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The quality of life impact of acute exacerbations of chronic bronchitis (AECB): A literature review

Jordana K. Schmier[1], Michael T. Halpern[1], Mitchell K. Higashi[2] & Alan Bakst[2]
[1]*Exponent, Alexandria, VA, USA;* [2]*GlaxoSmithKline, Collegeville, PA, USA.*
(E-mail: ischmier@exponent.com)

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Abstract

Background: The impact of acute exacerbations of chronic bronchitis (AECB), a common consequence of chronic obstructive pulmonary disease (COPD), is extensive, with symptoms ranging from mild to life threatening. Health-related quality of life (HRQL) is impaired in patients with COPD, but little is known about the direct effect of exacerbations on HRQL. *Methods*: MEDLINE and EMBASE literature searches were conducted; reference lists of identified articles were reviewed. *Results*: Eighteen studies reporting the impact on HRQL of acute exacerbations were identified. Study design and patient population varied. Six studies evaluated HRQL once; only four studies used both generic and disease-specific HRQL measures. Cross-sectional studies reported HRQL decrements during exacerbations and suggested that HRQL is a good predictor of health care resource utilization. Pharmacological treatment led to within-group improvements following AECBs. Non-pharmacological intervention studies were small and inconclusive. Longitudinal studies, assessing pharmacological and non-pharmacological interventions, found that HRQL improved from exacerbation to recovery, with responsiveness depending on sensitivity of the measure. Frequency of exacerbations was a significant predictor of HRQL. *Conclusions*: Exacerbations lead to substantial reductions in HRQL, both in physical as well as other domains. Further research should assess the impact of specific treatment regimens and the timeline for the recovery process.

Key words: Bacterial infections, Chronic bronchitis, Chronic obstructive pulmonary disease, Exacerbations, Quality of life

Abbreviations: AECB – acute exacerbation(s) of chronic bronchitis; AUC – area under the curve; COPD – chronic obstructive pulmonary disease; CRQ – chronic respiratory disease questionnaire; FEV_1 – forced expiratory volume in 1 s; HRQL – health-related quality of life; HUI – health utilities index; LTOT – long-term oxygen therapy; MYMOP – measure yourself medical outcomes profile; NHP – Nottingham health profile; PGWB – psychological general well-being scale; SF-36 – short form 36; SIP – sickness impact profile; SGRQ – St George's respiratory questionnaire; SOLDQ – Seattle obstructive lung disease questionnaire

Introduction

Chronic obstructive pulmonary disease (COPD), a progressive condition marked by irreversible airflow deterioration, has a substantial impact on patients' well being. Worldwide prevalence of COPD is estimated to be 9.34/1000 among men and 7.33/1000 among women, but is higher among older adults [1]. COPD is the fourth most common cause of death worldwide and in the US among patients over 45 years of age; direct health care costs in the US are estimated at $18 billion per year [2].

Key symptoms of COPD include cough, sputum production, and exertional dyspnea. Patients with bronchitic COPD are prone to acute exacerbations,

known as AECB (acute exacerbations of chronic bronchitis), characterized by extreme breathlessness and increased chest tightness, wheezing, cough, or sputum changes. Antibiotic treatment is recommended for an AECB with signs of airway infection, including increased sputum or fever; this etiology is responsible for 50–70% of AECB [1]. For these and particularly for non-infectious AECB, treatments can also include inhaled bronchodilators, theophylline, oral glucocorticosteroids, or non-invasive intermittent positive pressure ventilation (NIPPV) [1]. During severe exacerbations, forced expiratory volume in 1 sec (FEV_1) may be less than 1.0 l. These exacerbations can be life-threatening for those with severe COPD, with up to 10% mortality among patients admitted to the hospital [3]. Exacerbations can lead to long-term, irreversible lung function loss, further demonstrating the importance of appropriate and timely antibiotic treatment for exacerbations of bacterial etiology [4].

While there is no absolute consensus on the classification of COPD severity or the definition of AECB, several tools are available, including those of the European Respiratory Society, British Thoracic Society, and American Thoracic Society [5–7]. Anthonisen's classification scheme for describing exacerbation severity is the most commonly used [8]. In this scheme, a mild (Type 3) exacerbation is defined by the presence of one of three cardinal symptoms (increased dyspnea, sputum purulence, sputum production) as well as one or more additional minor symptoms (increase in nasal discharge, wheeze, sore throat, cough, fever); moderate (Type 2) is characterized by the presence of two of the three cardinal symptoms, and a severe exacerbation (Type 1) includes all three cardinal symptoms.

Health-related quality of life (HRQL) is a comprehensive measure of physical, psychological, and social functioning that is an important outcome across diseases. Its use as an evaluative tool in COPD has a strong history [9]. Several HRQL instruments, both generic and disease-specific, have been validated for use in the COPD population. In addition, much is known about HRQL in COPD patients; studies have evaluated the HRQL impact of numerous pharmacological and non-pharmacological therapies, including, for example, pulmonary rehabilitation [10], long-term oxygen therapy (LTOT) [11], and lung volume reduction surgery [12]. While both frequency/number of AECBs and HRQL are common endpoints in clinical trials of COPD therapies, little is known about the direct impact of AECB on HRQL.

Objective

The objectives of this paper are to assess the HRQL impact of AECB and the HRQL impact of treatment for these exacerbations. A secondary objective is to provide guidance on assessment of HRQL in this population.

Methods

We conducted literature searches of MEDLINE and EMBASE databases to identify articles with the MeSH headings and keywords related to COPD, exacerbations and HRQL. In MEDLINE, this included the use of the following word groups as keywords, MeSH headings, title words, or abstract words: *COPD*; *lung disease, obstructive*; *bronchitis*; *emphysema*; *exacerbation*(*s*); and *quality of life*. In EMBASE, we excluded letters and reviews and used the same words and searched in the fields for title, descriptors, identifiers, and abstract words. Articles published in languages other than English were excluded. The literature was reviewed from each database inception through April 2004. Articles were selected for review based on their assessment of HRQL associated with an AECB using a multidimensional, validated measure. Our guidelines for instruments appropriate for use in COPD are consistent with the definitions and lists on the American Thoracic Society Quality of Life Database web site (www.atsqol.org). We did not define exacerbations *a priori* but rather report how each paper defined them.

Results

Article identification

After excluding articles found in both databases, a total of 140 unique publications were identified.

These papers underwent an abstract review; most were retrieved for a full review. Reference lists of identified articles were also reviewed for additional relevant publications. Many papers were excluded because they mentioned HRQL but did not assess it. Others described frequency or severity of exacerbations, but did not assess the relationship between HRQL and exacerbations. These papers are useful for understanding the impact of COPD and its treatment on HRQL and exacerbations but do not address the objectives of this review.

We identified 18 studies (representing 20 published papers) assessing HRQL associated with AECB. These studies varied in their goals and assessment methods; however, they each used a validated instrument to assess generic or condition-specific HRQL at one or more time points in patients with documented COPD and an acute exacerbation. Of the 18 studies identified, 12 were conducted in Europe and 6 in North America. Following we summarize the study design and patient population, the choice of HRQL assessments, and then address the impact of AECB on HRQL and the impact of various treatments for AECB on HRQL.

Study design and patient population

The studies identified utilized a range of study designs. Two studies were double-blind and randomized [13, 14]; six others were randomized, but not blinded (often necessary because of the nature of intervention) [15–20]. One randomized study of pharmacological interventions was not randomized by patient, but rather by site [19]. The other 10 identified papers described prospective cohort studies. The studies were divided in methods used for identification of participants; several studies recruited patients presenting to the hospital or emergency room, while others had investigators identify current patients with diagnosed COPD.

Patients were fairly homogenous, as is the COPD population in general. The mean age of most study populations was in the upper 60's. With few exceptions, most study populations were just over half male. Mean FEV_1% predicted is between 30 and 40, when reported. Exacerbations were identified in a number of different ways. Half the studies used the Anthonisen criteria for identifying an exacerbation, however, they were almost evenly split between those requiring a severe, a moderate or severe, or any exacerbation at enrollment. Other studies used a symptom-based approach that was not fully specified, but as most of these studies recruited patients directly from hospitalizations, the likelihood that they experienced moderate to severe exacerbations is high. Finally, one study that recruited hospitalized patients looked for appropriate ICD-9 codes to identify an exacerbation [21].

Instrumentation

Three condition-specific instruments were utilized, while seven methods or instruments of assessing generic HRQL and utilities were used. Table 1 presents a brief overview of the generic instruments used in these studies and Table 2 summarizes the condition-specific instruments. The length of these tables raises an important issue about the instrumentation across these studies. Few instruments are used more than once, presenting difficulties in interpretation across studies. The instrument most widely used was the St George's respiratory questionnaire (SGRQ) [22], for which there are published guidelines for interpretation and which has been widely used in pharmacological and non-pharmacological interventions. Very few studies used both a generic and a disease-specific instrument. The objectives of two studies were designed specifically to examine instrument responsiveness and measurement properties [23, 24].

The impact of AECB on HRQL – non-intervention studies

Six studies that examined HRQL once during an AECB episode are detailed in Table 3 [21, 39–43] as are three additional longitudinal non-intervention studies [23, 24, 44]. These studies included fairly severe COPD patients, with FEV_1% predicted approximately 40. However, the range of scores for the SGRQ was wide (mean 54.4 on the activity component in Osman et al. [41] vs. 74.5 in Seemungal et al. [42]). The varied objectives of these papers make it difficult to aggregate their findings; in general, patients with or more severe exacerbations have lower quality of life, although appropriate treatment minimizes the impact of an exacerbation.

Table 1. Generic instruments used in acute exacerbations

Instrument name	Brief description	Change/interpretation
EQ-5D [25]	Number of items: 5 plus visual analogue scale Available score: total plus visual analogue scale Score range: 0–1; higher scores indicate better health status and 0–100; higher scores indicate better health status	Score calculated using weighting scheme derived from large (UK) population survey
Health utilities index (HUI) [26]	Number of items: 8 Available score: total Score range: 0–1; higher scores indicate better functioning	Score calculated using weighting scheme derived from large population survey
Medical outcomes study short form-36 (SF-36) [27–29]	36 items Available scores: two summary scores (physical component summary, mental component summary); eight scales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health) Score range for each summary/scale: 0–100; higher scores indicate better health status Abbreviated versions also available (e.g., MOS-6A)	Normative values are available for several countries and disease populations Not formally tested but general acceptance of 5 points on scales as indicative of clinically meaningful change [30] No empirical evidence of change scores on PCS and MCS
Measure yourself medical outcomes profile (MYMOP) [31]	Number of items: 4 Available scores: total score (mean of item scores) Score range: 0–6; higher scores indicate worse health	Untested. Individualized nature of two items is unique among reviewed instruments
Nottingham health profile (NHP) [32]	Number of items: 38 Available scores: six domains (physical mobility, pain, sleep, social isolation, emotional reactions, activity levels) Score range: 0–100; higher scores indicate worse functioning	Normative values are available for certain countries/populations
Psychological general well-being scale (PGWB) [33]	Number of items: 22 Available score: total, six subscales (anxiety, depressed mood, positive well-being, self-control, general health, vitality) Score range: 0–110; higher scores indicate higher well-being	Neither norms nor guidelines for interpretation of change are available. Not universally considered a multidimensional instrument; some classify as tool for psychological functioning only

Sickness impact profile (SIP) [34, 35]	Number of items: 136 Available scores: two overall domains (physical and psychosocial); 12 categories (sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior, communication) Score range: 0–100; higher scores indicate more impairment	Normative values not formally obtained; published values from various studies often used to assist interpretation

Single HRQL assessment

Two studies evaluated HRQL of patients hospitalized for exacerbations and followed them for at least 6 months to evaluate predictors of survival following an acute exacerbation [39, 40]. Almagro et al. identified consecutive patients hospitalized for exacerbations, assessed HRQL at baseline, and then examined mortality over 2 years [39]. The 96% follow-up at 2 years is remarkable. Not surprisingly, patients who were older or who had fewer social resources were significantly less likely to be alive at the end of the study, so were women and unmarried patients. In general, patients with worse scores on the SGRQ at baseline were less likely to survive; this was significant with the SGRQ total score (OR: 1.32; 95% CI: 1.14–1.53) and activity component (OR: 1.21; 95% CI: 1.04–1.4). In addition, using a cut off as an SGRQ activity component score of $\geqslant 66$, poor quality of life was independently associated with mortality.

Connors and colleagues prospectively followed COPD patients admitted to the hospital for an AECB for 6 months to determine predictors of survival [40]. One-third of the subjects did not survive to the 6-month assessment, and missing HRQL data were common. At the time of the exacerbation, patients reported substantial impairment in ADLs. At the 2-month assessment, scores on the sickness impact profile (SIP) indicated severe impairment. Comparative data on the SIP suggest that this indicated more impairment than among community-dwelling elderly and chronic low back pain sufferers and less impairment than patients with osteoarthritis of the knee or hip [34]. At the 6-month assessment, respondents viewed their rated their current health as fairly poor and almost one-fifth were willing to trade a year in their current health state for less than 6 months in perfect health. Despite the use of different measures at different time periods, this study demonstrates a substantial HRQL impairment associated with COPD and AECB.

Fan et al. [21] also assessed HRQL of patients with COPD at baseline and followed them for 1 year. The objectives of this study were to determine if HRQL, as evaluated with the seattle obstructive lung disease questionnaire (SOLDQ) [46], was a significant predictor of COPD hospitalizations for exacerbations. Only 4.3% of the over 3000 participants were hospitalized for

Table 2. Condition-specific instruments used in acute exacerbations

Instrument name	Brief description	Change/interpretation
Chronic respiratory questionnaire (CRQ) [36]	Number of items: 20 Available scores: total, four domains (dyspnea, fatigue, emotional function, mastery) Score range: 1–7; higher scores indicate better HRQL	Reported small/moderate/large clinically meaningful change = 0.5, 1.0, 1.5 points [35]
Seattle obstructive lung disease questionnaire (SOLDQ) [37]	Number of items: 29 Available scores: four domains (physical function, emotional function, coping skills, treatment satisfaction) Score range: 0–100; higher scores indicate better functioning/ skills/satisfaction	Neither norms nor guidelines for interpretation of change are available
St George's respiratory questionnaire (SGRQ) [22]	Number of items/responses: 50/76 Available scores: total, three components (activities, impacts symptoms) Score range: 0–100; higher scores indicate more impaired functioning	Reported small/moderate/large clinically meaningful change = 4, 8, 12 points [38]

COPD during the study period. Patients who were in the lowest quartile for the three domains of the SOLDQ and the physical component summary scores of the SF-36 had a significantly higher risk of being hospitalized for COPD than those in the highest quartile (scores adjusted for age, site, employment, smoking, distance from medical center). Further multivariate analyses examined the role of disease severity; although the physical function domain of the SOLDQ was a better predictor than the emotional function or coping skills, all remained significant predictors of COPD-related hospitalization.

Osman et al. used the SGRQ [22, 38] to assess HRQL at baseline of a 12-month study among patients presenting to acute care for an AECB [41]. There were significant differences on all SGRQ scores (total and all components) between patients who survived and were not re-admitted compared to patients who were re-admitted or died ($p < 0.05$). Initiation of domiciliary oxygen therapy was not associated with baseline HRQL, although patients prescribed nebulizers at discharge had significantly higher (worse) scores on the SGRQ total and the impacts and activity components than those who were not prescribed nebulizers ($p < 0.05$). Odds ratios adjusted for age, pulmonary function, and sex also indicated that re-admission was significantly related to SGRQ scores. The authors suggest that coping and distress, as reflected in the SGRQ, rather than symptoms and pulmonary function, may be drivers of re-admission.

Two studies prospectively followed patients who were required to keep a daily symptom diary [42, 43]. Seemungal and colleagues followed outpatients with COPD for 1 year and required them to record daily peak expiratory flow and symptoms [42]. Exacerbations were identified either by presentation at the clinic or retrospectively, by evaluation of diary data. Patients were categorized as having infrequent (<3) or frequent (⩾3) exacerbations during the study period. There were significant differences on all SGRQ scores by frequency of exacerbation. However, time since last exacerbation (mean 101 ± 74 days) was not related to SGRQ scores. Given the relationship between frequency of exacerbations and HRQL, the authors suggest that reduction of exacerbations appears to be an important tactic for improving HRQL among COPD patients.

Wilkinson et al. assessed HRQL in a subset of COPD patients who had completed 1 year or more

Table 3. Summary of reviewed studies – the impact of AECB on HRQL

Reference	Study design, population, country	Methods and instrumentation	Findings
Aaron et al. [44]	Prospective cohort study Patients with AECB presenting to emergency room $n = 70$ Mean age 70 years 57% male Mean $FEV_1 = 0.96$ (± 0.41) Canada	Assessment of HRQL and dyspnea at baseline and at relapse or 10 days later, if patient did not relapse Exacerbations defined using Anthonisen criteria (any severity level) Condition-specific: CRQ	Patients who did not relapse had significant and substantial improvements in all domains of the CRQ ($p < 0.001$, with large changes in dyspnea, fatigue and mastery and moderate change in emotional function). Patients who relapsed had a tendency to deteriorate on dyspnea, fatigue, and emotional function scales and to improve on the mastery scale. Control patients demonstrated no change (0–0.1 points).
Almagro et al. [39]	Prospective cohort study Patients with AECB being discharged from a hospital $n = 135$ Mean age 72 years 92% male Spain	Assessment of HRQL at baseline. Exacerbations defined as breathlessness, respiratory failure, or change in mental status due to COPD requiring hospitalization Disease-specific: SGRQ	Patients who were alive at 12 months had lower (better) scores on all SGRQ components, with differences on the activity component and the total score significantly different. A good SGRQ activity component score (defined as < 66) at baseline was a significant predictor of survival (OR: 2.62, 95% CI: 1.43–4.78).
Connors et al. [40]	Prospective cohort study Patients with AECB being admitted to a hospital $n = 1016$ Median age 70 years 52% male Median $FEV_1 = 0.8$ l United States	Assessment of HRQL and health status at 2 and 6 months after hospital admission. Exacerbations defined as breathlessness, respiratory failure, or change in mental state due to COPD requiring hospitalization. Generic: SIP (2 month interview); time trade-off (6 month interview)	At 2 months, patients exhibited SIP scores that indicated moderate to severe impairment (mean score: 20). At 6 months, almost two-thirds of respondents were willing to trade a year in their current health state for <1 year of perfect health; 17% were willing to accept <6 months of perfect health and half of the respondents rated their health status at 50 or less on a scale of 0–100, where 0 represented death and 100 represented perfect health.
Doll et al. [23]; Substudy: Doll et al. [45]	Prospective cohort study Patients with AECB presenting to study investigator $n = 755$, with 320 participating in the HRQL substudy Mean age 60 years 56% male AECB severity (Anthonisen): 29% mild, 46% moderate, 26% severe Germany	Assessment of HRQL at baseline (during AECB) and 6 months afterwards. Exacerbations defined using Anthonisen criteria (any severity level) Generic: NHP Condition-specific: SGRQ	Scores were significantly different between AECB and 6 months after AECB on all domains of the NHP (energy, pain, emotional reactions, sleep, social isolation, physical mobility, $p < 0.05$) and the activity, impacts, and total scores of the SGRQ (7.5, 8.1, 6.9 points, respectively, all $p < 0.001$). Substudy examined comparative responsiveness of NHP and SGRQ at exacerbation and 6 months later and found the SGRQ was less responsive (particularly the Symptoms component) than the NHP and other SGRQ component but more sensitive than the NHP.

Table 3. (Continued)

Reference	Study design, population, country	Methods and instrumentation	Findings
Fan et al. [21]	Prospective cohort study Patients reporting having chronic lung disease who were participants in a study implemented at Veterans Affairs medical centers $n = 3282$ Mean age 66 years 96% male United States	Assessment of HRQL at baseline Exacerbations defined as hospitalization with ICD-9 code 490–493, 496, 460–466, 480–487 Generic: SF-36 Condition-specific: SOLDQ	Patients in the lowest score quartile for each of the SOLDQ domains (physical function, emotional function, coping skills) had an increased risk of having a COPD-related hospitalization (i.e., exacerbation). Patients in the lowest quartile of the SF-36 PCS scores also had an increase risk of COPD-related hospitalization. Patients in the lowest quartile of the SF-36 MCS scores had no increased risk for COPD-related hospitalization.
Osman et al. [41]	Prospective cohort study Patients with AECB being admitted to a hospital $n = 266$ Mean age 68 years 52% male Mean FEV_1% predicted $= 38.8\%$ ($\pm 18.8\%$) Scotland	Assessment of HRQL at study entry Exacerbations defined as having a discharge diagnosis of COPD associated with the hospitalization Condition-specific: SGRQ	Scores of patients who completed the study and were not re-admitted were significantly higher on all components ($p < 0.05$) than those of patients who died or were re-admitted during the year. Differences indicated small but meaningful differences (3.3–5.6 points)
Paterson et al. [24]	Prospective cohort study Patients with AECB presenting to study investigator $n = 81$ Mean age 61 years 46% male Scotland	Assessment of HRQL at baseline (during AECB) and 1 week after completion of treatment Exacerbations defined using Anthonisen criteria (moderate or severe) Generic: MYMOP, medical outcomes study 6-item general health survey (MOS-6A), EQ-5D	MYMOP was more sensitive to change than the other instruments, suggesting it may be useful in short-term assessments of AECB.
Seemungal et al. [42]	Prospective cohort study Patients with COPD who had an AECB in prior year $n = 70$ 74% male Mean age 68 years Study design, population, country Mean FEV_1% predicted $= 40.0\%$ ($\pm 19.0\%$) England	Assessment of HRQL at end of study (12 months) Exacerbations defined using Anthonisen criteria (any severity level) Condition-specific: SGRQ	Patients having three or more exacerbations during the study year had significantly lower scores on all SGRQ components ($p = 0.002$) than patients with two or fewer exacerbations, with differences large (12–22 points).

Wilkinson et al. [43]	Retrospective assessment of diary cards. Patients with COPD who had completed diary cards for 1 year or more $n = 128$ Mean age 67 69% male Mean FEV_1% predicted = 40.8% ($\pm$15.6%) England	Assessment of HRQL at recruitment or first annual visit. Exacerbations defined using Anthonisen criteria (any severity level). Condition-specific: SGRQ	There was a significant relationship between reported (i.e., treated) exacerbations and total SGRQ scores ($r = -0.22$, $p = 0.018$), with those who reported more of their exacerbations having better HRQL. Significant relationships were also seen between reporting exacerbations and impact and activity components.

of diary cards as part of their participation in a multi-year study [43]. Exacerbations were identified if they required medical card (reported) or if they were recorded in diary cards (unreported). Patients were categorized based on the percentage of their exacerbations that were reported and HRQL was compared across quartiles. Those who reported more of their exacerbations had significantly better overall SGRQ scores as well as better scores on the impact and activity components. However, since HRQL was not evaluated at the same time point for all participants and could have been at recruitment or 1 year later, no causality can be inferred. Several possibilities are raised; patients with better HRQL may be more motivated to seek treatment, or those who seek treatment for exacerbations have better HRQL as a result of the treatment.

Multiple HRQL assessments and instrument responsiveness

Three studies assessed HRQL longitudinally; two of these were specifically concerned with the performance of various HRQL assessment tools [23, 24] while the third looked at the recovery process [44]. Doll and colleagues followed patients presenting with an AECB to internists or general practitioners for 6 months [23]. (Doll et al. also reports on the same study population [45].) Both the SGRQ and the NHP (Nottingham health profile) were completed at baseline and 6 months, although missing data were common. On all domains of the NHP and all SGRQ components except for symptoms, there were significant differences between mean scores at AECB and the non-AECB assessment. Differences on the SGRQ total, activity, and impacts scores exceeded the 4.0 points indicative of clinically meaningful change. There were significant differences by severity of AECB, using the Anthonisen criteria, on all SGRQ scores at the AECB and on symptoms, impacts, and total score at the non-AECB assessment.

A 1 week-long study found that the individualized measure yourself medical outcome profile (MYMOP) was more sensitive to change during recovery from an AECB than the generic EQ-5D and the MOS-6A [24]. The other found that from AECB to a stable period 6 months later, the generic NHP was more sensitive to change than the condition-specific SGRQ [45]. It also provides useful information on sociodemographic and clinical

characteristics that may affect HRQL. The MY-MOP is heavily symptom-weighted and therefore it is not surprising that it is more sensitive to short-term change than instruments that capture a broader array of functioning. The different recall periods of the instruments or the long time between assessments may have contributed to their responsiveness findings, suggest Doll and colleagues [45]. Together, these studies suggest that much more work needs to be done evaluating the responsiveness of instruments in order to make appropriate selections for future studies. In general, the complimentary use of generic and disease-specific instruments is advocated so the generic instrument can be used for comparisons across studies and the disease-specific instrument can be used to evaluate change. These studies question that assumption, but neither definitively resolves the issue.

HRQL of patients who relapsed vs. those who did not relapse after emergency room AECB treatment were compared by Aaron et al. [44]. Ten days after admission and completion of the chronic respiratory questionnaire (CRQ), or 48 hours after relapse (whichever came first), patients completed the CRQ a second time. Patients were treated with ipratropium and salbutamol, antibiotics, and/or oral steroids. Sixty-six patients participated, 49 of whom did not relapse. In addition, 10 control patients, recruited from the original cohort 9 months after their exacerbation, completed the same assessments during a clinically stable period. Among the patients who relapsed, mean time to relapse was 4.7 days. Patients who did not relapse demonstrated statistically and clinically significant improvement on all four CRQ domains ($p < 0.001$, all changes $\geqslant$1.4 points). No significant change in scores over time was observed for patients who relapsed or for control patients. Non-relapsing patients' CRQ scores at the follow-up assessment had improved and were similar to scores of control patients, indicating a return to non-exacerbation HRQL within 10 days. This finding, that HRQL at the time of an exacerbation is predictive of future exacerbations and/or survival, was also confirmed by other reviewed papers (e.g., [14, 15]).

The impact of treatment for AECB on HRQL

Nine studies assessed the impact of pharmacological or non-pharmacological treatments for AECB on HRQL. Brief summaries of the methods, instrumentation, and findings of each study are presented in Table 4.

Pharmacological treatment

Four studies assessing pharmacological treatment and HRQL at two or more time points during an AECB and recovery period were identified [13, 14, 18, 19]. In general, it appears that treatment is superior to no treatment, but there is little to recommend one treatment over another based on the instruments and duration of the studies identified here. There was a trend towards improvement in all treatment groups, making it difficult to detect between-group differences.

Recovery from an AECB may be enhanced by treatment with oral steroids. Aaron and colleagues [13] evaluated outcomes 10 days after discharge from the emergency room and randomization to treatment with oral prednisone or placebo. The primary study endpoint, relapse at 30 days, favored the prednisone-treated group ($p < 0.05$). There were significantly greater improvements in the dyspnea domain of the CRQ [36] and a trend toward improvements in the CRQ total score among prednisone-treated patients. Within group improvements in the dyspnea domain and total score all exceeded thresholds for minimal important difference.

The impact of choice of antibiotic on HRQL during AECB recovery is not yet known. Three studies that compared existing antibiotics did not find significant differences between treatment groups [14, 18, 19]. These three studies used different assessment methods (condition-specific instrument, generic instrument, utilities) and all conclude that HRQL improves with antibiotic treatment for an AECB but that the magnitude of improvement may not differ among existing treatments.

In the GLOBE study, which evaluated gemifloxacin and clarithromycin, there was a non-significant trend towards improved HRQL on the SGRQ with gemifloxacin-treated patients compared to those treated with clarithromycin [14]. This study reported on change from baseline to 26 weeks; it is likely that any benefit derived from the antibiotic treatment would have been detected in assessments closer to the exacerbation, but that the benefit was no longer detectable several

Table 4. Summary of reviewed studies – the impact of AECB treatment on HRQL

Reference	Study design, population, country	Methods and instrumentation	Findings
Aaron et al. [13]	Double-blind randomized placebo-controlled trial. Patients being discharged from emergency room after AECB, randomized to receive oral prednisone or placebo. $n = 147$ (74 receiving prednisone, 73 receiving placebo) Mean age 69/70 years 42% male Mean FEV_1% predicted = 38% Canada	Assessment of HRQL and dyspnea at discharge and 10 days later. Exacerbations defined using Anthonisen criteria (moderate or severe). Condition-specific: CRQ	Improvements in both groups; no significant difference in overall score. Significantly greater improvement in CRQ dyspnea domain in prednisone-treated patients (1.69 vs. 0.97 points, $p = 0.02$). Mean improvements in CRQ total score clinically meaningful but not significantly different (1.42 for prednisone-treated patients, 1.04 for placebo patients, $p = 0.14$). Did not report whether there were differences between groups at baseline.
Andersson et al. [15]	Prospective randomized study of long-term oxygen therapy (LTOT) vs. no LTOT Patients with AECB 5–7 days after hospital admission $n = 29$ Mean age 78 years 57% male Mean FEV_1% predicted = 30% ($\pm$11%) Sweden	Assessment of HRQL at baseline (5–7 days after hospital admission), and at 3, 6, and 12 months (baseline and 12-month data reported). Exacerbations defined as respiratory insufficiency caused by COPD requiring hospitalization. Generic: SF-36 Condition-specific: SGRQ	Substantial drop-out. No significance testing conducted. Patients randomized to LTOT improved by 8 points or more on seven SF-36 domains (exception was BP) and improved (lower scores) and by 10 points on the SGRQ impacts component and 14 points or more on the SGRQ total and symptom components. Patients randomized to no LTOT improved by 16 points or more on seven SF-36 domains (exception was SF), 7 points on the SGRQ symptom and impacts components and 9 points or more on the activity component and total score.
Behnke et al. [16]	Prospective randomized study of exercise training. Patients with AECB 4–7 days after admission $n = 30$ (15 receiving exercise training, 15 receiving usual care) Mean age 66 years 77% male Mean FEV_1% predicted = 36% Germany	Assessment of HRQL at baseline (4–7 days after hospital admission), and at 3 and 6 months. Exacerbations defined as hospital admission for COPD. Condition-specific: CRQ	Baseline CRQ scores were similar in the training and control groups. In the training group, CRQ total scores were significantly improved and significantly different from the control group at 3 and 6 months. In the control group, there was a clinically important change in the dyspnea domain at 3 months.

Table 4. (Continued)

Reference	Study design, population, country	Methods and instrumentation	Findings
Cilione et al. [47]	Prospective cohort study of inpatient pulmonary rehabilitation. Patients being released from hospitals following AECB n = 132 Mean age 68 years 59% male Mean FEV_1% predicted = 43% Italy	Assessment of HRQL at baseline and after 1 week (12 sessions) of inpatient pulmonary rehabilitation. Exacerbations defined as hospital admission for COPD. Condition-specific: SGRQ	Participants classified as improved or non-improved (based on the 6 min walk distance) had similar SGRQ scores (total, all components) at study entry. Total SGRQ score decreased from 55 to 49 as a result of rehabilitation.
Davies et al. [17]	Prospective cohort study After hospital admission for AECB, patients randomized to "hospital at home" or continued hospitalization n = 90 (50 available at follow-up) Mean age 70 years 50% male Mean FEV_1% predicted = 36% United Kingdom	Assessment of HRQL at baseline (at AECB) and at 3 months after randomization. Exacerbations defined as increase in breathlessness and in 2 of the following in the past 24 hours: cough frequency or severity, sputum volume or purulence, wheeze. Condition-specific: SGRQ	HRQL was similar between treatment groups at baseline and at 3 months. HRQL (SGRQ total) was significantly lower at baseline among patients who were later readmitted (77.1 vs. 67.4, $p = 0.012$).
Grossman et al. [18]; Also reported in Torrance et al. [48]	Prospective, randomized economic evaluation n = 240 (120 receiving ciprofloxacin, 120 receiving usual care for initial AECB and all additional AECBs during study) Mean age 55.3 years 44% male Canada	Assessment of HRQL at baseline, 3, 6, 9 and 12 months. Generic: NHP, HUI Condition-specific: SGRQ	Patients treated with ciprofloxacin throughout the study demonstrated a trend towards higher scores on the total, activity, and impact components of the SGRQ and on the energy, emotional reaction, social isolation, pain, sleep, and physical mobility scales of the NHP. No differences were significant. Differences on the SGRQ total and impact scores exceeded the threshold for clinically meaningful small (>4.0 points) differences. There was a trend towards higher QALYs (as derived from the HUI) over the year among the ciprofloxacin-treated patients (0.79 vs. 0.76, not significant).
Lorenz et al. [19]	Prospective, non-randomized cohort study comparing macrolides and moxifloxacin Patients with AECB presenting to study investigator. n = 322 (90 receiving moxifloxacin, 96 receiving azithromycin, 63 receiving clarithromycin, 83 receiving roxithromycin) Mean age 60 years 54% male Germany	Assessment of HRQL and symptoms. HRQL was assessed at days 1, 5, and 14 of therapy; symptoms were assessed daily Exacerbations defined using Anthonisen criteria (severe). Generic: NHP	There were no significant differences between groups in change over time; groups tended to improve during the study period.

Saudny-Unterberger et al. [20]	Prospective, randomized, controlled study Patients with AECB presenting at the hospital $n = 33$ (17 receiving nutritional support, 16 receiving usual care) Mean age 69 years 63% male Mean FEV_1% predicted = 33.8% Canada	Assessment of HRQL and dyspnea at baseline (during AECB) and 2 weeks postadmission. Exacerbations defined as hospital admission for COPD. Generic: general well-being questionnaire	There were no significant between-group differences in the magnitude of change for patient-reported dyspnea or the GWB, and only one of the pulmonary function tests (FVC,% predicted) was significantly different between groups. The treatment group did demonstrate significant within group improvements over time ($p < 0.05$).
Spencer et al. [14]	Double-blind, randomized controlled clinical trial $n = 438$ (214 receiving gemifloxacin, 224 receiving clarithromycin) 53% male Mean PEFR = 59% Europe	Assessment of HRQL at baseline, 4, 12 and 26 weeks. Exacerbations defined using Anthonisen criteria (severe). Analyses conducted as exacerbators (patients who had 1 or more additional exacerbations during the study period, $n = 134$) vs. non-exacerbators. Condition-specific: SGRQ	At baseline, exacerbators had clinically and statistically significantly lower (worse) scores on all SGRQ components and total score. Exacerbators' scores remained constant over time, while non-exacerbators had clinically and statistically significantly greater improvements on all scores with the exception of the activity component at 4 weeks. AUC analysis demonstrated clinically and statistically differences between exacerbators and non-exacerbators on all components ($p < 0.001$, total, activity, and impacts small differences, symptoms large difference). There was a trend towards lower scores among patients treated with gemifloxacin.

months later. There were also no significant differences between HRQL outcomes among patients treated with moxifloxacin vs. usual care [19] or between utilities in patients treated with ciprofloxacin vs. usual care [18]. The generic NHP [32] was used in the study evaluating differences between 14-day outcomes between moxifloxacin compared to macrolides. Almost one-fifth of respondents did not complete the NHP and there is no report of whether these patients differed from completers in terms of demographic or clinical characteristics or treatment outcome, so results must be interpreted with caution. Grossman and colleagues [18] evaluated the use of ciprofloxacin vs. usual care for an AECB at presentation and for all others during the 12-month study. (Torrance and colleagues use these data in their economic evaluation of ciprofloxacin [48].) There were no significant differences on any of the patient-reported outcomes, which included a generic, a disease-specific, and a utility measure; there were also no significant differences in clinical outcomes, including total number of days with exacerbation symptoms, duration of AECB, and interval between AECBs.

Non-pharmacological treatment

Five studies assessed non-pharmacological interventions for AECB: nutritional supplementation [20], LTOT [15], exercise training [16] and pulmonary rehabilitation [47], and a "hospital at home" intervention [17]. Although there are substantial differences between study designs, exercise training is the only intervention that resulted in both within group improvements and between-group differences. However, these studies were fairly small and some had high dropout rates; further research is necessary to confirm these relationships.

Saudny-Unterberger et al. [20] randomly assigned patients to receive aggressive nutritional support or usual care during their hospital stay; evaluations of HRQL, pulmonary function, dyspnea, and weight were conducted at baseline and 14 days later. The psychological general well-being schedule (PGWB) [33] was administered at both assessment points. Differences from baseline to day 14 between groups on the PGWB approached significance ($p = 0.066$). Change on the PGWB within the treatment group averaged an increase of 12 points and was significant ($p = 0.020$); patients in the control group experienced an average decrease in their PGWB score of 10 points (n.s.). Further research with a measure specific to COPD would help assess the impact of nutritional support on HRQL.

Andersson et al. [15] planned to assess changes in HRQL associated with LTOT in a 12-month longitudinal, randomized study. However, due to substantial mortality (11 of 29 patients died during the study period) and limited need for LTOT in the study population, no statistical testing was conducted. Despite this, other findings from the study are notable and the magnitude of change can still provide some useful information. In the hospital, 29 patients completed the SGRQ and the SF-36 [27]. Baseline scores on the SF-36 were low (below 60.0 on all scales). SGRQ scores ranged from 50.2 (impacts) to 67.5 (activity), indicating severe impairment. Assessments at 3 months are presented by LTOT status. In both treatment groups, patients demonstrated clinically meaningful improvements (5 points or more on the SF-36 and 4 points or more on the SGRQ) in most domains. In some domains, there were changes in different directions across groups, but the 3 month scores were similar across groups. With the small sample size, this may represent different outcomes, selection bias, or may be simply regression to the mean. Interestingly, across treatment groups, the greatest improvements over time on the SF-36 were in domains focused on psychological well being (vitality, role-emotional, and mental health) rather than in the physically focused domains. These findings suggest that further evaluation of the impact of LTOT is needed, an additional question to address is whether HRQL predicts survival or need for LTOT.

Patients who were randomized to an exercise training program after an AECB had significantly better HRQL, as assessed by the CRQ, at 3 and 6 months after entering the program compared to a control group [16]. Within group improvements on all CRQ domains were clinically and statistically significant in the training group, while in the control group, the only improvement was a clinically meaningful change in the dyspnea domain at 3 months. CRQ scoring was not conducted in the usual manner; interpretation of the values should be approached cautiously.

Consecutive patients enrolled in a pulmonary rehabilitation program following acute exacerbations completed the SGRQ before beginning the program [47]. At baseline, scores on the SGRQ total and components were similar between patients who improved in terms of exercise capacity and those who did not improve during the study. There were no significant changes in SGRQ scores with rehabilitation, although the total SGRQ score decreased by a mean of 6 points, exceeding the minimum threshold for clinical significance but not reaching statistical significance.

Finally, the HRQL of a "hospital at home" intervention, in which nurses attended to patients at home after treatment in the emergency department, was compared with hospital admission [17]. Only a subgroup of patients completed the SGRQ at the baseline assessment and less than three-fifths of those completed it at follow-up, but scores were similar at the baseline assessment and the 3-month assessment within and across treatment groups. However, only 16 of the 50 randomized to hospital care and 34 of the 100 randomized to home care completed the SGRQ at the follow-up assessment. Patients who were re-admitted within the study had significantly higher (worse) SGRQ scores at the baseline assessment. Given the eligibility requirements for the hospital at home intervention (e.g., not "too severe", no cardiac disease, sufficient social support), it is possible that the patients who were included were more likely to recover adequately without hospital admission than a general COPD population.

Discussion

General observations

AECB represent an important opportunity for patient outcomes evaluation. Some level of airflow obstruction is constant (or slowly increasing over time) in COPD, presenting the picture of a chronic disease in which physiological markers do not fluctuate. However, acute exacerbations present an episodic disease process, with similarities to a reversible condition such as asthma or migraine. Because the COPD experience includes both chronic and episodic components, evaluation of patient-reported outcomes focusing on the variations in patient experience and perceptions over time, such as HRQL, is important in COPD. Although the studies reported here differed in exacerbation severity, demographic characteristics, assessment methods, and duration, they point to interesting research questions for the future.

Evaluation of HRQL during an AECB is an opportunity to assess patient well being during a period of known clinical change. Several of the studies described here conducted only a cross-sectional assessment of HRQL and present descriptive and correlational data from a single point in time. These studies confirm the clinician's intuitive sense that patients' well being is impaired during severe symptomatic episodes. Studies routinely find that correlations between pulmonary function and HRQL are small to moderate [49, 50]. Future research could assess HRQL and pulmonary function serially after an AECB to understand the relationship between these important endpoints better.

Findings

The reports reviewed here suggested a relationship between number or frequency of exacerbations and HRQL. This conclusion echoes similar findings in other disease areas. For example, interictal HRQL was shown to be more impaired in patients with more frequent migraines – that is, HRQL was lower, even between migraines, than one would expect [51]; recent pulmonary exacerbations were significant predictors of HRQL in patients with cystic fibrosis [52]; and frequency of symptoms of gastroesophageal reflux disease was related to HRQL [53]. This suggests that in addition to assessing the frequency of exacerbations among chronic bronchitis patients, use of an infection-free interval (IFI) or another measure that accounts for the length of time between exacerbations or episodes as an outcome measure for AECB treatment (e.g., [54]) should also be considered. It also suggests that the occurrence of fewer exacerbations improves not only the HRQL during and immediately following the exacerbation, but that it also has an impact on longer term HRQL for COPD patients.

The relationship between HRQL and exacerbations could be causal in either direction. HRQL

may predict exacerbations. Several studies indicated that HRQL at enrollment was predictive of hospitalization, exacerbations, or the number of exacerbations [17, 19, 21, 41, 42]. This was true across a variety of condition-specific and generic assessment tools. It suggests the possibility of HRQL as a potential screening tool to be used to monitor patients for possible deterioration.

Based on the studies that evaluated the impact of pharmacological treatment for an exacerbation, it appears that treatment results in improvements over the short-term [13, 14, 18, 19]. However, even placebo resulted in significant within-group improvements within 10 days after an exacerbation [13]. This suggests several questions about the appropriate timing of HRQL assessments; that is, waiting until 10 days or more after treatment may be too long.

Limitations

There were a number of limitations in the studies presented and the ability to review them critically. The studies were disparate in their design, duration, and method of HRQL assessment. This precludes the possibility of a meta-analysis and makes it difficult to synthesize lessons learned. Study length and timing of assessments is important. The changes to be expected in the short term (i.e., acute exacerbation) compared to the long term may be very different; for example, while one might expect improvement in the CRQ Mastery scale after 1 year of successful maintenance therapy, in a 1-week study of outcomes following an exacerbation, one might expect improvements only in the physical domains of a condition-specific measure.

Further, several studies used only a generic instrument to assess HRQL. Generic instruments offer important advantages in group comparisons, since the same instruments can be used in various disease areas and the scores are directly comparable across studies and populations. However, the use of a generic instrument in a COPD population, which tends to be older and has more comorbidities than the general population with whom these instruments were developed, raises a concern about floor effects, i.e., if there is room on the scale to capture changes on patients who further deteriorate, as well as its responsiveness to COPD-specific concerns. Many of the generic instruments used in the papers included in this review do not have published information about normative values or guidelines for interpretation of change. Paired use of generic and condition-specific instruments, with the generic instrument providing comparability across studies and the disease-specific instrument focusing on the condition of interest and being more responsive to changes, is recommended in the COPD population [55].

Several of the studies describe the treatments that were provided, but they do not provide detailed HRQL outcomes by treatment. Other reviewed studies provide only minimal information on the impact of AECB treatment because statistical power was affected by high mortality or drop out. These studies suggest that antibiotic treatment leads to improvements in HRQL following an AECB, but do not provide enough information to influence treatment selection. The various non-pharmacological interventions evaluated do not conclusively support one program over another. Additionally, though all the studies examine the relationship between HRQL and exacerbations, not all directly evaluate the HRQL decrement associated with an exacerbation; for example, Seemungal et al. [42] reports how the frequency of exacerbations affects HRQL.

Finally, there are some concerns about the definition of exacerbation and timing of assessment. Most studies used Anthonisen's definition of an exacerbation, although some studies used any level of exacerbation, while others included moderate/severe or severe only. The studies that used other definitions all specified that patients had existing disease and required hospitalization for their COPD. Other papers that were considered but excluded from this review included patients newly diagnosed or did not explicitly require exacerbations were not included; for example, Traver compared quality of life among high and low resource use patients [56]. However, while resource use could mean exacerbations, it could also refer to frequent telephone calls to the physician and so the paper was excluded [56].

Future research

Future research can address many of these questions during the course of randomized assessments of treatments for AECB. As antibiotics are a

recommended treatment for AECB [1], a greater understanding of their impact on HRQL is crucial. HRQL measures, particularly disease-specific instruments for which there are published guidelines on interpretation (such as the SGRQ or CRQ), can be added to existing protocols. Assessments should be both short-term (i.e., immediately during and after the exacerbation) and long-term (i.e., 3 month or longer follow-up). Responsiveness of these instruments to patient or physician-rated change in symptoms as well as objective pulmonary function measures should also be assessed. Related to instrument responsiveness, it is important to evaluate the AECB in context; as HRQL may deteriorate rapidly during an AECB, even no treatment may result in HRQL improvements. The natural disease course as well as the statistical concern of regression to the mean should be considered in study design. It is also important to evaluate the impacts of antibiotic characteristics, such as administrations per day, duration of therapy, time to symptom improvement, and time to subsequent AECB episode, on HRQL. Study design should include careful attention to the HRQL data collection protocol to minimize missing data, which were a problem in existing studies. Studies should include direct comparisons of treatments for exacerbations, with sample size and power sufficient to detect differences. Finally, studies should present clear and detailed information on the treatments involved, the instruments used to assess HRQL associated with these treatments, and the magnitude of both the clinical and HRQL changes following treatment.

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Address for correspondence: Jordana K. Schmier, Exponent, 1800 Diagonal Road, Suite 355, Alexandria, VA 22314, USA
Phone: +571-431-7241; Fax: +1-571-431-7269
E-mail: jschmier@exponent.com