

# Exacerbation rate, health status and mortality in COPD – a review of potential interventions

Terence AR Seemungal<sup>1</sup>

John R Hurst<sup>2</sup>

Jadwiga A Wedzicha<sup>2</sup>

<sup>1</sup>Department of Clinical Medical Sciences, University of the West Indies, St. Augustine Campus, Trinidad and Tobago; <sup>2</sup>Academic Unit of Respiratory Medicine, Royal Free and University College Medical School, University College London, UK

**Abstract:** COPD is prevalent in Western society and its incidence is rising in the developing world. Acute exacerbations of COPD, about 50% of which are unreported, lead to deterioration in quality of life and contribute significantly to disease burden. Quality of life deteriorates with time; thus, most of the health burden occurs in more severe disease. COPD severity and frequent and more severe exacerbations are all related to an increased risk of mortality. Inhaled corticosteroids (ICS) have similar effects on quality of life but ICS/long-acting bronchodilator combinations and the long-acting antimuscarinic tiotropium all improve health status and exacerbation rates and are likely to have an effect on mortality but perhaps only with prolonged use. Erythromycin has been shown to decrease the rate of COPD exacerbations. Pulmonary rehabilitation and regular physical activity are indicated in all severities of COPD and improve quality of life. Noninvasive ventilation is associated with improved quality of life. Long-term oxygen therapy improves mortality but only in hypoxic COPD patients. The choice of an inhaler device is a key component of COPD therapy and this requires more attention from physicians than perhaps we are aware of. Disease management programs, characterized as they are by patient centeredness, improve quality of life and decrease hospitalization rates. Most outcomes in COPD can be modified by interventions and these are well tolerated and have acceptable safety profiles.

**Keywords:** COPD, exacerbation, health burden, mortality, inhaled steroids, long-acting bronchodilators, long-acting antimuscarinic agents, macrolide, disease management program, tolerability, safety, pulmonary rehabilitation, exercise

## Introduction

The term, chronic obstructive pulmonary disease (COPD), is of relatively recent origin but is related to the terms chronic bronchitis and emphysema that refer to some subsets of patients with COPD. These terms have a long history that can be traced as far back as the seventeenth and nineteenth centuries, respectively.<sup>1,2</sup> Laennec, in his 1837 treatise, gave the first clinical description of emphysema.<sup>3</sup> The respiratory world had to wait another hundred years before a spirometer could be designed to measure time-dependent expiratory volumes<sup>4</sup> and allow the physiology of airflow obstruction to be studied. Two phenotypes of COPD emerged, the so-called ‘American Emphysema’ and ‘British Bronchitis.’ Both Fletcher and Burrows showed similarities between these two conditions,<sup>5,6</sup> which were later shown to have similar mortality.<sup>7</sup> It is worth noting that at this stage the definition of COPD was clinicroadiological.<sup>7</sup> William Briscoe is believed to be the first person to use the term COPD in discussions at the 9th Aspen Conference<sup>8</sup> and Sukumalchandra and Williams were one of the first groups of authors to publish data using the term COPD.<sup>9</sup> Following these earlier works, the anatomic location of the primary lesion in COPD

Correspondence: Dr Terence Seemungal  
Department of Clinical Medical Sciences,  
University of the West Indies,  
St. Augustine Campus, Trinidad  
and Tobago  
Email [terence.seemungal@sta.uwi.edu](mailto:terence.seemungal@sta.uwi.edu)

was shown to be the small airway and the basis of COPD pathology was suggested to be inflammation.<sup>10–12</sup> In 1995 both the American Thoracic Society and the European Respiratory Society published for the first time standards for the diagnosis of COPD.<sup>13,14</sup> These standards established the spirometric basis for the definition of COPD.

COPD is now defined by airflow obstruction, which may be associated with chronic bronchitis, bronchiolitis, or emphysema.<sup>13</sup> Other synonyms that have historically been associated with COPD include chronic obstructive bronchitis, chronic airflow limitation, chronic airflow obstruction, chronic airways obstruction, nonreversible obstructive airways disease, chronic obstructive airways disease, chronic obstructive lung disease, and some cases of chronic asthma.<sup>15</sup>

The major manifestation of airflow obstruction in COPD is reduced maximum forced expiratory flow in 1 second ( $FEV_1$ ) and slow forced emptying of the lungs (forced vital capacity, FVC) such that the ratio of  $FEV_1$  to FVC is less than 70%. Another characteristic is that these physiologic features do not change markedly over months.<sup>14</sup> However, the natural history of this disease is that most of the lung function impairment is progressive.<sup>14</sup> Importantly, airway hyperactivity and partial reversibility may also be features of COPD provided that at maximal reversibility, the ratio of  $FEV_1$  to FVC is still less than 70%.<sup>16</sup>

The severity of COPD is classified in terms of  $FEV_1$  because  $FEV_1$  is reproducible and is considered the most significant predictor of prognosis in COPD as supported by a wide range of studies over time,<sup>17–22</sup> Since  $FEV_1$  depends on gender, age, and height, the derived variable  $FEV_1\%$  predicted ( $FEV_1\%$ ) is used.  $FEV_1\%$  is the ratio of postbronchodilator  $FEV_1$  to  $FEV_1$  predicted for age and height as determined from epidemiological studies.<sup>16</sup>

In this review we will look at the prevalence and importance of COPD as a common chronic disease: there is evidence that even from an optimistic view point the prevalence of COPD will rise markedly within the next 20 years. Most of the health burden in COPD arises from pharmacologic intervention whether as in- or outpatients. This is more marked in the later stages of COPD when exacerbations are more frequent. Thus COPD exacerbation has emerged as an important outcome measure in COPD. There are, however, several methodological issues with the concept of an exacerbation from event definition to counting of COPD exacerbations during interventional studies. The relationships of exacerbation to health status and difficulty in modifying physiological measures in COPD have brought health status into focus as an important outcome measure. However the

final outcome measure for any intervention is mortality. We may well have treatments that reduce mortality. After a review of each of these concepts we look at how various interventions both pharmacologic and nonpharmacologic modify these interventions. No intervention will be effective unless it is patient friendly and so we also consider patient-focused perspectives on treatment. We will not consider newer drugs where studies have yet to show effects on exacerbations, quality of life and mortality.

## The prevalence of COPD

Several studies have examined the prevalence of COPD both in the developed and developing world and concur on the importance of this condition,<sup>23–33</sup> In 1990, the total deaths from COPD were estimated at 2.2 million and it was ranked the sixth leading cause of death.<sup>25</sup> Even by conservative estimates it is thought that the worldwide number of deaths in 2020 will be 3.5 million and COPD will be ranked third amongst the leading causes of death.<sup>25</sup> During 2000, an estimated 10 million US adults reported physician-diagnosed COPD and in the USA alone, COPD was responsible for 8 million physician office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths.<sup>34</sup> The greatest risk factor for disease development in the developed world is tobacco smoke; however in the developing world biomass fuels have been implicated particularly in women.<sup>35</sup>

Worldwide, COPD affects 9.8% of men and 5.6% of women.<sup>36</sup> However a turn-of-the-century report from the UK indicated that the prevalence rates of COPD appear to have peaked in UK men but are continuing to rise in women.<sup>37</sup> This reverse in the gender trend in COPD prevalence in the developed world has been confirmed by reports from Austria that have found equal prevalence in both genders for COPD as well as tobacco use.<sup>38</sup> Thus the prevalence of COPD in women can be expected to rise worldwide over the next decade.<sup>39,40</sup>

## Exacerbation rates

The importance of COPD exacerbations to the natural history of COPD and disease burden has only been recognized within the past 10 years. In 1975, Tager and Speizer suggested that “once obstructive disease becomes manifest as abnormal  $FEV_1$ , intercurrent illnesses [exacerbations] have little effect on rates of  $FEV_1$  decline” and disease severity and thus the “current concern over rational use of antibiotics...and the economic burden that unnecessary use may represent... [requires] reassessment.”<sup>41</sup> Our current conceptualization of

COPD exacerbations has carried us well beyond the almost negligible concern expressed in the above statements.

Table 1 shows 9 studies of at least 1 year's duration in COPD patients conducted within the past 40 years. Many factors affect the ability of such studies to draw definitive conclusions about COPD exacerbations and make it difficult to compare studies. One major factor is the heterogeneous nature of COPD.<sup>42</sup> This factor is further accentuated because 3 of the studies<sup>17,43,44</sup> included unselected subjects whereas the other studies included only patients with COPD. Another variable is the method used to detect COPD exacerbation. Relying on the ability of patients to recall exacerbations<sup>17,45</sup> may not be as accurate as active surveillance.<sup>43,46,47</sup> Other confounding variables may include geography (eg, weather, climate, air pollution), genetic makeup of the population under study and frequency of follow-up. Data from the London COPD cohort suggest that in a single center study using a selected group of COPD patients, active surveillance may be the most important factor in detecting COPD exacerbations.<sup>46</sup>

The annual rate of COPD exacerbations has been estimated from several different studies to be as low as 0.5 to a high of 3.5 exacerbations per patient.<sup>46,48,49</sup> Hospitalization rates have depended on type of study but range from as low as 0.09 to 2.4 per patient per year.<sup>49</sup> Thus, from this brief survey it would appear that the more closely patients are followed up in studies the higher the detection rate for COPD exacerbations. However as far as we are aware, no long term study has found a mean exacerbation rate of greater than about 3 exacerbations/year and so this number may represent an upper limit to the mean rate in all populations and is of significance for interventional studies.

## Methodologic issues in exacerbation detection and type of exacerbation

### Frequency of monitoring

Of the studies mentioned in Table 1, the study of Kanner et al<sup>44</sup> is the only long-term study of exacerbations with a low detection rate despite close follow up with weekly telephone calls and 3-monthly clinics, but this may have been related to the inclusion of patients without COPD. Their findings are at variance with both the London COPD Study and the INSPIRE Study,<sup>46,47</sup> both of which used diary cards to detect exacerbations, and Monto et al who also monitored their patients by weekly telephone calls.<sup>43</sup>

### Event definition

Both Monto and Kanner used a similar definition of exacerbations consisting of increase in or new onset of cough, wheeze and sputum changes but Monto et al also included 'painful respirations.' On the other hand the London COPD Study and Anthonisen used a slightly more restrictive definition requiring at least one or more of an increase in or new onset of dyspnea, sputum purulence or sputum volume or one of these and any one of a cold, wheeze, cough, sore throat or fever.<sup>45,46</sup> Anthonisen's lower detection rate compared to the Monto, The London COPD and INSPIRE studies may have been related to his use of patient recall at the 3-monthly follow-up visits. Despite the heterogeneity in the definition of COPD exacerbation these studies all have one feature in common, which is that they used symptom-based definitions of an exacerbation of COPD.

Since the publication of the ISOLDE Study,<sup>50</sup> which used a treatment-based definition of exacerbation and the initial results of the London COPD Study, which like Anthonisen,

**Table 1** Comparison of 9 studies of exacerbations over 30 years

Author/Year	Country	N	Years	Patient type	Exac. freq	Follow up
Monto <sup>43</sup>	USA	142	1	COPD and NOCB <sup>a</sup>	2.33	Telephone weekly
Fletcher <sup>17</sup>	England	792	8	Unselected <sup>b</sup>	2.34	6 monthly
Kanner <sup>44</sup>	USA	84	4	Mixed <sup>c</sup>	0.34	Telephone Weekly
Anthonisen <sup>45</sup>	Canada	173	3.5	COPD	1.30	3 monthly
Seemungal <sup>48</sup>	UK	70	1.0	COPD	3.00	Diary cards
Seemungal <sup>46</sup>	UK	101	2.5	COPD	2.50	Diary cards
TORCH <sup>104</sup>	World wide	6112	3	COPD	1.13 <sup>z</sup>	3 monthly
INSPIRE <sup>51</sup>	Europe	1323	2	COPD	1.30 <sup>δ</sup>	Diary cards
UPLIFT <sup>136</sup>	World wide	5993	4	COPD	0.85 <sup>z</sup>	3 monthly

**Notes:** <sup>a</sup>NOCB, Nonobstructed chronic bronchitis; <sup>b</sup>Included normal subjects; <sup>c</sup>Mixed, COPD and other airway diseases; <sup>z</sup>Placebo group only; <sup>δ</sup>Mean value for both arms using the health care utilization definition. Using the symptom-based definition the mean number of exacerbations was approximately 3.00.

did not, there has been debate about the true incidence of COPD exacerbations. This question has now been answered by the INSPIRE Study which is the first long-term study of COPD exacerbations to compare the two types of exacerbations using the so-called symptom-based definition as well as the treatment-based definition.<sup>47,51</sup> The results of the INSPIRE study show that if a symptom-based definition is used exclusively then the exacerbation rate detected is 3 per year but if a treatment-based definition is used then the rate detected is approximately 50% of this or about 1.5 exacerbations per year. Thus about 50% of symptom-defined COPD exacerbations are not treated by physicians and this may represent a different type of exacerbation.

### Unreported exacerbations

The above observations lead logically to the hypothesis that about 50% of exacerbations are untreated, or at least not reported to physicians. This feature of COPD exacerbations was first detected by the London COPD Study.<sup>48</sup> Initial reports from the London COPD cohort suggested that the size of this reporting gap is about 50% but later reports suggested that it may be as high as 67%<sup>52</sup> which is consistent with reports from a Canadian cohort.<sup>53</sup> In a study of 625 exacerbations Wilkinson et al showed that patients with a higher reporting rate had a better quality of life.<sup>52</sup> Langsetmo et al in a 6-month study of 421 patients with 501 exacerbations have shown that several factors appear to predict the tendency not to report exacerbations and these include older age and more severe disease.<sup>53</sup> Further, a small number of symptoms at onset and weekends were associated with a tendency not to report exacerbations<sup>53</sup> or report later.<sup>52</sup> These results are supported by those of Vijayasaritha et al who reported on COPD exacerbations in a small number of COPD patients with alpha-1-antitrypsin deficiency and showed that the unreported exacerbations also had fewer symptoms at onset.<sup>54</sup>

### Reported exacerbations

Exacerbations receive the attention of the physician either in general practice or at hospital. COPD carries a greater burden than asthma with respect to general practice consultations and the consultation rate increases with age.<sup>55</sup> Data from The Lung Health Study showed that unscheduled general practice consultations may be a valid though indirect measure of exacerbation rates and that this parameter is responsive to therapy.<sup>56</sup>

A survey of medical admissions found that 7.3% of male and 3.2% of female admissions aged between 56 and 74 years had COPD.<sup>57</sup> The number of COPD hospital

admissions in a typical UK health district of 250,000 population is about 50% greater than for asthma.<sup>57</sup> Similarly in the USA about 50% of discharges classified as chronic airflow disease including asthma (ICD codes 490–496) were due to bronchitis (chronic or unqualified) corresponding to ICD9 codes 490 and 491.<sup>34</sup> Also in the UK, inpatient hospital stay exceeds that for asthma by a factor of 500%. Thus COPD carries a significantly greater hospital burden than asthma.

## Relationships to exacerbation

### Factors associated

Three of the studies quoted in Table 1 attempted to determine factors associated with frequent exacerbations. One of the first long term studies of COPD exacerbations was that of Fletcher et al who studied ‘chest episode’ frequency in a cohort of male postal workers over 10 years. These chest episodes were never rigorously defined by the authors but Fletcher found associations with migraine, hay fever and a history of childhood bronchitis which, apart from migraine, all became nonsignificant when age, phlegm score and airway obstruction were taken into account.<sup>17</sup> Fletcher concluded that “chronic mucus hypersecretion is a major cause of chest episodes” which is also supported by the Copenhagen City Heart Study.<sup>58</sup> Over the past 10 years several studies have found factors associated with the rate of COPD exacerbations and these include mucus hypersecretion,<sup>48,59</sup> lower airway bacterial colonization,<sup>60</sup> airway inflammation<sup>61</sup> and frequency of virus infection.<sup>62</sup> Exacerbations of COPD lead to a deterioration in the quality of life of COPD patients and contribute significantly to disease burden,<sup>48,50,63</sup> greater severity of COPD<sup>44,64,65</sup> and mortality.<sup>66</sup>

### Prior treatment

One of the first studies to show that withdrawal of inhaled steroids was associated with the occurrence of exacerbations was the Isolde study.<sup>67</sup> This has been found in other studies since then but Suissa et al have reanalyzed data from the OPTIMAL Study according to whether patients were initially ICS-exposed or ICS-naive.<sup>68</sup> They found that patients with prior ICS treatment who are switched to bronchodilator during randomization are more likely to exacerbate compared to those remaining on ICS. But importantly, they found no difference between treatments in the ICS-naive patients. Thus regardless of definition used, the prior medication history of the patients may be important when exacerbation rates are an outcome measure in COPD studies. This has not been taken into account during analysis of exacerbations in any study of COPD so far.<sup>68</sup>



## Statistical issues

Most of the interventional studies referred to later on used the health care utilization definition of an exacerbation when counting exacerbations as an outcome measure. However, statistical modeling of exacerbation rates has turned out to be rather complex. Cohort studies have shown evidence for a phenotypic frequent exacerbator.<sup>48,60</sup> While the occurrence of exacerbations within individual patients may follow a Poisson distribution, exacerbations between patients may not. One suggestion that such exacerbations may follow a gamma distribution has been debated.<sup>69,70</sup> Where differences between treatment arms are large such theoretical issues may not be of importance but when differences are small the choice of statistical model will determine the importance of the result.

## Health status and health burden

Measurement of health status in COPD has become more frequent since the work of Jones and colleagues<sup>71</sup> and it is a European requirement that all clinical trials of new drugs for COPD should incorporate a symptomatic measure, such as a health status questionnaire, as a coprimary endpoint.<sup>72</sup>

## Quality of life as a concept

The concept of quality of life is a difficult one to measure; it may be defined as the gap between that which is desired and that which is achievable.<sup>71</sup> Because of the difficulty of measurement of this parameter and the fact that we in the health services are concerned with more specific targets, clinicians have sought a more restrictive term, health-related quality of life (HRQoL), which is the subjective experience of health on quality of life.

Studies of HRQoL in COPD over a wide range of severity have consistently shown that patients with COPD have significant decrements in their HRQoL.<sup>73,74</sup> In COPD patients, quality of life scores have been used in the assessment of effects of medication,<sup>75</sup> depression,<sup>76</sup> oxygen therapy,<sup>73</sup> intermittent positive pressure ventilation,<sup>77–79</sup> pulmonary rehabilitation,<sup>80–82</sup> hospital readmission<sup>83</sup> and exacerbations.<sup>48,84</sup>

## Health-related quality of life questionnaires

Questionnaires used for assessment of quality of life may be categorized as generic or disease-specific. Generic questionnaires were designed to make standardized comparative assessments between populations of patients. However most questionnaires of this type (for example the Sickness Impact Profile, Short Form 36) may be rather insensitive to changes in health.<sup>75</sup> Disease-specific questionnaires include the

Chronic Respiratory Questionnaire (CRQ)<sup>85</sup> and St. George's Respiratory Questionnaire (SGRQ).<sup>86</sup>

The CRQ attempts to overcome the problem of generic questionnaires by customizing the questionnaire to the individual patient and patients are encouraged to compare their current state of health with their previous reports. A self-reported version of the questionnaire exists<sup>87</sup> and the minimal clinically important difference between scores using this questionnaire has been reported as 0.5.<sup>88</sup>

The advantage of the SGRQ<sup>86</sup> is that it has standardized instructions, which require the same response. There is no evidence that by so doing the SGRQ is less sensitive than other questionnaires to different levels of health.<sup>75</sup> However as a standardized questionnaire, the SGRQ has the advantage of allowing direct comparison between different patient populations and treatment groups and has been shown to be responsive when used for these comparisons.<sup>71,89</sup> Because of this standardization further analysis of the disturbances to life that occur in airways disease are possible. The SGRQ is scored from 0 (good) to 100 (poor) through a total score. However the SGRQ examines disturbances to quality of life by the symptoms component of the score, which assesses the degree of distress due to frequency and severity of respiratory symptoms, the impacts component, which addresses psychosocial effects and the activities score, which assesses effect on daily activities.<sup>86</sup> The SGRQ measures changes in health status and it has been shown that a clinically significant difference is equivalent to a 4-unit change in the SGRQ score.<sup>90</sup> The importance of the SGRQ in COPD has been further supported by recent studies showing relationships with systemic biochemical parameters.<sup>91–93</sup>

## Disability and COPD

Disability adjusted life years (DALYs) is a measure of health burden that consists of the sum of years of living lost (YLLs) and years of living with disability (YLDs).<sup>25</sup> In 2001 smoking was projected as the major risk factor for 4 million deaths and contributed about 5% of DALYs worldwide.<sup>94</sup> Deaths due to smoking are expected to rise to about 8.4 million by 2020.<sup>25</sup> By 2020 COPD will be expected to contribute about 4.1% of total DALYs worldwide. One study in Brazil has estimated that COPD accounts for 32% of all DALYs<sup>95</sup> and this is consistent with trends already predicted by Murray that increases in DALYs for COPD will be greater in the developing world.<sup>25,96</sup> Interventions, which decrease mortality in COPD, will decrease YLLs but there will also be an increase in YLDs. Since no currently known intervention is

associated with cure in COPD, DALYs may not be a suitable outcome measure at present in COPD.

## Economic burden of COPD

Data from the Office of National Statistics in the United Kingdom showed that there were 203,193 hospital admissions for COPD in 1994.<sup>97</sup> The average length of inpatient stay was 9.9 days. The National Health Service Executive published data in 1996 showing that the medical cost of COPD in the United Kingdom was £846 million or £1,154 per person per year.<sup>98</sup> The bulk of this cost was due to pharmaceutical treatment.<sup>99</sup> Similar data from the United States showed that 72.8 % of yearly expenditure of US\$14.7 billion was due to hospitalization and that approximately 50% of the total Medicare payments for those with COPD were incurred by approximately 10% of the Medicare beneficiaries (Division of Epidemiology, NHLBI).

A US study of per patient direct costs (in \$US 2005), using recent data yielded attributable cost estimates (costs deemed to be related to COPD) in the range of \$2,700 to \$5,900/patient annually, and excess cost estimates (total costs incurred by COPD patients minus total costs incurred by non-COPD patients) in the range of \$6,100 to \$6,600 annually.<sup>100</sup> Most of the health burden from COPD comes from hospital visits in late disease.<sup>34</sup> In a study of health insurance claims over the period 1999 through 2002, Nurmagambetov et al found that the number of hospital admissions and length of stay in hospitals decreased while the number of outpatient visits increased over this period. During this period the estimated COPD-related total medical costs per patient decreased 22% largely because of a decrease in the cost of hospitalizations for COPD, thus showing that COPD costs can be effectively reduced through decreasing hospitalization<sup>101</sup> and these changes have been related to quality of life scores.<sup>102</sup> These data suggest that hospital admission rates are a suitable measure of health burden in COPD and respond to interventions.

## Mortality

### Mortality rates in COPD

There is substantial variability among and even within countries and between sexes in COPD mortality.<sup>103</sup> For example, deaths from COPD are greater in Scotland than the rest of the UK. Though cold temperatures may be a factor in this, it is not entirely clear that this is in fact so, as the death rates from COPD in Canada do not exceed those of the USA, and COPD death rates in Norway are not particularly high (28 per 100,000 males).<sup>103</sup> Death rates are lower among women than men in all countries. Surveys of deaths in the US show a substantial increase in death

rates from COPD between 1985 and 1995, consistent with an increasing time trend in reporting of COPD.<sup>103</sup>

## Mortality and lung function

In a multicenter prospective study of positive pressure breathing over 33 months, Anthonisen et al found a mortality rate of 23% and showed that mortality in COPD was related to postbronchodilator FEV<sub>1</sub> and response to bronchodilators.<sup>18</sup> This study involved 985 patients with a mean FEV<sub>1</sub> of 36% predicted. When patients were stratified by FEV<sub>1</sub>, patients in the strata with FEV<sub>1</sub> less than 40% predicted had greater mortality even with adjustment for age. Mortality in the group with a FEV<sub>1</sub> > 50% predicted was only slightly different from that of the group of healthy smokers. The results of this study are strongly supported by the MIDSPAN study, conducted in the general population in Renfrew and Paisley in Scotland starting in 1972 through 1976 and following mortality over 15 years.<sup>21</sup> The Scottish study was based on 4439 deaths and the study showed that low FEV<sub>1</sub> was related to deaths from all causes but also vascular disease and lung cancer.<sup>21</sup> Further support for the relationship of FEV<sub>1</sub> to prognosis in COPD comes from the atherosclerosis risk in communities study in which Mannino et al showed that survival in COPD patients is related to GOLD stage.<sup>16</sup>

Taken together, these studies suggest that impaired lung function is related to mortality in the general population. They also show that in the COPD population FEV<sub>1</sub> below 50% of predicted is strongly related to mortality. Thus interventions at this stage of COPD or earlier may be particularly effective.

## Mortality and COPD exacerbations

Using a service-based definition of COPD exacerbation defined by need for emergency department treatment, SolerCataluña and colleagues were able to show for the first time that exacerbation frequency influenced mortality.<sup>66</sup> This was a study of 304 men with COPD in Spain over 5 years. The study showed that patients with 3 or more exacerbations had a survival rate of 30% at 5 years whereas those without exacerbation had a survival rate of 80%. Survival rate was also influenced by need for readmission, those requiring readmission having a 20% survival at 5 years.<sup>66</sup>

In-hospital mortality varies between less than 10% and 60%, based on the severity level of the population studied.<sup>49</sup> Mannino et al analyzed data from the Atherosclerosis Risk in Communities (ARIC) study and found that the overall rate of death varied from 5.4 per 1000 person years among normal subjects to 42.9 among subjects with GOLD Stage 3 or 4 COPD.

Death rates from COPD depend on degree of severity, the highest death rate from COPD occurring in severe COPD.<sup>16</sup>

## Causes of death in COPD

Vascular diseases and lung cancer appear to be major causes of death but more so in the severe COPD category.<sup>16</sup> SolerCataluña showed that respiratory causes accounted for 67% of deaths in their cohort.<sup>66</sup> The TORCH Study was the first interventional study in COPD with mortality as a primary outcome measure.<sup>104</sup> The study was a randomized double blind trial with 4 treatment arms: placebo, salmeterol, fluticasone and salmeterol/fluticasone (SFC). The study recruited 6112 patients in 444 centers in 42 countries and the mortality rate in the 3-year study period was 875 subjects. The study was well designed to study mortality and had an independent adjudication committee for causes of deaths, thus eliminating between-country variations in death certification. Unlike the SolerCataluña study,<sup>66</sup> the TORCH study found an almost equal contribution of respiratory (35%) and cardiovascular causes (27%) of deaths in COPD. However the death rates between the two studies were different, the TORCH study having an average annual death rate of 4.7%, about 50% of that of the SolerCataluña study.<sup>66</sup> Thus these two studies may have been describing the same events but in two different types of COPD subjects.

## Interventions

### Inhaled corticosteroids (ICS)

The first long-term randomized controlled trial (RCT) of ICS to show a significant effect in COPD was the ISOLDE study of 751 UK subjects with FEV<sub>1</sub> < 85%. The rationale for the ISOLDE study was based on 3 previous studies all having positive effects on FEV<sub>1</sub> decline. One, a large, retrospective, open-label study, involved oral corticosteroids;<sup>105</sup> another study was conducted in a combined pool of asthma and COPD patients;<sup>106,107</sup> and finally, meta-analyses of ICS including (beclomethasone users).<sup>108</sup> Though the ISOLDE study aimed for all severities of COPD, the mean FEV<sub>1</sub> at recruitment was in fact 50% (SD 14.7%). This was the first prospective study to find an effect of ICS on any outcome measure in COPD. The study found no difference in the primary endpoint that was the annual decline in FEV<sub>1</sub> in common with previous studies of budesonide.<sup>58,109</sup> However the ISOLDE study found a 25% reduction in exacerbation rates in the fluticasone (500 µg BD) arm compared to the placebo arm.<sup>50</sup> Fluticasone propionate significantly reduced the rate of decline in quality of life, delaying the average time for a clinically important reduction in health status

from 15 to 24 months compared to placebo. This was a landmark study in COPD therapeutics as it showed for the first time that health status declines at a measurable rate of 3.2 unit/year (in the placebo arm) and further that this outcome may be modified.<sup>63,110</sup> From then on health status and exacerbation rates became accepted outcome measures in most interventional studies in COPD.

The earlier long term studies of Vestbo<sup>58</sup> and Pauwels<sup>109</sup> either found no effect on, or did not look at, health status or exacerbations. In the Vestbo study, though exacerbations were an outcome measure, there appears to be no precise definition unlike the ISOLDE study where exacerbations were defined by need for treatment. Further, in both the Vestbo and Pauwels studies the patient population was mild COPD (mean FEV<sub>1</sub> 87% and 77% predicted, respectively) compared to ISOLDE: 50%. The results of the ISOLDE study were supported by the shorter (1 year) TRISTAN study,<sup>111</sup> which showed a 19% reduction in exacerbation rates but no significant difference in hospitalization or quality of life scores for fluticasone relative to placebo. Hence the GOLD guidelines (2004) suggest that ICS be used in COPD for severe disease with FEV<sub>1</sub> < 50% or where there are frequent exacerbations.

Following the essentially negative Vestbo and Pauwels studies two further studies of budesonide in more severe COPD patients (FEV<sub>1</sub> 36%) over 1 year with primary outcome measure as the rate of oral steroid-treated exacerbations, also found no effect for the ICS on exacerbation rate<sup>112,113</sup> and only one study found improved quality of life in the ICS arm.<sup>113</sup> It is likely that the difference between outcomes in the two studies was due to the differing designs. Medications were withdrawn prior to recruitment in the Szafranski study<sup>112</sup> but patients in the Calverley study<sup>113</sup> were optimized with oral steroid therapy prior to randomization as was done in the ISOLDE Study. Though the primary outcome measure of both the Calverley and Szafranski studies was exacerbation rate, it is interesting that both studies found only a trend toward a reduced exacerbation rate in the budesonide arm. Thus it is likely that they were underpowered to detect a difference in effects of ICS and had they been conducted over a longer period (eg, the ISOLDE Study, 3 years) the results might have been different. However we cannot draw definitive conclusions on relative efficacy of these ICS in COPD from these studies as there have been no 'head to head' comparisons between fluticasone and budsonide

### Long-acting $\beta_2$ -agonists (LABAs)

The latest GOLD guidelines recommend use of a long-acting inhaled beta-adrenergic receptor agonist ( $\beta_2$ -agonist) for

maintenance treatment of COPD.<sup>114</sup> Several studies of LABAs have looked at exacerbations as outcome measures. In a 4-month, randomized, placebo-controlled study of 670 COPD patients, Boyd et al found no difference in exacerbation with salmeterol; however in a similar study which also included an ipratropium arm Mahler et al found similar exacerbation rates in all arms but significantly prolonged time to the first exacerbation for salmeterol compared to placebo ( $p = 0.005$ ) as well as ipratropium ( $p = 0.0411$ ).<sup>115,116</sup> By the end of the study, 17% of the patients in the salmeterol arm had at least one exacerbation as compared to 27% and 31% in the ipratropium and placebo arms, respectively.<sup>116</sup> Dahl et al conducted a placebo-controlled comparative study of formoterol (2 dose strengths: 12 and 24  $\mu\text{g}/\text{day}$ ), ipratropium and placebo in 780 patients with moderate to severe COPD over 3 months.<sup>117</sup> They found no difference in exacerbations requiring treatment but there was a significant decrease in mild exacerbations (ie, those requiring reliever use only) between the formoterol arms and the placebo arm. Larger studies all showed significant falls in exacerbation rates in the salmeterol arm of 20%<sup>111</sup> and 15%<sup>104</sup> but not formoterol<sup>112,113</sup> though there was a significant difference in mild exacerbations requiring just reliever use in the latter two studies.

The first study to describe a significant effect of a LABA on quality of life in COPD was the 4-month placebo-controlled study of salmeterol in 283 COPD patients. The study showed a highly significant improvement in the salmeterol arm of the study.<sup>75</sup> This was supported by another study which used the CRQ to measure quality of life<sup>116</sup> and a later study using formoterol.<sup>117</sup> However, the subsequent 3-month study of Rennard et al found only a nonsignificant trend toward better quality of life in the salmeterol arm compared to placebo.<sup>118</sup>

The early studies found no difference in mortality between LABA and placebo, arguably because of their short durations. Based on many of these small studies, a meta-analysis of 22 trials concluded that  $\beta_2$ -agonists are associated with an increased risk of respiratory deaths.<sup>119</sup> However this meta-analysis included only seven studies of salmeterol, all of duration 3 to 6 months and even less (five studies) of formoterol of duration 3 to 12 months.<sup>119</sup> None of these 12 studies was individually powered to detect differences in death rates. In contrast, a prospective study of 416 patients in five Nordic countries detected an association between treatment with LABAs and decreased death rates following discharge from hospital.<sup>120</sup> The only study of COPD patients that was powered to detect a difference in death rates between

interventional and placebo arms was the TORCH study. This study showed no statistically significant difference between placebo and salmeterol in death rates but the two survival curves diverged within the first year and the final hazard ratio was compatible with a trend toward improved survival in the salmeterol arm (adjusted hazard ratio: 0.879 [95% CI 0.729–1.061]), compared to placebo.

There are now data that the LABA, salmeterol, may improve survival in COPD. According to Suissa et al, the TORCH study may be analyzed as a  $2 \times 2$  factorial trial (ie, LABA, ICS, both, neither).<sup>70</sup> Results by this analysis show that salmeterol is associated with a 17% reduction in mortality over the 3 years of the study.<sup>68</sup>

### ICS–LABA combination therapy

Several studies have examined the therapeutic strategy of combination therapy. Four of these have been comparative placebo-controlled studies with SFC<sup>104,111</sup> or formoterol-budesonide.<sup>112,113</sup> The formoterolbudesonide studies all excluded any ‘cardiovascular disorder that may have put patients at risk’ but the SFC studies did not exclude such patients. All of these studies recruited patients with moderate to severe COPD and all found similar decrements in exacerbation rates of about 25% compared to placebo and a modest improvement in quality of life relative to placebo. Only the TORCH study was designed with mortality as the primary outcome measure. However the primary analysis found no statistically significant difference in mortality between the SFC and placebo arms ( $p = 0.052$ ) perhaps because as the authors suggested, an interim analysis was undertaken to look at mortality indices for which the sample size calculation did not allow. The trends in the survival curves of the two arms are certainly suggestive of an effect on mortality that is supported by the prespecified secondary analyses.<sup>104</sup>

Comparison of ICS with ICS–LABA preparations was undertaken in all four studies. The exacerbation rate with ICS–LABA was no different from ICS in all the four studies. However, in two studies, ICS–LABA was better than ICS alone in total SGRQ score<sup>104,111</sup> but only in the activities and impacts subscales of the SGRQ<sup>113</sup> with no difference in the other study.<sup>112</sup> In the TORCH study, mortality was significantly better in the SFC arm compared to the fluticasone arm ( $p = 0.028$ ) but not compared to the salmeterol arm ( $p = 0.58$ ). Thus it appears that addition of the LABA to fluticasone significantly modified the therapeutic effects of the ICS.<sup>104</sup> However, as stated above, when a factorial analysis of the TORCH data is performed, it appears that this may all be due to the LABA.<sup>68</sup>



## Long-acting antimuscarinic agents

Interest in long-acting antimuscarinic antagonists (LAMAs) followed from the ERS and ATS recommendations for the use of the short-acting anticholinergic, ipratropium in COPD.<sup>113,121</sup> The pathophysiologic basis for anticholinergic agents in COPD is the increased vagal tone thought to exist in the airways of COPD patients<sup>122,123</sup> and this work has been supported by more recent work on the physiology of tiotropium activity on the airways,<sup>124–130</sup> Three major studies, conducted within the last 6 years have established the role of the LAMA, tiotropium, in stable COPD.<sup>131–133</sup> The Casaburi study was a 12-month placebo-controlled study of 921 patients with FEV<sub>1</sub> of 39% predicted in 50 centers and the Niewoehner study was a 6-month study of 1829 patients with FEV<sub>1</sub> 36% in 26 Veterans Medical Centers. Both the Casaburi and Niewoehner studies showed about a 14% decrease in patients with exacerbations, a 15%–20% decrease in annual exacerbation rates and in the case of the Casaburi study a 47% decrease in hospitalization rates for exacerbations. In addition, the Casaburi study found that 49% of patients on tiotropium had more than a 4-unit increase in SGRQ total score; these results were supported by the comparative study of Donohue et al.<sup>134</sup>

None of the above studies was powered to detect differences in mortality. However mortality was a secondary outcome measure of the UPLIFT study (Table 1).<sup>135</sup> Mortality for all patients in this study was determined on an intent to treat basis and was known at 45 months in 98% subjects (tiotropium) and 97% (placebo).<sup>136</sup> At the predetermined endpoint of 4 years and 30 days there was no significant difference between the two arms of the study (odds ratio, 0.89;  $p = 0.09$ ); however after unblinding, analysis showed that there was a decreased risk of death in the tiotropium arm at 4 years (odds ratio 0.87; 95% CI 0.76–0.99).<sup>136</sup>

## LAMA vs ICS-LABA

There are two studies which allow us to compare these drugs: the INSPIRE and OPTIMAL studies. The largest comparative study so far published is the 2-year INSPIRE study<sup>47,51</sup> which involved 1323 patients randomized to SFC or tiotropium with FEV<sub>1</sub> of 39%. The study showed the rate of treated exacerbations, the primary outcome measure, was about 1.30 in both arms and the rate of all exacerbations whether treated or not was about 3.0 in both arms. However there was an unexpected 29% greater risk of dropout from the study in the tiotropium arm. The study found that at the end of 2 years, there was a 2.1 unit ( $p = 0.038$ ) improvement in quality of life as measured by the SGRQ in the SFC arm

compared to the tiotropium arm but this may have been due to a healthy survivor effect, as patients whose wellbeing was deteriorating more rapidly withdrew sooner, more so in the tiotropium arm.<sup>47</sup> There was also a 3% mortality rate on treatment in the SFC arm compared to 6% in the tiotropium arm ( $p = 0.008$ ), which was also unexpected. There is no clear explanation for this difference which the authors attributed to an improvement in survival due to SFC consistent with the results of the TORCH study.

The INSPIRE study also detected a difference in exacerbation phenotype in that antibiotic-treated exacerbations were more frequent in the SFC arm ( $p = 0.028$ ) but systemic corticosteroid-treated exacerbations were more frequent in the tiotropium arm ( $p = 0.039$ ) and there was a trend toward fewer hospitalizations for COPD exacerbations in the SFC arm (13% vs 16%;  $p = 0.085$ ).<sup>47</sup> These two results taken together are suggestive of a trend toward less severe exacerbations in the SFC arm. However this must be balanced against an increased risk of pneumonia in the SFC patients (8% vs 4%). One hypothesis that may explain this observation is that in some way SFC decreased the severity of exacerbations, making it less likely that they would be treated.

In the OPTIMAL Study, tiotropium–placebo ( $N = 156$ ) was compared to tiotropium–salmeterol ( $N = 148$ ) or a triple therapy combination with tiotropium SFC ( $N = 145$ ) over 1 year; all comparisons were between the placebo and nonplacebo arms.<sup>137</sup> The primary analysis showed no differences in annual exacerbation rates between the three arms of the study though the rate was lowest in the tiotropium SFC arm. However, there was a significant decrease in exacerbations requiring hospitalization in the SFC containing arm (rate ratio 0.53; 95% CI 0.33–0.86), thus suggesting that addition of SFC reduced the severity of exacerbations which was supported by a significant reduction in all-cause hospitalization. There were also differences in favor of tiotropium SFC in HRQoL. Thus it appears that addition of SFC to tiotropium decreases health burden in COPD. There was no mortality difference on treatment between the two arms. The results of the OPTIMAL study have been supported by two recent studies of triple therapy which showed physiological benefit for the triple therapy combination.<sup>138,139</sup> The UPLIFT study design allowed use of other inhaled therapy in both arms and 74% of subjects in this study were on ICS, and thus the UPLIFT study may be seen to extend the results of the OPTIMAL study in that UPLIFT showed that there was a 14% decrease in exacerbation rates on top of usual care ( $p < 0.001$ ) compared to placebo.<sup>136</sup>

The data from the UPLIFT study taken together with those of the OPTIMAL study are suggestive of a superior effect for the combination ICS–LABA–LAMA. An economic analysis of this option showed that while the health burden was less (because of better quality of life and fewer hospitalizations) this was achieved at considerable economic cost.<sup>140</sup> Thus the option of ICS–LABA–LAMA requires further study.

## Macrolide use in COPD

### Effects of antibiotics in non-COPD obstructive lung diseases

The evidence that antibiotics, specifically macrolides, may be useful in COPD comes from studies in two other obstructive lung diseases. Studies in diffuse panbronchiolitis, a disease that is prevalent in Far Eastern populations, showed that erythromycin improves survival and symptoms.<sup>141–143</sup> This stimulated work in cystic fibrosis a disease common in Caucasian populations where azithromycin has been shown to decrease cystic fibrosis exacerbations and symptoms.<sup>144–147</sup>

Should macrolides have an effect on COPD? The effectiveness of macrolides in these two diseases led to investigations in the far more globally prevalent COPD. An initial open label study showed a decrease in COPD exacerbations in Japanese subjects.<sup>148</sup> These results have been strongly supported by the recently concluded ELECT study.<sup>149</sup>

### The ELECT Study

This randomized, placebo-controlled trial of erythromycin 250 mg twice daily in 109 moderate to severe stable COPD patients already on optimal therapy, was conducted in the long-running London COPD Cohort over 1 year. Patients were excluded if in the opinion of the investigator they had unstable cardiovascular status, for example congestive cardiac failure, cardiac arrhythmias or prolonged corrected QT duration on the electrocardiograph. The primary analysis showed a 35% fall in the exacerbation rate in the interventional arm. Secondary analyses showed that the median time to the first exacerbation was 271 days vs 89 days in the placebo arm ( $p = 0.020$ ). Exacerbations in the erythromycin arm had a median duration of 9 days vs 13 days in the placebo arm ( $p = 0.001$ ). The investigators were unable to find any differences in serum C reactive protein or serum interleukin (IL6) between the two arms of the study. There were no differences in sputum markers (IL6, IL8, myeloperoxidase) between the two arms of the study, though this analysis was limited by the variability in spontaneous sputum production by patients in the study. There was one death only in the study: in the placebo arm. Safety analyses showed no trend toward more adverse events

or macrolide resistance in the interventional arm over the 1 year of study. Thus the macrolide erythromycin would appear to be well tolerated over 1 year in moderate to severe COPD patients and it reduces COPD exacerbation duration and rates, but the mechanism by which this is achieved is not clear.

## Phosphodiesterase inhibitors

These are a class of nonsteroidal anti-inflammatory drugs that may be useful in COPD. Prior comparative studies with LABAs have not shown much promise<sup>150</sup> but in a recent RCT involving 110 COPD patients, the theophylline arm was associated with a lower frequency of COPD exacerbations, fewer days of COPD exacerbations and improved quality of life indices. Mortality data were not available for this study.<sup>151</sup> The only large controlled study of the newer phosphodiesterase inhibitors is a 647-patient study of cilomilast, which has reported a 39% reduction in exacerbation rates and an improvement in health status using the SGRQ by 4.1 units compared with placebo ( $p = 0.001$ ).<sup>152</sup> Inhibition of another receptor subtype (PDE7A) has also been suggested to lead to decreased inflammation in COPD.<sup>153</sup> Our understanding of prevention of COPD exacerbations using this class of drugs is evolving.

## Immunostimulatory agents and vaccines

### Vaccines

In a study of elderly patients with chronic lung disease, Nichol et al found that influenza vaccination is associated with significant health benefits with fewer outpatient visits, fewer hospitalizations and a reduced mortality.<sup>154</sup> In a Cochrane database review of four studies in COPD, Granger et al found little effect for the injectable antipneumococcal vaccines,<sup>155</sup> but Alfageme et al studied the 23 serotype pneumococcal polysaccharide vaccine in 596 COPD patients and showed that the pneumococcal vaccine was effective in the prevention of community acquired pneumonia compared to placebo in patients less than 65 years old or those with severe airflow obstruction ( $FEV_1 < 40\%$ ) without a difference in mortality.<sup>156</sup> Larger studies are required to examine the effects of the vaccine in those over 65 with COPD.

### Immunostimulatory agents

There are inconsistent reports of the effectiveness of these agents in COPD. One study, the detoxified oral immunoactive bacterial extract, OM85, was associated with fewer COPD exacerbations and hospital admissions<sup>157</sup> but a systematic review of 13 trials involving 2066 patients found no consistent evidence of a benefit, though the drug is currently in use.<sup>158</sup>

## Mucolytic agents

A Cochrane database review of 26 trials involving 7335 patients with COPD has shown that mucolytic agents are associated with a 20% reduction in exacerbation rates and decreased days of disability.<sup>159</sup> However there were contrasting effects observed in two RCTs. In the BRONCHUS study of 523 patients from 10 European countries, n-acetylcysteine had no effect on exacerbation rates but subgroup analyses showed a small decrease in patients who were not on regular inhaled steroids.<sup>160</sup> The PEACE study of carbocysteine in 709 Chinese COPD patients found a 25% reduction in exacerbation rates and improved quality of life in the interventional arm.<sup>161</sup> The reasons for these differences may depend on the differing populations studied.<sup>161</sup> The studies were both of similar sizes and had similar exclusion criteria. However the BRONCHUS study recruited less severe patients with FEV<sub>1</sub>% predicted 57% vs 43% in the PEACE study. Also in the BRONCHUS study 70% of patients were on ICS vs 16.7% in the PEACE study. The authors in the PEACE study speculated that the difference in the two studies arose because of the differing pharmacologic properties of carbocysteine which may in part depend on inhibition of viral adherence to the airway.<sup>161</sup> The authors further speculated that some of the differences between the two study results may also be due to pharmacogenetic differences between Caucasian and Chinese populations as well as the lesser use of ICS in the Chinese population.

## Nonpharmacologic therapies pulmonary rehabilitation and exercise

A 1-year RCT of 200 disabled COPD patients with FEV<sub>1</sub> 39% showed that there were no differences in number of hospitalizations following a 6-week rehabilitation program but fewer days in hospital and fewer primary care home visits in the rehabilitation group.<sup>162</sup> This indicates that pulmonary rehabilitation may affect severity of exacerbations but not the rate which has been supported by a study of housebound COPD patients,<sup>163</sup> though another study with repeated yearly rehabilitation programs found a decreased rate of hospitalization and exacerbations.<sup>164</sup> There were also significant improvements in quality of life scores that remained significant at 1 year after the program<sup>162,165</sup> and fewer deaths in the interventional group (3 vs 9).<sup>162</sup>

The results of the Griffiths study differ somewhat in conclusion from those of a systematic review of 6 randomized controlled trials of pulmonary rehabilitation involving 230 patients (but not including the Griffiths Study) where

there was a decreased risk of readmission to hospital (pooled relative risk 0.26 [0.12–0.54]) and decreased mortality (RR 0.45 [0.22–0.91]).<sup>166</sup> A Cochrane review of 31 RCTs of pulmonary rehabilitation found significant improvements in quality of life using the CRQ and in two of the three domains of the SGRQ.<sup>212</sup> However effects of pulmonary rehabilitation may depend of the initial level of dyspnea<sup>82</sup> and repeated pulmonary rehabilitation programs may lose some effectiveness, though they are associated with preserved quality of life indices despite physiologic deterioration.<sup>167</sup> Pulmonary rehabilitation is now an accepted intervention in COPD regardless of age or debility<sup>82,163,168</sup> with important benefits for patients on outcomes such as the exercise capacity and quality of life but there is no consensus on its effects on COPD exacerbations and there is weak evidence for at least a short term effect on mortality.

GarciaAymerich et al<sup>169</sup> have also shown in a 1-year study that patients with high levels of usual physical activity were at reduced risk of readmission to hospital. These results have been supported by analysis of data from the Copenhagen City Heart Study.<sup>170</sup> In this study patients were classified by self-reported physical activity and those who reported some degree of physical activity had a lower risks of hospitalization and all-cause mortality (hazard ratio 0.76, 95% CI 0.65–0.90) and a trend toward decreased respiratory mortality.<sup>170</sup>

## Noninvasive ventilation

The use of noninvasive ventilation (NIV) in acute hypercapnic respiratory failure is an accepted intervention.<sup>171</sup> However the evidence for its use in stable COPD is controversial. In one study of a highly selective group of 13 stable COPD patients with frequent admissions for decompensated type two respiratory failure and who tolerated the ventilator, there were significant falls in inpatient length of stay and number of hospital admissions compared to a period prior to intervention.<sup>172</sup> In a larger 2-year RCT of NIV with and without long-term oxygen therapy involving 90 patients, there was an improvement in quality of life in the NIV arm but no difference in survival or exacerbations leading to hospitalization.<sup>173</sup> However a recent prospective observational study of 99 patients with, and 41 without NIV, showed that survival rates were significantly higher in patients with NIV compared to those without this therapy (hazard ratio; 0.380; 95% CI 0.138–0.606) and this difference persisted after adjustment for baseline differences.<sup>174</sup> Interestingly there were beneficial effects in those with high base excess, low pH, low FEV<sub>1</sub> or low hemoglobin or excessive hyperinflation.<sup>174</sup> In a small Chinese study of

40 patients with hypercapnic respiratory failure, randomized with and without NIV, there was a decrease in exacerbations by 3.9/year ( $p < 0.01$ ) and a trend toward improved mortality in the interventional group.<sup>175</sup> Thus, the observation made 6 years ago is still valid; there is a need for well-designed controlled studies to evaluate the effects of NIV on survival, quality of life and exacerbations.<sup>176</sup>

## Long-term oxygen therapy (LTOT)

The role of LTOT was established about 28 year ago by two major studies.<sup>177,178</sup> Guidelines for oxygen use have been generally agreed to by several consensus panels.<sup>179</sup> LTOT improves mortality in COPD patients with respiratory failure but there appears to be no effect in the less severe patients.<sup>177,178,180</sup> There are also positive effects on quality of life<sup>73,181</sup> but no proven effect on COPD exacerbations. The relationship with improved quality of life may lead to speculation that this may in part be due to decreased exacerbation rates but most of these studies did not include exacerbation rates as an outcome measure and the MRC study found no relationship with rates of hospitalization.<sup>178</sup>

## Safety and tolerability

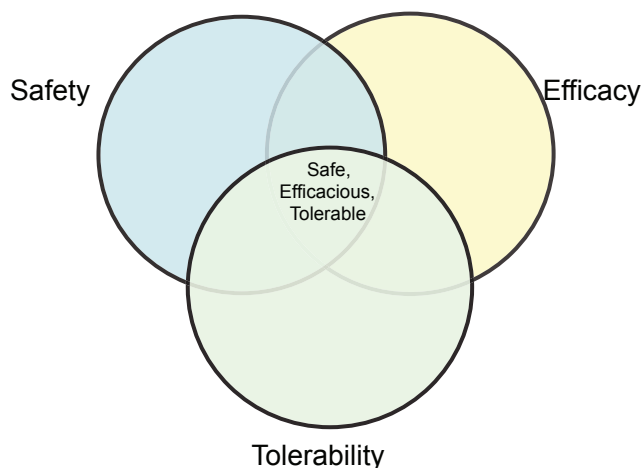
The sections above have highlighted the many therapies that have demonstrated efficacy in reducing exacerbation rate, and thereby impacting favorably on health status and mortality. In this section we will review data on safety and tolerability for the more commonly used pharmacologic interventions where there have been several consistent results. However, the key point remains as to whether such interventions are safe, and tolerable. This is the subject of the following two sections. Only then can we achieve the ‘Holy Grail’ of pharmacotherapy in providing the right drug, at the right dose, to the right patient at the right time.

It is important to make the distinction, having assumed efficacy, between safety and tolerability. A tolerable drug may be unsafe, and likewise a safe drug may be intolerable. There are complex interactions between efficacy, tolerability and safety in individual patients (Figure 1). The ideal preparation is efficacious, safe and tolerable.

Useful tolerability data may be obtained from those few key large trials that have now been performed in patients with COPD, and meta-analyses of smaller studies. These safety and tolerability data are summarized in Table 1.

## Tolerability/patient preference

The TORCH trial<sup>104</sup> showed that even in highly motivated and monitored clinical trial environments 34% of patients



**Figure 1** The interaction of safety, tolerability and efficacy.

had discontinued a LABA–ICS combination at 3 years, and this rate (and those of the individual components) was significantly better than placebo. Withdrawal from the combination was significantly lower than that with the components alone, suggesting a relationship between efficacy and tolerability. This withdrawal rate matched that for the LABA–ICS combination in the INSPIRE trial,<sup>47</sup> a head-to-head comparison with the long-acting anticholinergic drug tiotropium bromide and in which tiotropium was associated with a 42% withdrawal rate. Interpretation of the data from the INSPIRE study has not been supported by that of the UPLIFT study which showed a lower dropout rate in the tiotropium arm, though the designs of these two studies were different in that the INSPIRE study was largely a comparison of two arms each with monotherapy but the UPLIFT study allowed polytherapy in each arm.<sup>136</sup> In the OPTIMAL Study<sup>137</sup> premature discontinuation rates were as follows: 47% (tiotropium–placebo), 43% (tiotropium–salmeterol) and 26% (tiotropium–SFC) ( $p < 0.001$ ). Discontinuation was due to a perceived lack of medication efficacy or physician directed and due to a perceived deterioration in health status. Of these early withdrawals the proportion receiving an open label ICS–LABA combination were 74%, 70% and 54%, respectively.<sup>137</sup> These results appear to support those of the INSPIRE study on withdrawals and may indicate a trend in patient preference. However compliance/satisfaction within a trial may not reflect behavior in clinical practice. One retrospective study in the Netherlands found that about 37% of new users of tiotropium continued treatment for 1 year, compared with 14% for ipratropium, 13% for LABA, and 17% for ICS–LABA but compliance was increased in all groups after hospitalization.<sup>182</sup> These results are supported by those of a Canadian study of inhaled steroids between 1990 and 1995.<sup>183</sup> Differential



withdrawal rates also complicate interpretation of data from trials, as a greater number of more severe patients are likely to withdraw from the placebo arm leaving the placebo arm containing a higher proportion of milder patients, potentially biasing against the beneficial effects of an intervention but also making an intent to treat analysis difficult (Table 2).

Combining the tolerability/patient preference results of the three long term studies discussed above, it would appear that the most tolerable combination is ICS–LABA–LAMA but it is too early to draw a definitive conclusion at this stage.

The smaller studies involving the mucolytic agents or erythromycin found no differences in withdrawal rates compared to placebo.<sup>149,160,161</sup>

## Safety

The TORCH data were the first to suggest that ICS-containing regimens may be associated with an increased risk of a complication termed ‘pneumonia,’ but it should be noted that radiological confirmation of pneumonia was not required and so these pneumonia episodes may not be more precisely characterized.<sup>104</sup> The results are however supported by the INSPiRE data which reported pneumonias in 8% in the SFC arm and 4% in the tiotropium arm. Most of these pneumonias required hospitalization and there were three deaths due to pneumonia in INSPiRE, all in the SFC arm. However in spite of this, INSPiRE still reported a mortality reduction on treatment in favor of SFC.<sup>47</sup>

Reassuringly, TORCH did not demonstrate an increase in the development of cataracts with ICS-containing regimes, or a reduction in bone mineral density or increase in fracture risk. Similarly, LABA-containing regimes were not associated with excess cardiovascular events.<sup>104,116,184,185</sup> ICS was associated with an increased incidence of oropharyngeal candidiasis.

The safety of tiotropium has been reported in a meta-analysis of nine randomized trials including data from 8002 patients.<sup>186</sup> The data did not support an effect of tiotropium on all-cause (or pulmonary) mortality (OR 0.96, 95% CI 0.63–1.47). Only dry mouth was more common than with placebo, but when compared with other comparator drugs such as ipratropium or salmeterol there was an increased risk of urinary tract infection and, with further allowance for heterogeneity, an observed increased risk of arrhythmias (OR 2.33, 95% CI 1.11–4.88). All three of the major tiotropium studies<sup>131–133</sup> excluded patients who had a recent myocardial infarction, heart failure or cardiac arrhythmias. Thus the publication of a recent meta-analysis

**Table 2** Safety and tolerability

Intervention	Safety	Tolerability	Remarks	Reference
ICS vs LABA vs Both vs Placebo	Significant increase in risk of ‘pneumonia’ in patients taking an ICS containing preparation (19.6% both, 18.3% ICS vs 12.3% placebo $p < 0.001$ or 13.3% LABA). ICS also associated with oropharyngeal candidiasis. No apparent effect of ICS on BMD or fracture risk, or of LABA on cardiovascular events.	Placebo: 44% withdrawal. RR in following groups compared to placebo 0.69 (0.62–0.78, $p < 0.001$ ) for both, 0.78 (0.70–0.86, $p < 0.001$ ) for LABA and 0.81 (0.72–0.90, $p < 0.001$ ) for ICS.	3 year study, 6184 in safety analysis	TORCH
ICS + LABA vs Tiotropium	Lower mortality in SFC vs TIO (3% vs 6%, $p = 0.032$ ) which may relate to more cardiovascular events in TIO. Increased pneumonia in SFC vs TIO (8% vs 4%).	ICS + LABA withdrawal 35% vs tiotropium 42% $p = 0.005$ .	2 year study, 1323 patients randomized	INSPIRE
Tiotropium	All cause mortality vs placebo: OR 0.96, 95% CI 0.63–1.47. Compared with placebo greater dry mouth but not constipation, urinary retention or vascular/arrhythmias.		8002 patients	Barr <sup>186</sup> Meta-analysis
ICS	Increased oropharyngeal candidiasis RR 2.1, 95% CI 1.53–3.10; bruising RR = 2.1; 95% CI 1.6–2.8 and lower mean cortisol. No mortality effect. Effect on BMD variable. No differences in cataract or fracture (but short follow up).		9 trials, 3976 patients	Alsaedi <sup>188</sup> Systematic analysis
LABA	No increased adverse events, clinical, laboratory or ECG, compared to placebo over 12 weeks.		135 salmeterol, 143 placebo.	Mahler <sup>116</sup>

**Abbreviations:** ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; BMD, bone mineral density; RR, relative risk; SFC, salmeterol–fluticasone; TIO, tiotropium; OR, odds ratio; CI, confidence interval.

of seventeen trials involving ipratropium or tiotropium which showed an increased risk of cardiac complications in COPD patients met with some consternation<sup>187</sup> and the need for a long term prospective study was felt necessary to answer the question of safety definitively. The UPLIFT study (Table 1) was recently published and has shown a decreased risk of cardiac complications in the tiotropium arm vs placebo arm at 4 years, though it is to be noted that patients in both arms of the study were also on other inhaled therapies.<sup>136</sup>

A systematic review of RCTs of ICS in COPD also showed no overall mortality effect (RR 0.84, 95% CI 0.60–1.18)<sup>188</sup> and significant increases in oropharyngeal candidiasis and bruising. No increased risk of fractures or cataracts were observed in the short follow-up periods, and effects on bone mineral density were variable. Similarly, effects on serum cortisol levels varied. This must be interpreted on the background of larger studies demonstrating effects of ICS on cataracts,<sup>189,190</sup> osteoporosis<sup>191</sup> and adrenal suppression.<sup>192</sup>

The side effects of LABA are well described. However, the particular concern in COPD has always been of cardiovascular risk, particularly with regard to tachyarrhythmias, following stimulation of cardiac  $\beta$ -adrenoceptors. Small studies of less than 1 year's duration have assured us of the cardiovascular safety of salmeterol (50  $\mu$ g twice daily) and formoterol in COPD.<sup>115,116,150,184,193–195</sup> The question was also addressed in a meta-analysis of 1410 patients from 7 trials up to 1 year in duration using the LABA salmeterol (50  $\mu$ g BD) in comparison to 1443 on placebo.<sup>184</sup> The relative risk for cardiovascular adverse events was 1.03 (95% CI 0.81.3;  $p = 0.838$ ). Unlike other drug classes, meta-analyses of efficacy of LABA in COPD have not generally reported safety and tolerability. These results have been confirmed in the 1-year prospective studies for both salmeterol<sup>111</sup> and formoterol<sup>112,113</sup> and for salmeterol over 4 years.<sup>104</sup>

With regard to the newer drugs used in COPD no significant cardiovascular side effects were reported for erythromycin<sup>149</sup> or cilomilast<sup>152</sup> but cilomilast was associated with a significantly greater incidence of gastrointestinal side effects affecting daily life (17% vs 8% placebo). No safety issues have been reported in long-term studies of the mucolytic agents.<sup>160,161</sup>

## Patient-focused perspectives

### Metered dose inhalers

Pressurized metered dose inhalers (pMDIs), though easy to use, are critically dependent on inhalational technique to achieve acceptable lung deposition, which can be improved

through use of add-on valve holding chambers (spacers), but these are seldom used in the clinical practice possibly because they are cumbersome.<sup>196</sup> Inclusion of a dose counter may significantly improve patient satisfaction with metered dose inhalers.<sup>196</sup>

### Breath-actuated devices

These include the dry powder inhalers (DPIs). They are environmentally safe, easily carried by the patient and do not incur patient-centered difficulty with hand inhalation coordination as may occur with pMDI usage. However, in a systematic review of COPD and asthma, Lavorini et al found that there were several problems with their use: (a) failure to exhale before actuation, (b) failure to breathhold after inhalation, (c) incorrect positioning of the inhaler, (d) incorrect rotation sequence, and (e) failure to execute a forceful and deep inhalation.<sup>197</sup> In a small study of elderly COPD patients with matched controls, Janssens et al found that 30% of COPD patients did not achieve the recommended flow rate<sup>198</sup> and these results are supported by other studies.<sup>199,200</sup> Thus significant training may be required for patients to achieve therapeutic benefit from their inhalers.

### Nebulizers

Nebulizers are relatively difficult and time consuming to use and need to be maintained. However their use requires less coordination compared to inhalers and one study of 82 patients in the UK found that patients felt overwhelmingly that the benefits of using a nebulizer outweighed potential disadvantages.<sup>201</sup>

Thus from a patient-centered perspective, the choice of an inhaler device is a key component of COPD therapy and this requires more attention from physicians than perhaps we are aware of.

### Disease management programs

The major features of these programs are (1) adherence to guidelines (2) use of a nurse with special training in that disease and (3) central coordination with patientcenteredness.<sup>202</sup> During the Dutch Quality of Care Through Patients Eyes (QUOTE) Study of patients with asthma and COPD, the proportion of patients reporting good accessibility improved from 57% to 73% and good coordination of care from 63% to 77% ( $p < 0.05$  in both cases).<sup>203,204</sup> Patient satisfaction improved as the study progressed.<sup>203</sup> Thus coordination of care and accessibility to health care personnel are two key features of patient satisfaction. An intensive disease-specific self-management programme carried out in Canada has

been shown to reduce hospital readmission rate<sup>205</sup> or deaths following hospitalization but not readmissions,<sup>206</sup> though a systematic review of nurse interventions failed to show a consistent effect on hospitalization.<sup>207</sup> Another randomized study of organized care was based on a so-called chronic platform ‘chronic platform,’ which was a web-based application that facilitated phone calls to the case manager, as well as record keeping via phone calls, home visits or home video conferencing, and which again emphasized improved communication and nurse practitioner importance.<sup>208</sup> Patient satisfaction was not an outcome measure in this study but patients in the interventional arm had significantly less readmissions to hospital,<sup>208</sup> similar to those of a Spanish study of integrated care.<sup>209</sup>

The results of the above two European and Canadian studies are different from those of a Dutch study which found no effect of a self-management program in 248 COPD patients.<sup>210</sup> However the Dutch study involved less severe patients who had not been admitted to hospital. Thus self management programs are associated with significant improvements in several processes<sup>211</sup> and may be more useful in the more severe patients who have had at least one hospitalization. Finally we may observe that it appears to be too early to determine whether self-management programs will have an effect on mortality but their fairly uniform effect on exacerbation severity as assessed by hospital admission rates is certainly consistent with this hypothesis and supported by the results of the SolerCataluña study.<sup>66</sup>

## Conclusions

Amongst the common chronic diseases, the term COPD is relatively new but is extremely prevalent in Western society and its incidence is rising in the developing world. COPD is generally underdiagnosed and undertreated. Exacerbations of COPD, about 50% of which are reported to physicians, lead to a deterioration in the quality of life and contribute significantly to disease burden. There is heterogeneity in the definition of COPD exacerbations, and for interventional studies to decrease exacerbation rates in a reproducible manner we must have a more precise definition of a COPD exacerbation. So far an objective marker is lacking but current efforts may soon yield positive results.

Patient quality of life deteriorates with time. Most of the health burden of COPD occurs in the more severe disease and is due to hospitalization which is an outcome measure that can be modified. COPD severity, and frequent and more severe exacerbations are all related to an increased risk of mortality.

Most of these outcome measures can be modified by current therapeutic strategies. Most inhaled steroid medications evaluated in long-term studies have similar effects on quality of life but may appear to differ in their effects on COPD exacerbations. The combination ICS–LABA and the LAMA, tiotropium, are likely to decrease mortality but perhaps only when used over a period of several years. In addition to this, they both improve health status and exacerbation rates. In a single center study the macrolide, erythromycin, has been shown to decrease the rate of COPD exacerbations but effects on mortality and quality of life are unknown. The new phosphodiesterase inhibitor cilomilast has been shown to improve quality of life and exacerbation rates but has significant gastrointestinal side effects.

Nonpharmacologic strategies are also of importance in COPD. Pulmonary rehabilitation is indicated in all severities of COPD and improves quality of life; effects on exacerbation rate and mortality are unclear. An unquantified degree of regular physical activity is associated with decreased hospitalization and mortality and may even prevent or delay onset of COPD. Noninvasive ventilation is associated with improved quality of life but studies have been too small to provide strong evidence for an effect on mortality. Long-term oxygen therapy improves mortality but only in hypoxic COPD patients. Disease management programs have a more holistic approach with emphasis on patient centeredness and communication, and are associated with decreased hospitalization rates and improved quality of life, but so far there are no studies of mortality. Most of these interventions are well tolerated and their safety profile in long-term studies has been shown to be good.

In the past 30 years there have been marked improvements in the treatment of COPD. We now have interventions that are well tolerated and safe and decrease exacerbation rates and improve quality of life. Comparative studies of the nonpharmacologic and pharmacologic approaches are lacking. We must concentrate more efforts on patient education. Recent studies using drug combinations have been unable to achieve more than a 25% fall in exacerbation rates and thus there may be a need for research into new modalities of treatment. Whether LABA or ICS reduce mortality is no longer of relevance, as it is clear that the combination ICS–LABA reduces exacerbation rates and improves quality of life and is thus more efficacious than the individual therapies. Future research will look at combining therapies with different mechanisms of treatment such as ICS–macrolides or LAMA–phosphodiesterase. The goal would be to decrease exacerbation/hospitalization rates by

more than 50% either singly or in combination with current modalities of treatment.

## Disclosure

The authors declare no conflicts of interest.

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