated in frequent exacerbators, defined by two or more exacerbations per year, compared to infrequent exacerbators. Also, baseline CAT scores were weakly but significantly related to concurrent fibrinogen levels. We have previously shown that plasma fibrinogen levels are elevated in stable patients with COPD (23) and that increased systemic inflammation, as measured by fibrinogen, in stable COPD patients over time is directly linked to disease progression, as defined by lung function decline (27). Further work is required to explore whether CAT scores may potentially be a useful marker of disease progression over time in COPD.

Since our results indicate that CAT scores may reflect levels of systemic inflammatory markers, albeit weakly, this finding may have particular relevance in clinical trials of anti-inflammatory therapeutic agents in COPD. The effects of anti-inflammatory therapies are difficult to assess as changes in FEV$_1$ tend to be small (28) and exacerbation frequency as an outcome has to be assessed over at least a 12 month period. Further study is now required of CAT scores during anti-inflammatory interventions in COPD.
The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) is a patient-reported outcome diary specifically designed to quantify the frequency, severity, and duration of exacerbations of COPD in clinical trials (21). EXACT scores have been shown to differentiate patients who were stable from patients with mild and moderate exacerbations as judged by clinicians (21). However, to date no published data has demonstrated the relationship of EXACT scores to levels of systemic inflammation and lung function changes seen at exacerbation and during recovery. Furthermore, in published papers thus far, the EXACT has been used in conjunction with a personal digital assistant (21, 29) or Blackberry® smartphone (30), potentially limiting its widespread uptake in routine clinical practice.

We have shown that the CAT is a potentially useful, widely applicable tool which can aid assessment of exacerbation severity. The CAT can be easily and rapidly completed in many healthcare settings and could potentially be integrated into care bundles of COPD patients without additional cost. Patient recognition of exacerbation symptoms and prompt treatment improves exacerbation recovery and reduces the risk of hospitalization in COPD patients (31). Further evaluation is now required of the CAT within exacerbation management strategies to assess utility of the tool within clinical practice.

In conclusion, the CAT provides a reliable score of exacerbation severity. CAT scores increase at exacerbation and reflect exacerbation severity as determined by lung function and exacerbation length. A weak relationship was also found between systemic inflammatory markers and CAT scores at exacerbation. Thus, the CAT is a valuable instrument to enhance and standardize COPD exacerbation assessment. Incorporating this questionnaire into assessment strategies may aid health care professionals to determine the severity of
exacerbations, particularly in situations where access to other objective measures of severity is limited. The CAT may also prove useful in clinical trials to objectively assess the ability of novel interventions to reduce exacerbation severity.

**Acknowledgements**

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REFERENCES


Figure legends

Figure 1. COPD Assessment Test

Figure 2. Mean baseline CAT scores between frequent and infrequent exacerbators (161 patients). Vertical lines represent standard errors.

Figure 3. Relationship between log_{10} fibrinogen and CAT score at baseline (282 samples from 144 patients).

Figure 4. Mean CAT scores at baseline and exacerbation for 152 exacerbations (75 patients). Vertical lines represent standard errors.

Figure 5. Time course of CAT scores, PEFR and diary card symptom counts during exacerbation recovery (52 patients). Vertical bars represent standard errors. Horizontal lines indicate mean baseline scores.
Table 1. Clinical characteristics of patients in the baseline, exacerbation and recovery analyses

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‡ Comparison between 75 patients with exacerbation CAT scores at exacerbation and 86 patients in whom an exacerbation was not examined.

† Comparison between 52 patients with exacerbation CAT scores during recovery and 109 patients in whom a recovery time course was not examined.
Table 2. Effect of Comorbidities on Baseline CAT Score

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</tr>
<tr>
<td>(n=130)</td>
<td>(n=29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cardiovascular disease (excluding hypertension)</td>
<td>17.8 ± 8.0</td>
<td>18.9 ± 6.6</td>
<td>0.396</td>
</tr>
<tr>
<td>(n=102)</td>
<td>(n=57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17.7 ± 8.4</td>
<td>18.6 ± 6.7</td>
<td>0.469</td>
</tr>
<tr>
<td>(n=73)</td>
<td>(n=86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>18.0 ± 7.5</td>
<td>22.9 ± 5.4</td>
<td>0.119</td>
</tr>
<tr>
<td>(n=153)</td>
<td>(n=6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity (body mass index &gt;30kg/m²)</td>
<td>18.0 ± 7.7</td>
<td>18.7 ± 6.4</td>
<td>0.655</td>
</tr>
<tr>
<td>(n=122)</td>
<td>(n=36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>18.5 ± 7.6</td>
<td>16.5 ± 6.2</td>
<td>0.205</td>
</tr>
<tr>
<td>(estimated glomerular filtration rate &lt;60ml/min)</td>
<td>(n=126)</td>
<td>(n=29)</td>
<td></td>
</tr>
<tr>
<td>Severe chronic kidney disease</td>
<td>18.1 ± 7.4</td>
<td>21.0 ± 4.5</td>
<td>0.500</td>
</tr>
<tr>
<td>(estimated glomerular filtration rate &lt;30ml/min)</td>
<td>(n=152)</td>
<td>(n=3)</td>
<td></td>
</tr>
</tbody>
</table>
Utility of the COPD Assessment Test\textsuperscript{TM} (CAT) to evaluate severity of COPD exacerbations

Alex J Mackay\textsuperscript{1} * MBBS MRCP, Gavin C Donaldson\textsuperscript{1} PhD, Anant RC Patel\textsuperscript{1} MB BS MRCP, Paul W Jones\textsuperscript{2} PhD FRCP, John R Hurst\textsuperscript{1} PhD FRCP, Jadwiga A Wedzicha\textsuperscript{1} MD FRCP

Use of CAT at exacerbation

Results were unaffected by the timing of the baseline. In 98 exacerbations where a baseline CAT score was available prior to the index exacerbation, the CAT score rose from an average baseline value of 19.0 to 24.3 (p<0.001) at exacerbation. In the main analysis, in 152 exacerbations using baselines obtained during stable periods that occurred prior to or following exacerbations, the CAT score rose from an average baseline value of 19.4 to 24.1 (p<0.001) at exacerbation.

Effect of exacerbation frequency phenotype on CAT change at exacerbation

It does not appear that our exacerbation data from 75 patients who experienced 152 exacerbations was affected by a few patients with frequent exacerbations. In analyses which examined the average change from baseline to exacerbation for each of the 75 patients, the mean change was 4.98 units, compared to 4.70 in the main results for 152 exacerbations.
**Exacerbation characteristics**

The symptomatic characteristics of exacerbations did not affect the magnitude of CAT rise at exacerbation, except those few exacerbations characterized by the presence of the 3 symptoms of dyspnea, cold and sore throat only, which had significantly increased rises in CAT scores at exacerbation compared to those without (n=8, mean 11.5, SD 8.2 vs n=144, mean 4.4, SD 6.3, p=0.003). Exacerbations associated with symptoms of both increased sputum volume and purulence did not display a significantly increased change in CAT score compared to those without (n=61, mean 5.3, SD 6.7 vs n=91, mean 4.4, SD 6.5, p=0.392). This may be due to the absence of a specific question assessing sputum purulence in the CAT.

**Peak CAT scores**

CAT scores rose further following exacerbation onset to reach a maximum, peak CAT score. CAT scores in the recovery subgroup increased from a mean baseline score of 18.3 (SD 7.5) to a mean peak score of 26.5 (SD 7.1; p<0.001, Figure E2).

**Repeatability during exacerbations**

Of the 75 patients included in the main exacerbation analysis, 38 underwent at least one further subsequent exacerbation. No difference was seen in the magnitude of change from baseline to exacerbation between their first and second exacerbation (mean 5.2 vs 5.3, p=0.924). 19 of the 52 recovery subgroup patients recorded CAT scores during a second exacerbation. There was no difference in peak CAT score between first and second
exacerbation (mean 27.0 (SD 7.86) versus 26.4 (8.5); p=0.687, Figure E3) or in the change from baseline to peak score (6.7 (SD 4.9) versus 6.1 (5.1); p=0.687).

**Temporal relationships between CAT scores, PEFR and symptom counts (figure 5 in main manuscript)**

Symptom counts were obtained by summing each increased respiratory symptom recorded on the London cohort diary cards per day (see online figure E5). The mean baseline symptom count (denoted by horizontal line) lies at greater than zero because patients may record sporadic increases in 1 or more symptoms but not reach the definition of an exacerbation (increase for two consecutive days in respiratory symptoms, with at least one major symptom (dyspnea, sputum purulence or sputum volume) plus either another major or a minor symptom (wheeze, cold, sore throat, and cough)). This phenomenon of patients experiencing sporadic increases in respiratory symptoms following the end of an exacerbation is also the reason for the slight elevation of symptom counts above baseline at 12 days (recovery time). The last day of recorded worsening symptoms before two consecutive symptom-free days defined the end of the exacerbation.
Figure Legends

Figure E1. Schematic timeline of CAT scores (x) recorded during exacerbation. Exacerbation CAT score (▲) was the CAT score recorded on the day treatment commenced. CAT Recovery □ was the time taken from exacerbation onset for the CAT score to return to baseline value. This figure is for illustrative purposes only and does not indicate real data.

Figure E2. Change in CAT scores from baseline to peak exacerbation value for 52 exacerbations (52 patients).

Figure E3. Repeatability of CAT changes at separate exacerbations (19 patients).

Figure E4. Front of Symptom Diary Card

Figure E5. Back of Symptom Diary Card
How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Examples: I am very happy ✓ 3 2 1 0 I am very sad

I never cough 0 1 2 3 4 5 I cough all the time

I have no phlegm (mucus) in my chest at all 0 1 2 3 4 5 My chest is completely full of phlegm (mucus)

My chest does not feel tight at all 0 1 2 3 4 5 My chest feels very tight

When I walk up a hill or one flight of stairs I am not breathless 0 1 2 3 4 5 When I walk up a hill or one flight of stairs I am very breathless

I am not limited doing any activities at home 0 1 2 3 4 5 I am very limited doing activities at home

I am confident leaving my home despite my lung condition 0 1 2 3 4 5 I am not at all confident leaving my home because of my lung condition

I sleep soundly 0 1 2 3 4 5 I don’t sleep soundly because of my lung condition

I have lots of energy 0 1 2 3 4 5 I have no energy at all

TOTAL SCORE

Figure 1.
157x222mm (96 x 96 DPI)
Figure 2.
89x72mm (96 x 96 DPI)
Figure 3.
93x65mm (96 x 96 DPI)
Figure 4.
87x64mm (96 x 96 DPI)
Figure 5.
78x142mm (96 x 96 DPI)
Figure E1.
159x89mm (96 x 96 DPI)
Figure E2.
84x60mm (96 x 96 DPI)
Instructions for filling in the DIARY CARDS

EVERY DAY...

1. After taking morning medications record the best of 3 attempts at the PEAK FLOW blowing test in the box on the sheet.
2. Please record any WORSENING of symptoms ABOVE YOUR USUAL daily level. The symptoms we are interested in are listed below, just put the appropriate letter in the box on the sheet. Continue recording until the symptom has gone away or got back to the level you consider 'normal'.

<table>
<thead>
<tr>
<th>Letter</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>increased BREATHLESSNESS.</td>
</tr>
<tr>
<td>B1</td>
<td>increased SPUTUM COLOUR.</td>
</tr>
<tr>
<td>B2</td>
<td>increased SPUTUM AMOUNT.</td>
</tr>
<tr>
<td>C</td>
<td>a COLD (such as a runny or blocked nose).</td>
</tr>
<tr>
<td>D</td>
<td>increased WHEEZE or CHEST TIGHTNESS.</td>
</tr>
<tr>
<td>E1</td>
<td>SORE THROAT.</td>
</tr>
<tr>
<td>E2</td>
<td>increased COUGH.</td>
</tr>
<tr>
<td>F</td>
<td>FEVER.</td>
</tr>
</tbody>
</table>

If you experience a worsening in any of these symptoms please phone us to arrange an assessment visit, and do this BEFORE starting any antibiotic or steroid tablets. The phone number is ************.

Anant or Alex will have the phone and we can usually arrange to see you later the same day.

Please phone if you are not sure what to write down or you have any questions.

3. Please record any CHANGE to your usual treatment for as many days as it applies.

<table>
<thead>
<tr>
<th>Letter</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>I am in Hospital.</td>
</tr>
<tr>
<td>I</td>
<td>I am taking more than usual INHALED STEROID (red/brown/purple)</td>
</tr>
<tr>
<td>R</td>
<td>I needed to take extra RELIEVER (blue/green/grey/iodo/bson). HOW MANY PUFFS? Write, eg R3 for 3 puffs, R2 for 2 etc.</td>
</tr>
<tr>
<td>S</td>
<td>I am taking STEROID (Prednisolone) TABLETS. HOW MANY TABLETS? Write, eg S6 for 6 tablets, S5 for 5 etc.</td>
</tr>
<tr>
<td>X</td>
<td>I am taking ANTIBIOTIC TABLETS. PLEASE RECORD WHICH (write the name on the diary card).</td>
</tr>
</tbody>
</table>

4. Finally, please estimate the time that you were out of your own home on the previous day.

Figure E5.

160x225mm (96 x 96 DPI)