

7 Managing Stable COPD

7.1 Introduction

COPD is a heterogeneous disease that affects different patients in different ways. Some patients may be more troubled by breathlessness, others may develop ankle swelling and others may be experiencing frequent hospital admissions. The management of an individual patient's disease should be guided by the symptoms and disability that they experience. At different times in the natural history of their disease different features may predominate and their management will change to reflect this. COPD also has effects outside the lung for example on peripheral muscles and may lead to mood or cognitive changes which should also be assessed.

This section presents statements and recommendations about the efficacy and role of therapies in stable COPD. Section 8 presents statements and recommendations about the efficacy and role of therapies in managing exacerbations of COPD.

The assessment of a patient's symptoms should take into account the presence of the symptoms listed in section 6.2, the clinical signs listed in section 6.3, the results of spirometry and the frequency of exacerbations. Using the algorithm in section 5.2, the results of the assessment can be used to identify therapies that are appropriate for that individual at that time.

7.2 Smoking Cessation

Getting patients with COPD to stop smoking is one of the single most important interventions. Stopping smoking slows the rate of decline in FEV₁ with consequent benefits in terms of progression of symptoms and survival.

The GDG reviewed the smoking cessation evidence for both pharmacological and non-pharmacological approaches as they related specifically to COPD. Studies were rejected either because they were non-specific to COPD or due to small sample size.

One Cochrane systematic review by van der Meer et al was identified⁴⁵ which was specific to chronic obstructive pulmonary disease and contained five studies⁴⁶⁻⁵⁰. The review authors highlighted that only two of the five studies were of high quality and hence these were reviewed on an individual basis^{46;50}. An additional two trials were identified^{51;52} and one NICE Technology Appraisal⁵³ met our quality appraisal criteria. Three studies^{46;51;52} were all part of the Lung Health Study.

The guideline remit was to consider smoking cessation approaches as they relate *specifically* to COPD. However the project scope also highlighted that the NICE Technology Appraisal on "Smoking cessation treatments and nicotine replacement therapy", which is non-specific to COPD, should inform the COPD guideline.

7.2.1 Benefits of stopping smoking

▷ Evidence statements

The Lung Health Study highlighted that participants in the two smoking intervention groups showed significantly smaller declines in **FEV₁** than did those in the control group. Average decreases from baseline to 5 years were 267ml for the control group, 209ml for the smoking intervention group without study bronchodilator and 184ml with study bronchodilator. ($p < 0.002$)^{46,51}. **Ib**

Kanner, as part of the Lung Health Study evaluated the effects on **symptoms** of chronic cough, chronic phlegm production, wheezing and shortness of breath. The prevalence of each of the four symptoms in the two intervention groups was significantly less than in the usual care group ($p < 0.0001$). Smokers with early COPD who were assigned to a smoking cessation intervention had fewer respiratory symptoms after 5 years of follow-up⁵². **Ib**

7.2.2 Smoking cessation therapy

▷ Evidence statements

Tashkin investigated the effect of sustained release **bupropion** compared to placebo in promoting abstinence from smoking in patients with mild to moderate COPD. This study specifically focused on a COPD population⁵⁰. **Ib**

Continuous smoking abstinence rates from wk 4 to 7 were significantly higher in participants receiving bupropion than those receiving placebo (28% vs. 16%, $p = 0.003$). Weeks 4 to 12 (18% vs. 10%) and weeks 4 to 26 (16% vs. 9%) smoking cessation was also higher in participants receiving bupropion than those taking placebo ($p < 0.05$).

The National Institute of Clinical Excellence guidance focuses on pharmacological approaches (nicotine replacement therapy and bupropion) to smoking cessation (although not specifically COPD)⁵³. **NICE**

Nicotine Replacement Therapy (NRT)

There is currently insufficient evidence to conclude that one form of NRT is more effective than another. In the small number of studies undertaken with specific subgroups (pulmonary disease) results were generally inconclusive on an individual study basis, but in aggregate were consistent with the overall pooled results.

Bupropion

From a meta analysis of ten RCTs the odds ratio for smoking cessation of bupropion vs. placebo was 2.16 (1.51 to 3.10) for 6 and 12 months. In terms of percentages of smokers quitting, the average over all trials shows that about 9% had not smoked for the 12 months following placebo therapy and about 19% had not smoked following bupropion therapy. The results for specific subgroups (pulmonary disease) were

generally consistent with the overall pooled results. *Bupropion should be used in conjunction with appropriate support.*

Bupropion vs. NRT

There have been only two RCTs of bupropion vs. nicotine replacement therapy. For bupropion vs. patch, the odds ratio at 12 months for continuous abstinence was 2.07 (1.22 to 3.53) in favour of bupropion, and for bupropion plus patch versus bupropion it was 1.28 (0.82 to 1.99). In the second study, which compared bupropion to NRT gum, there was no significant difference between the groups in quit rates.

Combination of NRT and bupropion

In the single study so far conducted, the result was in favour of the combination of NRT and bupropion against bupropion alone, but the difference was not statistically significant.

▷ Health Economic Evidence

A HTA report⁵⁴ contains a review of the economic evidence of smoking cessation interventions in the UK and a decision analytic model built by the authors. Although all of this is for smoking cessation in general and not specific to COPD, most of the literature and the model suggest that smoking cessation is a reasonably cost effective intervention.

Smoking cessation interventions, including the use of nicotine replacement therapy and/or bupropion SR are relatively cost effective in terms of the cost per life year saved.⁵⁴

RECOMMENDATIONS

R24	An up to date smoking history, including pack years smoked (number of cigarettes smoked per day, divided by 20, multiplied by the number of years smoked), should be documented for everyone with COPD.	Grade D
R25	All COPD patients still smoking, regardless of age, should be encouraged to stop, and offered help to do so, at every opportunity.	Grade A
R26	Unless contraindicated, bupropion or nicotine replacement therapy combined with an appropriate support programme should be used to optimise smoking quit rates for people with COPD.	Grade B
R27	NICE Technology Appraisal Guidance No 39 ⁵³ recommends: <i>If a smoker's attempt to quit is unsuccessful with treatment using either NRT or bupropion, the NHS should normally fund no further attempts within 6 months. However, if external factors interfere with a person's initial attempt to stop smoking, it may be reasonable to try again sooner.</i>	NICE

7.3 Inhaled bronchodilator therapy

Although COPD is characterised by substantially irreversible airflow obstruction, bronchodilators have been the mainstay of pharmacotherapy^{25,38}. Beta₂-agonists, anticholinergics and theophylline have all been used to treat COPD.

The structural changes in the airways prevent bronchodilators returning airway caliber to normal. Clinically relevant improvements in FEV₁ may be too small to identify against the background day to day variation in an individual patient. Inhaled agents are preferred to oral because of the reduction in systemic side effects. Beta₂-agonists act directly on bronchial smooth muscle to cause bronchodilation whereas anticholinergics act by inhibiting resting bronchomotor tone. As well as improving breathlessness through their direct bronchodilator effects, both classes of drugs also appear to work by reducing hyperinflation (both static and dynamic). This probably explains why clinical benefits may be seen without clear changes in the FEV₁.

7.3.1 Short-acting beta₂-agonists

Beta₂-agonists act directly on bronchial smooth muscle to cause bronchodilatation. They are the most widely used bronchodilators for COPD. The dose response relationship for salbutamol in patients with largely or completely irreversible COPD is almost flat^{55,56}. The time to peak response is slower than in patients with asthma and the side-effect to benefits ratio is such that there is little benefit in giving more than 1 mg salbutamol. Their effects on airway caliber last for up to 4 hours and can be used on a regular, or as required, basis. Short-acting beta₂-agonists are the most commonly used short-acting bronchodilators in COPD.

One systematic review was found looking at their efficacy⁵⁷. The review comprised of 13 RCTs⁵⁸⁻⁷⁰, however 4 of these were from the same cohort of patients^{59-61,63}. All the RCTs were of a crossover design and had variable washout periods, 7 being undocumented whilst the rest ranged from washout periods of 10 hours to 2 weeks. The majority of evidence for short-acting beta₂-agonists comes from older (date range 1975 to 1991), short-term (1 to 8 weeks duration), small studies (sample size range n=5 to n=48), some of which used older compounds (interventions included isoproterenol, metaproterenol, salbutamol and terbutaline)⁵⁷.

▷ Evidence statements

Daily **breathlessness** scores were reduced with the use of short-acting beta₂-agonists (SMD 1.33, 95% CI 1.01 to 1.65, p<0.0001)⁵⁷. **Ia**

One study⁵⁹ measured the effects of short-acting beta₂-agonist changes on **health related quality of life**. This study was included in the systematic review referred to above⁵⁷ however the data was not available for meta analysis, n=32. The study showed significant improvements in the dyspnoea (p=0.003) and fatigue (p=0.0003) domains using the Chronic Respiratory Disease Questionnaire (CRDQ). **Ib**

Short-acting beta₂-agonists improve **FEV₁** (WMD 0.140 L, 95% CI 0.04 to 0.25, p=0.008)⁵⁷. **Ia**

Short-acting beta₂-agonists appear to be as effective when used on an **as needed basis** as when used regularly on a background of other bronchodilators⁷¹. **Ib**

7.3.2 Short-acting anticholinergics

Cholinergic nerves are the main neural bronchoconstrictor pathway in the airways and the resting tone is increased in patients with COPD⁷². Anticholinergic drugs cause bronchodilatation by blocking this bronchoconstrictor effect. Cholinergic effects on the airway are mediated by muscarinic receptors and these also mediate effects on mucus secretion.

There were no systematic reviews comparing short-acting anticholinergics in comparison to placebo or other bronchodilating drugs. In view of the availability of data from longer term studies several trials were rejected due to small sample size⁷³⁻⁷⁵ or short trial duration⁷⁶. Four trials⁷⁷⁻⁸⁰ had methodological limitations, which precluded making recommendations based upon the papers findings. Trials also used a variety of differing endpoint outcome measures.

▷ Evidence statements

Three studies⁸¹⁻⁸³ demonstrated significant increases in **FEV₁** with the use of short acting anticholinergic drugs when compared to placebo, $p < 0.001$, $p < 0.026$ and $p < 0.001$ respectively. **Ib**

One study⁸³ found that **dyspnoea** measured by the Transition Dyspnoea Index (TDI) was significantly improved with short-acting anticholinergics compared to placebo. **Ib**

Two other studies found no significant differences for **symptoms**⁸² or **dyspnoea**⁸¹ or **walking distance**⁸¹ with the use of short-acting anticholinergics compared to placebo. **Ib**

One study⁸³ found that health related **quality of life** (measured using the Chronic Respiratory Disease Questionnaire (CRDQ)) was significantly higher for short acting anticholinergics compared to placebo ($p = 0.007$). **Ib**

Two studies^{81;82} found no significant differences between short-acting anticholinergics and placebo groups for **quality of life**. **Ib**

Three studies looked at the need for **rescue medication**⁸¹⁻⁸³. Two trials^{81;83} found a decrease in use of rescue medication, $p < 0.047$ ⁸³. One study⁸² found no significant difference in use of rescue medication when using short-acting anticholinergic compared to placebo. **Ib**

7.3.3 Long-acting beta₂-agonists

The bronchodilator effects of long-acting beta₂-agonists are similar to the short-acting agents but their duration of action is around 12 hours. There are two long-acting beta₂-agonists: salmeterol and formoterol. These drugs have quite different molecular structures and there are thought to be different mechanisms responsible for the longer duration of action of these two molecules.

We found one systematic review⁸⁴ comparing long-acting beta₂-agonists with placebo. This deals predominantly with salmeterol, as there were few published studies of the effects of formoterol at the time it was undertaken. The review comprised of eight RCTs^{83;85-91}, six were of a parallel group design of 12-16 weeks duration. Two were cross over studies^{87;90}. Appleton et al⁸⁴ highlights two important points. Firstly, that there was variation in the methodological quality of the included studies and secondly that few of the results could be combined in meta analyses due to differences in methods of reporting outcomes.

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One of the studies included in the systematic review⁸⁴ has only been published in abstract form⁸⁶ and it includes data published by Mahler et al⁸³. Therefore this study is not included in table 9.

Shukla et al (2002)⁹² in a Canadian Health Technology Assessment included nine trials, all but one (which is Russian) are taken into account within the Appleton systematic review⁸⁴.

In addition to the trials included in the systematic review, seven other trials were identified^{82,93-98}.

As well as this, Mahler et al⁹⁶, Calverley et al⁹⁸ and Szanfranski et al⁹⁷ were identified as three separate studies that had single salmeterol or formoterol compared to placebo comparative arms within studies reporting on the use of combination drugs and hence these were included.

Because of the variability in the results of the trials of these drugs they have been summarised in table 9.

Table 9 Summary of results of studies on long-acting beta₂-agonists

Trial	Sample size	Duration (weeks)	Drug	Dose (ug)	FEV ₁	FVC	Diary symptoms	Night	Rescue	Dyspnoea	Exercise test	HRQL	Exacerbations	Reference
<i>vs Placebo</i>														
Rennard 2001(a)	405	12	S	50	↑	↑	NS	NS	↑	NS	NS	NS	NS	81
Van Noord 2000	144	12	S	50	↑	NS	↑	NS	↑	-	-	-	NS	91
Mahler 1999	411	12	S	50	↑	↑	NS	NS	↑	↑	-	↑	↑	83
Boyd 1997(b)	674	16	S	50	↑	-	↑	↑	↑	↑	NS	-	NS	85
Boyd 1997(b)	674	16	S	100	↑	-	↑	↑	↑	↑	NS	-	NS	85
Grove 1996	29	4	S	50	↑	NS	-	-	-	↑	NS	-	-	87
Ulrik 1995	63	4	S	50	NS	NS	↑	↑	↑	-	-	-	-	90
Donohue 2002	623	26	S	50	↑	↑	-	-	↑	NS	-	NS	-	99
Albers 2002 (c)	687	12	F	6	↑	-	↑	NS	↑	NS	NS	-	NS	93
Albers 2002 (c)	687	12	F	12	↑	-	↑	NS	↑	NS	NS	-	NS	93
Albers 2002 (c)	687	12	F	24	↑	-	↑	↑	↑	↑	NS	-	NS	93
Rossi 2002	854	52	F	12	↑	↑	NS	-	↑	-	-	↑	↑	94
Rossi 2002	854	52	F	24	↑	↑	NS	-	↑	-	-	↑	↑	94
Dahl 2001	780	12	F	12	↑	-	↑	-	↑	-	-	↑	NS	82
Dahl 2001	780	12	F	24	↑	-	↑	-	↑	-	-	↑	NS	82
Brusco 2003(d)	1207	26	S	50	↑	-	-	-	-	↑	-	NS	NS	95
Mahler 2002	691	24	S	50	↑	-	-	↑	↑	NS	-	NS	-	96
Calverley 2003	1465	52	S	50	-	-	NS	NS	↑	-	-	NS	↑	98
Szanfranski 2003	812	52	F	12	↑	↑	-	-	-	-	-	-	NS	97

Table 9 continued

Trial	Sample size	Duration (weeks)	Drug	Dose (ug)	FEV ₁	FVC	Diary symptoms	Night	Rescue	Dyspnoea	Exercise test	HRQL	Exacerbations	Reference
Rutten Van Molken 1999 (e)	144	12	S	50								NS		89
Jones 1997 (f)	283	16	S	50								↑		88
Jones 1997 (f)	283	16	S	100								NS		88
<i>vs Ipratropium</i>														
Rennard 2001 (a)	405	12	S	50	NS	NS	NS	NS	NS	NS	NS	NS	NS	81
Dahl 2001	780	12	F	12	↑	-	↑ _≠	-	↑	-	-	↑	NS	82
Dahl 2001	780	12	F	24	↑	-	NS	-	↑	-	-	↑	NS	82
<i>vs Tiotropium</i>														
Donohue 2002	623	26	S	50	↓	↓	-	-	↓	↓	-	NS	-	99
Brusasco 2003 (d)	1207	26	S	50	↓	-	-	-	-	NS	-	NS	NS	95

N.B. ↑ denotes statistically significant superiority versus comparator group (e.g. increased FEV₁, reduced symptoms scores etc), NS denotes no statistically significant benefits versus comparator group, ↓ denotes statistically significant inferiority versus comparator group, - denotes not assessed.

Drugs: S = salmeterol, F = formoterol

- (a) Over 77% of patients in this study showed at least 12% or 200ml reversibility to salbutamol
- (b) An inclusion criterion for this trial was an increase in FEV₁ of 5-15% 15 minutes after the inhalation of salbutamol
- (c) 23% of patients in this trial showed an increase of at least 10% in FEV₁ after terbutaline
- (d) This study includes patients reported in the study by Donohue et al. but includes additional outcome measures.
- (e) This trial reports the health related quality of life outcomes in a sub-group of the patients in the study by van Noord et al. 2000⁹¹.
- (f) This trial reports the health related quality of life outcomes in a sub-group of the patients in the study by Boyd et al. 1997⁸⁵.

▷ Evidence statements

Long-acting beta₂-agonists compared to placebo in stable COPD

There was variation in the results within the systematic review⁸⁴ for **symptom scores** **Ia** across four studies^{83;85;90;91}. The largest of the trials⁸⁵ demonstrated that long-acting beta₂-agonists reduce symptom scores. Day time (p=0.01). Night time (p=0.001).

There were three subsequent randomised controlled trials^{82;93;94}. Using standard **Ib** therapeutic doses only one trial⁸² found that **symptom scores** were reduced (p<0.001).

With regard to the reduction of **breathlessness**, five trials within the systematic review⁸⁴ **Ia** found no significant differences between long-acting beta₂-agonist and placebo. One trial with the largest sample size (n= 674)⁸⁵ demonstrated that long-acting beta₂-agonist reduce the degree of breathlessness produced by exercise.

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- There were two subsequent randomised controlled trials^{93;95} with large sample sizes that demonstrated a statistically significant difference with the use of long-acting beta₂-agonists in **reducing dyspnoea** (p=0.002 and p<0.05 respectively). **Ib**
- In addition to this Brusasco⁹⁵ found that for **TDI** focal score a higher percentage of patients achieved a change of at least one unit with salbutamol (41.2%) than with placebo (29.8%) p<0.01. **Ib**
- Mahler et al⁹⁶ showed a significant reduction in overall **use of supplemental** albuterol after treatment with salmeterol compared with placebo (p≤0.045). **Ib**
- A significant increase in the overall percentage of **nights with no awakenings** requiring albuterol was observed for salmeterol compared with placebo (p<0.001).
- Long-acting beta₂-agonists have no proven effect on **walking distance**⁸⁴. **Ia**
- The systematic review⁸⁴ demonstrated that there was variation in trial results for **health related quality of life** (HRQL) and hence the trial results are looked at on an individual basis for this outcome. **Ia**
- Three studies^{82;88;94} showed that long-acting beta₂-agonists significantly improved **HRQL** using the St George's Respiratory Questionnaire (SGRQ). p<0.01, p=0.030, p=0.01 respectively. **Ib**
- Four other studies also looked at **health related quality of life**^{81;83;89;95} two^{81;83} of which used the Chronic Respiratory Diseases Questionnaire (**CRDQ**), one⁹⁵ used the SGRQ to measure HRQL and one used the SGRQ and CRDQ⁸⁹. **Ib**
- Rutten van Molken⁸⁹ and Brusasco⁹⁵ did not find any statistically significant differences.
- Rutten van Molken⁸⁹ also found no significant difference in the proportion of patients achieving clinically relevant improvements (13% in the salmeterol and 12% in the placebo groups using the **CRDQ** and 24% of the salmeterol and 23% of the placebo groups using the **SGRQ**).
- Mahler et al⁸³ found that at week 12 the mean **CRDQ** overall score was significantly higher for salmeterol (p=0.007) than for placebo. The proportion of patients who achieved an increase of ≥10 points in overall score (the minimum change indicative of an important difference) was significantly higher at week 12 in the salmeterol (46%, p=0.002) than in the placebo group (27%) in non-reversible patients.
- Rennard et al⁸¹ using the **CRDQ** showed that the proportion of patients who achieved a clinically significant change of 10 from the baseline was 46% in the salmeterol group and 38% in the placebo group.
- Brusasco⁹⁵ found that the percentage of patients achieving a **SGRQ** improvement of at least 4 units was 43.2% in the salmeterol group and 39.3% in the placebo group.
- The systematic review⁸⁴ found that long-acting beta₂-agonists compared to placebo did not significantly affect the incidence of COPD **exacerbations**, however this meta analysis was only based upon two RCTs^{85;91}. **Ia**
- One cross over study⁹⁰ n=63, not combined in the meta analysis but also included in **Ib**

the systematic review ⁸⁴ found no significant difference in **exacerbations**.

Two subsequent trials by Dahl ⁸² and Brusasco ⁹⁵ also found no significant difference in **exacerbations**. **Ib**

However, two trials^{94;98} found significant differences favouring long-acting beta₂-agonists compared to placebo for **exacerbations**. **Ib**

Rossi et al⁹⁴ in a large multicentred trial over one year found that formoterol was significantly superior to placebo for the mean percentages of bad days defined as “**mild COPD exacerbation**” p≤0.008. **Ib**

A large (n=1465) multicentre RCT⁹⁸ showed that compared with placebo, salmeterol significantly reduced the number of **exacerbations** per patient per year and the number of exacerbations that needed treatment with oral corticosteroids. The rate of exacerbations fell by 20% (p=0.0027) in the salmeterol group compared to placebo. **Ib**

Acute episodes of symptom exacerbation that required oral corticosteroids were reduced by 29% in the salmeterol group (p=0.0003) compared with placebo.

7.3.4 Long-acting anticholinergics

Tiotropium is currently the only long-acting anticholinergic bronchodilator available. Its duration of action is such that it can be given once daily.

There have been no systematic reviews yet comparing tiotropium with placebo, short-acting drugs or long-acting beta₂-agonists. Because of the existence of larger longer-term studies on anticholinergic drugs it was felt unnecessary to include the shorter-term studies. There were a number of randomised controlled trials comparing these drugs. Two publications compare the effects of long-acting anticholinergics with long-acting beta₂-agonists and placebo. One of these ⁹⁵ includes patients described in the earlier paper ⁹⁹ but a potential limitation of this paper is the fact that it does not explicitly cite the earlier study or provide specific information on the other trial that is included. However, whenever possible the paper with the largest sample has been used to formulate the evidence statements.

The results of these have been summarised in table 10.

7.3.4.1.1 Table 10 Summary of results of studies on long-acting anticholinergics

Trial	Sample size	Duration (weeks)	Drug	Dose (ug)	FEV ₁	FVC	Diary Symptoms			Rescue medication use	Dyspnoea	Exercise test	HRQL	Exacerbations	Reference
							Diary	Night							
<i>vs Placebo</i>															
Littner 2000	169	4	T	4.5	↑	↑	-	-	-	-	-	-	-	-	100
Littner 2000	169	4	T	9	↑	↑	-	-	-	-	-	-	-	-	100
Littner 2000	169	4	T	18	↑	↑	-	-	-	-	-	-	-	-	100
Littner 2000	169	4	T	36	↑	↑	-	-	-	-	-	-	-	-	100
Casaburi 2000	470	13	T	18	↑	↑	↑	↑	↑	-	-	-	-	-	101
Casaburi 2002	921	52	T	18	↑	↑	↑	-	↑	↑	-	↑	↑	-	102
Donohue 2002	623	26	T	18	↑	↑	-	-	↑	↑	-	↑	-	-	99
Brusasco 2003 (a)	1207	26	T	18	↑	-	-	-	-	↑	-	↑	↑	-	95
<i>vs Ipratropium</i>															
Vincken 2002	535	52	T	18	↑	↑	-	-	↑	↑	-	↑	↑	-	103
<i>vs Salmeterol</i>															
Donohue 2002	623	26	T	18	↑	↑	-	-	↑	↑	-	NS	-	-	99
Brusasco 2003 (a)	1207	26	T	18	↑	-	-	-	-	NS	-	NS	NS	-	95

N.B. ↑ denotes statistically significant superiority versus comparator group (e.g. increased FEV₁, reduced symptoms scores etc), NS denotes no statistically significant benefits versus comparator group, ↓ denotes statistically significant inferiority versus comparator group, - denotes not assessed.

Drugs: T = tiotropium

(a) This study includes patients reported in the study by Donohue et al.⁹⁹ but includes additional outcome measures.

▷ Evidence statements

Long-acting anticholinergics compared to placebo in stable COPD

Four studies^{95;100-102} demonstrated a significant increase in **FEV₁** and **FVC** in favour of long-acting anticholinergics compared to placebo. $p < 0.001$ ¹⁰¹, $p < 0.01$ ¹⁰² and $p = 0.001$ ⁹⁵. **Ib**

A one year clinical trial¹⁰² found that long-acting anticholinergic significantly improved morning and evening **PEFR** compared to placebo ($p < 0.005$). **Ib**

Three studies^{95;101;102} used differing measures for assessing **symptoms**. Casaburi^{101;102} found that symptom scores for wheezing and shortness of breath were significantly improved ($p < 0.01$ ¹⁰¹ and $p < 0.05$ ¹⁰²) for long-acting anticholinergics compared to placebo. **Ib**

Two studies^{95;102} measured dyspnoea using the Transition Dyspnoea Index (**TDI**) and both found that long-acting anticholinergic was superior to placebo ($p < 0.001$ respectively).

In addition, Brusasco et al⁹⁵ and Casaburi et al¹⁰² found that the proportion of patients achieving a change of at least 1 unit in TDI focal scores for long-acting anticholinergic compared to placebo were significantly higher ($p < 0.01$ respectively).

Two studies^{95;102} measured HRQL using the St George's Respiratory Questionnaire (SGRQ). Both found significant improvements with the use of long-acting anticholinergic over placebo. $p < 0.05$ and $p < 0.01$ respectively. **Ib**

Brusasco⁹⁵ also found that the proportion of patients with a clinically meaningful change (CMC) in the **SGRQ** score (of at least 4 units) was superior in the long-acting anticholinergic group (48.9%) compared to the placebo group (39.3%), $p < 0.05$.

Two studies^{95;101} looked at the amount of **rescue medication** required and found that it was used less often in the long-acting anticholinergic group compared to placebo. $p < 0.001$ and $p < 0.0001$ respectively. **Ib**

Two studies measured **exacerbation rates**^{95;102}. Casaburi¹⁰² found that the proportion of patients experiencing exacerbation was lower in the long-acting anticholinergic group (36%) compared to the placebo group (42%), with a reduction of 14% and a p value of < 0.05 . **Ib**

Brusasco⁹⁵ found that patients treated with long-acting anticholinergic had significantly fewer exacerbations per patient year than the placebo group ($p < 0.05$).

There was no significant difference in the proportion of patients having at least one **exacerbation**, but long-acting anticholinergic delayed the time to the first exacerbation ($p \leq 0.001$) compared to placebo.

Long-acting anticholinergics compared to short-acting anticholinergics in stable COPD

One study¹⁰³ looked at the effects on **FEV₁ and FVC** and found that long-acting anticholinergic was superior to short-acting anticholinergic, $p < 0.05$. **Ib**

In a one year clinical trial¹⁰³ long-acting anticholinergic significantly improved morning and evening **PEFR** compared to short-acting anticholinergic, $p < 0.01$. **Ib**

Only one study¹⁰³ measured **dyspnoea**. TDI focal score for long-acting anticholinergic was superior to short-acting anticholinergic, $p < 0.05$. **Ib**

Only one study¹⁰³ measured **HRQL** using SGRQ. There were significant improvements in the SGRQ total and impact scores with long compared to short-acting anticholinergic. SGRQ impacts mean difference score -4.28 ± 1.32 ; 95% CI -6.87 to -1.68 ; $p = 0.001$. SGRQ total mean difference score -3.30 ± 1.13 ; 95% CI -5.51 to -1.09 ; $p = 0.004$. **Ib**

One study¹⁰³ looked at **rescue medication** and found that it was used less often in the long compared to short-acting anticholinergic group, $p < 0.05$. **Ib**

Vincken¹⁰³ found that the proportion of patients who experienced **exacerbations** was significantly lower in the long (35%) compared to short (46%) acting anticholinergic group during the trial, $p = 0.014$. **Ib**

Long-acting anticholinergic compared to long-acting beta₂-agonists in stable COPD

Brusasco⁹⁵ compared long-acting anticholinergic to long-acting beta₂-agonist. The **FEV₁** measures were statistically significant in favour of long-acting anticholinergic compared to long-acting beta₂-agonist ($p < 0.05$). **Ib**

There was no significant difference in the TDI **dyspnoea** focal score⁹⁵. **Ib**

There were no statistically significant outcomes for **HRQL** measured using the SGRQ when comparing long-acting anticholinergic to long-acting beta₂-agonist⁹⁵. **Ib**

There were no statistically significant differences between the two groups for **rescue medication** use⁹⁹. **Ib**

Over 6 months, there was no statistically significant difference in **exacerbation rates**⁹⁵. **Ib**

Please see section 7.7 for combination therapy relating to short-acting beta₂-agonists and short-acting anticholinergics.

▷ Health economic evidence

Ten papers of potential relevance to the subject area were found. All studies used different costing models and none were based in the UK. The majority of the studies were undertaken in the USA and had been sponsored by pharmaceutical companies. The GDG felt that studies based in the USA were of limited use, as their health care system is so different. Costing from these studies are therefore of little relevance to the UK.

The GDG were unable to derive any evidence statements based on this health economic evidence and felt that none was useful for contributing to the formulation of the recommendations.

RECOMMENDATIONS

R28	Short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation.	Grade B
R29	The effectiveness of bronchodilator therapy should not be assessed by lung function alone but should include a variety of other measures such as improvement in symptoms, activities of daily living, exercise capacity, and rapidity of symptom relief.	Grade D
R30	Patients who remain symptomatic should have their inhaled treatment intensified to include long-acting bronchodilators or combined therapy with a short-acting beta ₂ -agonist and a short-acting anticholinergic.	Grade A
R31	Long-acting bronchodilators should be used in patients who remain symptomatic despite treatment with short-acting bronchodilators because these drugs appear to have additional benefits over combinations of short-acting drugs.	Grade A
R32	Long-acting bronchodilators should also be used in patients who have two or more exacerbations per year.	Grade D

R33

The choice of drug(s) should take into account the patient's response to a trial of the drug, the drug's side effects, patient preference and cost.

Grade D

7.4 Theophylline

Theophylline and its derivatives have been used for many years to treat patients with COPD. The mechanism of action of these drugs remains uncertain¹⁰⁴ but it is generally assumed that they relax airway smooth muscle. Theophylline may also increase diaphragmatic strength in patients with COPD¹⁰⁵ and have effects on mucociliary clearance¹⁰⁶. It also has extra pulmonary effects, particularly improvement in cardiac output¹⁰⁷ that may also be beneficial in patients with COPD. Because of potential toxicity and significant interactions with other drugs^{108 109} theophylline is no longer considered initial empirical treatment. When reference is made to theophylline it is to the long-acting/slow release formulations, unless otherwise stated.

One systematic review was found¹¹⁰, which looked at oral theophylline compared to placebo in patients with stable COPD. Twenty worldwide RCTs of a cross over design were included in the systematic review with a total sample size of n=480. Study durations ranged from 7 to 90 days. All but two of the studies were double blind and none were open label studies (see comments pertaining to Rossi et al 2002⁹⁴ below). Eleven studies did not describe the washout periods and as such this means that there may be possible contamination. This may have resulted in a possible over estimation of the carry over effects of theophylline within the placebo group. Concomitant therapy varied from none to any other bronchodilator plus corticosteroid. Ages ranged from 59 to 69 years.

One additional study by Rossi et al (2002)⁹⁴ was identified, which compared formoterol, theophylline and placebo arms within the same study (n=854, of which n=122 placebo and n=209 theophylline group) over a 12-month duration. However the study was limited by the fact that the slow release theophylline arm was open label and hence both the physicians and participants were aware of the drug intervention. The authors state their rationale as "*the required dose titration of oral slow release theophylline made blinding impossible and it was therefore administered at individualised doses on the basis of plasma concentrations in an open-label fashion*". This may have been underpinned by an ethics committee requirement however this is not stated. As this is a recently published study this may be a significant difference in the way in which study designs for this particular drug are now conducted compared to the data spans contained within the systematic review¹¹⁰ when the dates ranged from 1979 to 1995. Rossi et al.⁹⁴ acknowledge this limitation and highlight that importantly "*the unblinded nature of the theophylline arm might have contributed to the very high dropout rate associated with the treatment*". Total discontinuation rates were quoted as formoterol (12µg) 25%, formoterol (24µg) 19%, placebo 27% and theophylline 39%⁹⁴.

This study illustrates the difficulty of undertaking a placebo-controlled double blind trial of the efficacy of theophylline. The need to balance achieving adequate, but not toxic therapeutic levels conflicts with the blinding of the investigators and patients. Early studies did not address this.

The trials cited above did not look at the therapeutic range for theophyllines.

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▷ Evidence statements

There was a statistically significant improvement in **FEV₁** and **FVC** in favour of the theophylline group compared to placebo. FEV₁ WMD 100ml; 95% CI; 40 to 160 ml. FVC WMD 210ml; 95% CI; 100 to 320 ml ¹¹⁰. **Ia**

Theophylline was also significantly more effective at increasing **FEV₁** than placebo at every time point and for each visit (all $p < 0.005$) in the study by Rossi et al. ⁹⁴ and the difference was clinically relevant at 5,7,8,10,11 and 12 hours. **Ib**

There was a statistically significant improvement in oxygen uptake (**VO₂ max**) in favour of the treatment group. WMD 195 ml/min; 95% CI; 113 to 278 ml/min. Two studies (Fink 1994 and Newman 1994 with a sample size of $n=32$)^{111;112} contributed to the data ¹¹⁰. **Ia**

There was a statistically significant improvement in **PaO₂** with treatment. WMD 3.18 mmHg; 95% CI; 1.23 to 5.13 mmHg ¹¹⁰. **Ia**

There was a statistically significant decrease in **PaCO₂** with theophylline compared to placebo. WMD -2.36 mmHg; 95% CI -3.52 to -1.21 mmHg ¹¹⁰. **Ia**

Participants **preferred** theophylline to placebo. RR 2.27; 95% CI 1.26 to 4.11. Authors acknowledge an error in the text describing the data for this outcome but confirm that the results and meta view are correct as they stand. Two studies (Alexander ¹¹³ $n=40$ and Mulloy ¹¹⁴ $n=10$) contribute to this data ¹¹⁰. **Ia**

Nausea was experienced more often in the theophylline group compared to the placebo (RR 7.67; 95%CI; 1.5 to 39.9) ¹¹⁰. **Ia**

There were no statistically significant differences for **distance walked**, VAS for **breathlessness**, symptoms of **wheeze** and **dyspnoea**, **exacerbations** or dropouts¹¹⁰. **Ia**

There were no statistically significant differences between the treatment groups for total **diary symptom scores or use of rescue medication** ⁹⁴. **Ib**

No data was available for **health status or mortality** ¹¹⁰. **Ia**

There were fewer “moderate” and “severe” **exacerbations** over 12 months in patients treated with theophylline compared to placebo (5% vs 8% ($p=0.019$) and 6 vs 20) in an open label designed study ⁹⁴. **Ib**

Statistically significant improvements in the total **SGRQ** score over 12 months (compared to baseline) were seen for theophylline compared to placebo in an open label designed study ($p=0.013$)⁹⁴. **Ib**

▷ GDG consensus statements

The plasma levels of theophylline must be monitored to ensure that they are adequate but do not reach the toxic range¹⁰⁹. **IV**

Although these drugs are effective, their usefulness is limited by the need to monitor plasma levels and their potential for interaction with other medication. **IV**

The need to monitor plasma levels and the potential for interaction with other medication restricts the therapeutic use of theophylline and its derivatives to patients who have already tried long-acting bronchodilators or who are unable to use inhaled therapy. **IV**

RECOMMENDATIONS

R34	Theophylline should only be used after a trial of short-acting bronchodilators and long-acting bronchodilators, or in patients who are unable to use inhaled therapy, as there is a need to monitor plasma levels and interactions.	Grade D
R35	Particular caution needs to be taken with the use of theophylline in elderly patients because of differences in pharmacokinetics, the increased likelihood of co-morbidities and the use of other medications.	Grade D
R36	The effectiveness of the treatment with theophylline should be assessed by improvements in symptoms, activities of daily living, exercise capacity and lung function.	Grade D
R37	The dose of theophylline prescribed should be reduced at the time of an exacerbation if macrolide or fluoroquinolone antibiotics (or other drugs known to interact) are prescribed.	Grade D

7.5 Phosphodiesterase type 4 inhibitors

Only one RCT published to date was found pertaining to a phosphodiesterase-4 inhibitor (Cilomilast) compared to placebo for the treatment of COPD over a 6-week duration¹¹⁵. Ages ranged from 40 to 80 years and with the exception of short-acting beta₂-agonists and anticholinergic agents, all other COPD medications were discontinued. The GDG felt that there was insufficient long-term data on which to base any evidence statements or recommendations.

7.6 Corticosteroids

There is little evidence that inhaled steroids have any effects on the inflammatory cells present in COPD: neutrophils, unlike eosinophils are relatively insensitive to the effects of steroids. Even high doses of inhaled steroids do not reduce the number of inflammatory cells or the levels of cytokines^{116,117}. Currently up to 70% of patients with COPD are prescribed an inhaled steroid and approximately 5% are prescribed oral steroids^{13 118}. The rationale for this is unclear and at least some of this prescribing may have been based on an extrapolation from the effects of these drugs in asthma and their effects at the time of an exacerbation (see section 8.11.3).

7.6.1 Inhaled corticosteroids

A systematic literature search, limited to a research design of systematic reviews and RCTs, yielded a hit rate of 260 potential papers applicable to inhaled steroids and stable COPD. Because the GDG was interested in the long-term effects of inhaled steroids and long-term data are available, together with the fact that the results of shorter studies may be affected by changes in lung function seen in the first six months, the evidence statements in this section are based on studies of at least 36 months duration. The evidence for the effects of inhaled corticosteroids when combined with long-acting beta₂-agonists is considered in section 7.7.

The GDG identified one systematic review¹¹⁹; this systematic review did however include studies with duration of 6 to 40 months. However, there was significant heterogeneity between the longer term studies included in this systematic review, possibly due to the severity of COPD in the patients recruited. In addition to critically appraising the systematic review, the studies of ≥ 36 months duration were independently critically appraised and these included ISOLDE¹²⁰, duration 36 months, The Lung Health Study¹²¹, duration 40 months, Vestbo 1999¹²², duration 36 months and EUROSCOP¹²³, duration 36 months. The rationale for this was the need to ascertain further outcomes (not presented in the systematic review) and hence the need to ensure the quality aspects of these primary papers prior to presenting evidence statements for inhaled steroids. The systematic review looked at the outcomes for exacerbation, adverse events and mortality¹¹⁹.

A systematic review (van Grunsven PM et al 1999)¹²⁴ was excluded, as the durations of the studies were 24 to 30 months but only data up to 24 months was used in the meta analysis. The Derenne et al (1995)¹²⁵ study (contained within the meta analysis) was only published in abstract form however >80% of the patients in the meta analysis were from this study.

In addition to the included papers identified above, one additional paper was found¹²⁶, which was an analysis of the EUROSCOP¹²³ trial and pertained to the effects of treatment on bone mineral density in patients with COPD treated with inhaled steroids. One *post hoc* analysis of the ISOLDE data was also identified which looked at the correlation between the response to oral steroids and the response to inhaled steroids³⁷ and a further *post hoc* analysis which looked at effects on exacerbation rates according to the severity of airflow obstruction¹²⁷.

The GDG was also aware of two quasi-experimental database studies looking at the relationship between prescription of inhaled steroids and mortality^{128;129} and one looking at the effect of dose¹³⁰. All of these have methodological limitations, particularly the lack of randomisation.

The four identified RCTs¹²⁰⁻¹²³ were all placebo-controlled trials of inhaled steroids.

Vestbo 1999¹²² (n=290) and Burge 2000¹²⁰ (n=751) included a systemic steroid run in phase. The Lung Health Study¹²¹ (n=1116) and EUROSCOP¹²³ (n=1277) did not have a systemic steroid run in phase.

Issues for consideration include a variety of differing inhaled steroid drugs and dosages which included budesonide 400ug twice daily¹²³, budesonide 800ug a.m. and 400ug p.m. for six months followed by 400ug twice daily for 30 months¹²², and fluticasone propionate 500ug twice daily¹²⁰ and triamcinolone acetonide 600ug twice daily (100ug per inhalation) for each group six inhalations twice daily were prescribed resulting in a dose of 1200ug per day for the triamcinolone group¹²¹. The Renkema et al (1996)¹³¹ study contained within the systematic review¹¹⁹ administered budesonide 1600ug a day whilst Paggiaro et al (1998)¹³² also in the

systematic review by Alsaedi¹¹⁹ gave fluticasone 1000ug per day. The primary outcomes also varied for each trial and as such secondary outcomes may have been underpowered. Recruitment strategies differed between trials, Vestbo et al.¹²² recruiting participants from an already on-going epidemiological study whilst EUROSCOP¹²³ undertook a mass media recruitment campaign. Severity of COPD and definitions of exacerbations varied between trials whilst ages ranged between the trials from 30 to 75 years.

▷ Evidence statements

- A study in patients with mild COPD showed no effect on **exacerbation rates**¹²². **Ib**
- A study in patients with more severe COPD (mean FEV₁ of 50% predicted) showed a 25% reduction in **exacerbation rates** from 1.32 per year on placebo to 0.99 per year on fluticasone¹²⁰. **Ib**
- A *post hoc* analysis has shown that this effect is most marked in patients with an FEV₁ < 50% predicted¹²⁷ (having a median of 1.47 exacerbations per year). **Ib**
- A further study¹²¹ in a group of patients with a similar mean FEV₁ also showed a significant reduction in visits to a physician for respiratory illness (1.2 vs 2.1 per 100 patient years, p=0.03). **Ib**
- Vestbo¹²², Pauwels¹²³ Burge¹²⁰ and the Lung Health Study¹²¹ found no significant differences in annual **rate of FEV₁ decline**. **Ib**
- The systematic review¹¹⁹ found no significant differences between inhaled steroids and placebo on **mortality** rates. **Ia**
- The systematic review¹¹⁹ showed that inhaled steroid therapy compared to placebo was associated with increased rates of: **oropharyngeal candidiasis** (RR 2.1; 95% CI 1.5 to 3.1) **skin bruising** (RR 2.1; 95% CI 1.6 to 2.8). **Ia**
- Alsaedi¹¹⁹ highlights that the definitions of adverse events were not uniform over the trials. **Ia**
- There were no significant differences for **cataract or fracture rates**¹¹⁹ for the drug dosages used, however the follow-up was generally of short duration. The drug dosages for the trials referred to in the Alsaedi systematic review¹¹⁹ are quoted under issues for consideration in the introduction to inhaled corticosteroids. **Ia**
- The systematic review¹¹⁹ found the results of **bone mineral density** variable between studies. **Ia**
- The Lung Health Study¹²¹, in a subgroup analysis of n=328 participants found significantly lower bone density measurements in the lumbar spine and femur (p<0.01) in patients treated with inhaled steroids. **Ib**
- However the EUROSCOP study¹²³ and a separate paper utilising the same study population was subsequently published¹²⁶ exploring bone mineral density in n=192 patients with mild COPD. There were no significant changes in bone mineral density at any site or fracture rates in the inhaled steroid group compared with the placebo group over the 3-year duration. **Ib**

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- Burge et al ¹²⁰ compared inhaled steroid to placebo in patients with moderate to severe COPD over a 36-month duration. The total **SGRQ** score was not significantly different between the groups over the first 6 months of the trial. However the SGRQ score deteriorated at a faster rate by 3.2 units/year on placebo and 2.0 units/year in the inhaled steroid group (p=0.0043). **Ib**
- Vestbo et al ¹²² looked at inhaled steroids compared to placebo in mild and moderate COPD over a 36-month duration. Although **symptoms** decreased during the study period there were no statistically significant differences between the two groups. **Ib**
- The Lung Health Study ¹²¹ found that the “incidence of respiratory symptoms over the preceding 12 months measured by the ATS Division of Lung Disease questionnaire at the 36 month visit, did not differ significantly between the treatment groups with the exception of dyspnoea, which was more frequent in the placebo group (p=0.02)”. **Ib**
- The response to inhaled steroids could not be predicted by the response to a short course of oral steroids ³⁷. **Ib**
- ▷ GDG consensus statements
- The GDG was aware of additional, quasi-experimental data in large populations that suggest that the use of inhaled steroids may be associated with reductions in mortality. **IV**
- The benefits of inhaled steroids have been shown in studies using a variety of doses of varying steroid molecules. **IV**
- There is insufficient evidence to establish the minimum dose of inhaled steroid required to achieve the proven benefits. **IV**
- There is limited experience of doses higher than 1000 µg fluticasone per day (or equivalent) and no evidence of superiority. **IV**
- ▷ Health economic evidence statements
- Four papers were identified. One had already been reviewed under bronchodilators. Two papers were excluded, as they did not have a follow up period greater than 36 months. The paper by Dragonetti et al¹³³ demonstrated that because the use of inhaled corticosteroids has no effect in patients with mild COPD, it is an unnecessary cost to prescribe steroids for this patient group.

RECOMMENDATIONS

	None of the inhaled corticosteroids currently available are licensed for use alone in the treatment of COPD. The following recommendations therefore include usage outside licensed indications, and prescribers need to remember that responsibility for such prescribing lies with them.	
R38	Oral corticosteroid reversibility tests do not predict response to inhaled corticosteroid therapy and should not be used to identify which patients should be prescribed inhaled corticosteroids.	Grade A
R39	Inhaled corticosteroids should be prescribed for patients with an FEV ₁ ≤ 50% predicted, who are having 2 or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12 month period. The aim of treatment is to reduce exacerbation rates and slow the decline in health status and not to improve lung function per se.	Grade B
R40	Clinicians should be aware of the potential risk of developing osteoporosis and other side effects in patients treated with high-dose inhaled corticosteroids (especially in the presence of other risk factors), and should discuss the risk with patients.	Grade D

7.6.2 Oral corticosteroids

One meta-analysis that included ten trials was found that compared oral steroids to placebo¹³⁴. The primary outcome measure was FEV₁.

In addition to the trials included in the meta-analysis, two RCTs were identified both of which are of a crossover design and compare oral steroids to placebo^{135;136}. A further two RCTs^{137;138} were excluded due to methodological limitations.

Factors for consideration within this topic include:

- sample size between trials varies (ranging from n=18 to n=168)
- trial follow-up periods vary (ranging from 2 weeks to 6 weeks) and hence data is available for acute, short-term studies only
- the trials vary as to whether or not they use washout periods
- a variety of different steroid drugs and dosages are used
- geographical locations vary.

It is important to note that all of the studies of suitable methodological quality are focused upon the short-term effects relating to FEV₁. No long-term studies were identified. Hence the effects of sustained oral steroid therapy on FEV₁ and the potential long-term side effects of sustained therapy have not been established.

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▷ GDG consensus statements

There are no published studies that establish which, if any, patients benefit from long term oral steroid therapy. **IV**

The GDG is aware that there are a small group of patients who experience frequent exacerbations and/or severe breathlessness for whom long term oral steroid therapy is the only pragmatic way of managing them. **IV**

The RCP guidelines¹³⁹ on steroid-induced osteoporosis advise commencing prophylactic treatment without further monitoring or assessment in patients over the age of 65 who are starting long-term corticosteroid treatment. **IV**

RECOMMENDATIONS

R41	Maintenance use of oral corticosteroid therapy in COPD is not normally recommended. Some patients with advanced COPD may require maintenance oral corticosteroids when these cannot be withdrawn following an exacerbation. In these cases, the dose of oral corticosteroids should be kept as low as possible.	Grade D
R42	Patients treated with long term oral corticosteroid therapy should be monitored for the development of osteoporosis and given appropriate prophylaxis. Patients over the age of 65 should be started on prophylactic treatment, without monitoring.	Grade D

7.7 Combination therapy

Since beta₂-agonists, anticholinergic drugs and theophylline affect airway calibre and lung function through different mechanisms combining drugs of these classes may potentially give clinical benefits to patients. An additional advantage of this approach is the ability to limit potential side effects of the drugs by avoiding having to use individual drugs near the top of their dose response curves.

There are similar theoretical advantages in combining a bronchodilator with its effects on symptoms, with an inhaled steroid with its effects on exacerbations to produce additive or synergistic clinical benefits.

The following four types of combination therapy were considered and evidence is presented for each combination separately:

- beta₂-agonist and anticholinergic
- beta₂-agonist and theophylline
- anticholinergic and theophylline
- long-acting beta₂-agonist and inhaled steroid.

A full literature search was also undertaken for anticholinergic and inhaled steroid but no evidence was found for this combination.

For each of these combinations, no systematic reviews were found, however a good body of RCT data was identified:

Beta₂-agonists and anticholinergics

Two randomised, double-blind, placebo-controlled parallel trials; Van Noord 2000⁹¹ (n = 144), Chapman 2002¹⁴⁰ (n = 409) and 3 randomised, double-blind, non placebo-controlled parallel trials; Auerbach 1997¹⁴¹ (n = 652), Bone 1994¹⁴² (n = 534), Gross 1998¹⁴³ (n = 863) and 1 randomised, double-blind, crossover; D'Urzo 2001¹⁴⁴ (n = 172). One study report¹⁴⁵ provided additional information about 2 critically appraised trials^{141;142}.

Beta₂-agonists and theophylline

One randomised, double-blind, placebo-controlled parallel trial; Zu Wallack 2001¹⁴⁶ (n = 943).

Anticholinergics and theophylline

One randomised, double-blind, placebo-controlled parallel trial; Bellia 2002¹⁴⁷ (n = 236) and 1 randomised, double-blind crossover trial; Nishimura 1995¹⁴⁸ (n = 24).

Beta₂-agonists and inhaled steroids

Three randomised, double-blind, placebo-controlled parallel trials; Calverley 2003⁹⁸ (n = 1465), Szanfranski 2003⁹⁷ (n = 812), Mahler 2002⁹⁶ (n = 691).

Factors for consideration within this topic include:

- considerable pre-screening of patients
- small patient populations in some studies
- only some studies are placebo controlled
- only some studies select both responders and non-responders to beta₂-agonists
- concomitant medication is permitted in some studies, whereas in others it is restricted
- age limits differ e.g. >18 yrs and > 40 yrs
- drug washout periods vary
- severity of COPD varies between studies.

▷ Evidence statements on combinations of beta₂-agonists and anticholinergics

During 12 weeks of treatment, **FEV₁** responses to ipratropium and salmeterol combination were significantly increased compared with salmeterol alone and placebo (n = 144) (p<0.01)⁹¹. **Ib**

Among salmeterol/anticholinergic treated patients, morning pre-treatment **FEV₁** levels improved significantly above baseline levels. This effect persisted during the six month treatment period. These improvements in lung function were significantly greater in the salmeterol /anticholinergic group than in the placebo/anticholinergic group for all but the last clinic visit. Analysis of adjusted treatment differences showed the mean improvement over the 24-week period was significantly higher in the salmeterol/anticholinergic group than in the placebo/anticholinergic group (p<0.01)¹⁴⁰. **Ib**

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- Mean peak **FEV₁** responses to ipratropium + albuterol were significantly greater than those to each of the components on all test days (day 1, 29, 57 and 85)¹⁴¹. **Ib**
- Mean peak **FEV₁** responses to ipratropium + albuterol were significantly greater than those to each of the components on all test days (day 1, 29, 57 and 85). Clinically significant mean **FEV₁ response** (>15% above baseline) was observed in all three treatment groups on all test days¹⁴². **Ib**
- Mean change from pre-dose to peak **FEV₁** was significantly greater with ipratropium/albuterol combination compared with either albuterol alone or ipratropium alone in 863 subjects over 12 weeks ($p < 0.001$)¹⁴³. **Ib**
- Compared with baseline values, premedication **FEV₁** increased following 3 weeks treatment with formoterol/ipratropium and decreased following treatment with salbutamol/ipratropium ($n = 172$ subjects treated over 6 weeks). Estimated treatment difference was 0.116 L ($p < 0.0001$). Peak postmedication **FEV₁** was significantly higher with formoterol/ipratropium than with salbutamol/ipratropium ($p < 0.0001$). AUC of **FEV₁** for formoterol/ipratropium was much higher than for salbutamol/ipratropium ($p < 0.0001$)¹⁴⁴. **Ib**
- During 12 weeks of treatment, **FVC** responses to ipratropium and salmeterol combination were significantly increased compared with salmeterol alone and placebo ($p < 0.01$)⁹¹. **Ib**
- Overall **FVC** response to ipratropium/albuterol combination was significantly greater than the response to either ipratropium or albuterol alone ($p < 0.01$ to $p = 0.04$)¹⁴². **Ib**
- During 12 weeks of treatment a significant decrease was seen in **daytime symptoms score** between both salmeterol alone ($p < 0.005$) and salmeterol + ipratropium ($p < 0.001$) compared with placebo. No significant difference was seen between salmeterol and combination groups. There were also no differences in **night symptoms** between ipratropium and salmeterol combination compared with salmeterol alone and placebo⁹¹. **Ib**
- COPD **symptom scores** did not change and did not differ between ipratropium + albuterol combination and individual component groups^{141 142}. **Ib**
- Mean **total symptom score** was 0.6 points lower during 6 weeks treatment with formoterol/ipratropium than with salbutamol/ipratropium ($p = 0.0042$)¹⁴⁴. **Ib**
- Baseline **PEFR** and **PEFR** did not differ significantly between ipratropium/albuterol combination compared with either ipratropium or albuterol alone and did not change during 12 weeks of treatment¹⁴². **Ib**
- Over 12 weeks improvements in **morning PEFR** were significantly better in both ipratropium/salmeterol combination group and salmeterol alone group than in the placebo group ($p < 0.001$). No difference was observed between the salmeterol and combination treatment groups. Improvements in **evening PEFR** were significantly better in both ipratropium/salmeterol combination group compared with salmeterol alone ($p < 0.01$). No difference was observed between the salmeterol and placebo treatment groups⁹¹. **Ib**

- Morning PEFR** did not differ significantly between ipratropium + albuterol combination and individual component groups and did not change during the study. **Evening PEFR** values in the ipratropium/albuterol group were significantly greater than those for the albuterol group ¹⁴¹. **Ib**
- Over 6 weeks, the mean morning premedication **PEFR** increased during both treatment periods; however the change in favour of formoterol/ipratropium was statistically significant compared with ipratropium/salbutamol ($p < 0.001$) ¹⁴⁴. **Ib**
- During 12 weeks of treatment, compared with placebo treatment with both salmeterol and ipratropium/salmeterol combination therapy were associated with a higher percentage of days and nights without use of **additional salbutamol** ($p < 0.01$). No significant difference was observed between the two active treatments⁹¹. **Ib**
- There were no significant difference between ipratropium and albuterol group and individual component groups in **use of concomitant respiratory medication** ¹⁴¹. **Ib**
- After 12 weeks treatment there were no significant differences between ipratropium/albuterol combination and either component alone in **distance walked** in 6 minutes ¹⁴³. **Ib**
- Scores for the **SGRQ** were reduced from baseline for all components of the questionnaire (symptoms, activity, impact on daily life) among patients treated with salmeterol for 6 months, with a significant improvement in the symptom component ($p < 0.005$), the impact on daily life component ($p = 0.05$) and the total score ($p < 0.05$). There was no significant difference between the salmeterol/anticholinergic group and placebo anticholinergic group ¹⁴⁰. **Ib**
- During 12 weeks of treatment, 35 patients experienced a COPD **exacerbation**, 18 (36%) in the placebo group, 11 (23%) in the salmeterol group and six (13%) in the salmeterol and ipratropium group ($p < 0.01$ combination treatment vs placebo) ⁹¹. **Ib**
- During the 6 month treatment period, 26% of salmeterol-treated patients and 33% of placebo-treated patients experienced at least one **exacerbation** of COPD ($p = 0.117$). Fewer salmeterol-treated patients experienced more than 2 exacerbations (non significant) ¹⁴⁰. **Ib**
- The number of patients with no COPD **exacerbations** during the 6 week treatment period was slightly higher with formoterol/ipratropium than with salbutamol/ipratropium: 55 patients (43.6%) and 49 patients (30.8%)¹⁴⁴. **Ib**
- During 12 weeks of treatment, no significant difference in **adverse events** was seen in salmeterol alone, placebo and ipratropium/salmeterol combination groups⁹¹. **Ib**
- Incidence of **adverse events** recorded during a 6 month study were similar for both treatment groups, with at least one adverse event being reported by 72% of patients in the salmeterol group and 71% patients in the placebo group¹⁴⁰. **Ib**
- Most common **adverse events** were related to the respiratory system in both treatment groups, with exacerbations of COPD being the most common event reported by 44 patients (22%) receiving placebo and 41 patients (20%) receiving salmeterol. Events considered to be related to drug treatment were recorded in 11% of patients in the salmeterol group and 10% of the patients in the placebo group¹⁴⁰. **Ib**

- No significant differences were found in **adverse events** over 12 weeks in 863 patients treated with ipratropium/albuterol combination and either component alone ¹⁴³. **Ib**
- ▷ Evidence statements on combinations of beta₂-agonists and theophylline
- Mean pre-dose **FEV₁** and **FVC** values significantly improved compared with baseline in both the salmeterol/theophylline group and the salmeterol group at week 4, week 8 and week 12 ($p < 0.001$). Mean pre-dose **FVC** values significantly also improved compared with baseline in the theophylline group ($p < 0.021$), with the exception of the pre-dose **FVC** assessment at week 12. The salmeterol/theophylline combination group experienced significantly greater improvement in **FEV₁** & **FVC** than either the salmeterol alone group or the theophylline alone group ($p < 0.02$) ¹⁴⁶. **Ib**
- Patients in the salmeterol/theophylline combination group experienced significantly more **symptom-free days** ($p = 0.023$) compared with the theophylline group ¹⁴⁶. **Ib**
- Over 12 weeks patients in the salmeterol/theophylline combination group experienced significantly greater improvements in **PEFR** compared with either the salmeterol alone group or theophylline alone group ¹⁴⁶. **Ib**
- Salmeterol/theophylline combination group required significantly fewer **supplemental albuterol** treatments during the 12 weeks of the study compared with either the salmeterol alone group or theophylline alone group ¹⁴⁶. **Ib**
- Salmeterol/theophylline combination group experienced significantly greater improvements in **dyspnoea** ((TDI) scores) compared with either the salmeterol alone group or theophylline alone group ¹⁴⁶. **Ib**
- During the study by Zu Wallack et al. ¹⁴⁶, each treatment group experienced significant improvements compared with baseline in overall **CRDQ** scores. **Ib**
- The mean overall change from baseline in the salmeterol/theophylline group (+11.2 points) was clinically meaningful (>10 points) and was significantly greater ($p < 0.019$) at week 4 compared with the salmeterol group and the theophylline alone group.
- At week 12, mean improvements in overall **CRDQ** scores were +12.7 points in the salmeterol/theophylline group, +7.6 points in the salmeterol group, and +8.6 points in the theophylline group. A significantly higher percentage of patients in the salmeterol/theophylline group (52 to 54%) experienced a clinically important improvement overall compared with the salmeterol group (36 to 45%) or the theophylline group (31 to 42%) at week 4 and week 12 ($p < 0.014$).
- Salmeterol/theophylline combination treatment was rated as providing significantly greater overall **satisfaction with treatment** compared with the theophylline group at all time points ($p < 0.012$) and compared with the salmeterol group at week 8 and week 12 ($p < 0.041$). Salmeterol treatment provided significantly greater **satisfaction with treatment** with respect to side effects than either treatment involving theophylline ($p < 0.028$).

- Over 12 weeks **exacerbations** were experienced by significantly fewer patients in the salmeterol/theophylline group (40 patients, 48 exacerbations) compared with the theophylline group (62 patients, 96 exacerbations; $p = 0.023$), but not the salmeterol group (56 patients, 71 exacerbations; $p = 0.076$)¹⁴⁶. **Ib**
- The proportion of patients reporting **adverse events** was not significantly different among treatment groups; however, the proportion of patients reporting adverse events that were judged to be related to study drug was significantly higher in both of the groups that received theophylline compared with the salmeterol group, most notably for gastrointestinal (GI) events ($p < 0.042$)¹⁴⁶. **Ib**
- ▷ Evidence statements on combinations of anticholinergics and theophylline
- Although **FEV₁** and **FVC** values increased in patients treated with the oxitropium/theophylline combination, oxitropium alone and theophylline alone groups at weeks 4-8, no statistically significant differences between groups was observed¹⁴⁷. **Ib**
- Without inhalation of bronchodilators, **FEV₁** was significantly lower during ipratropium/salbutamol combination compared with ipratropium/salbutamol/theophylline combination ($p < 0.01$)¹⁴⁸. **Ib**
- At 15 and 60 minutes after inhalation of salbutamol, 400ug the **FEV₁** was significantly lower during ipratropium/salbutamol combination compared with ipratropium/salbutamol/theophylline combination ($p < 0.01$)¹⁴⁸. **Ib**
- At 15 and 60 minutes after inhalation of ipratropium 80ug, the **FEV₁** was significantly lower during ipratropium/salbutamol combination compared with ipratropium/salbutamol/theophylline combination ($p < 0.01$). The **FVC** was not significantly different between the ipratropium/salbutamol combination compared with ipratropium/salbutamol/theophylline combination before and 15 and 60 minutes after the inhalation of the bronchodilating agents¹⁴⁸. **Ib**
- Decreased symptom intensity for **cough frequency, cough intensity** and **dyspnoea** were observed in the majority of patients in all three groups over 8 weeks; however, no significant differences were observed between groups¹⁴⁷. **Ib**
- No significant alteration of **cough, sputum, wheezing, and shortness of breath** was observed throughout the different phases of treatment¹⁴⁸. **Ib**
- Morning and evening baseline pre-dosing **PEFR** showed very little change at week 8 in oxitropium/theophylline combination, oxitropium alone and theophylline groups. In contrast, the morning post-dosing **PEFR** markedly increased in all three groups, particularly in the combination group, however, no statistically significant difference was observed between treatment groups for either morning or evening post-dosing **PEFR** change¹⁴⁷. **Ib**
- Both pre-inhalation and post-inhalation values of daily **PEFR** were significantly higher during the ipratropium/salbutamol/theophylline combination period than during the ipratropium/salbutamol period ($p < 0.01$)¹⁴⁸. **Ib**

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Total **SGRQ** score decreased in all groups; oxitropium/theophylline combination, oxitropium alone and theophylline alone and the change was statistically significant compared with baseline ($p < 0.002$). The decrease in total score reached the level of “clinical significance” only in patients treated with oxitropium whether alone (4 ± 1.1 units) or in combination with theophylline (4.7 ± 1.1 units). The variance measure (standard error or standard deviation) is undefined in the primary paper. The decrease was mainly due to changes in activity and impact scores. No significant differences between treatments were observed¹⁴⁷. **Ib**

The proportion of patients reporting treatment-related **adverse events** ($p < 0.02$) and gastrointestinal treatment-related adverse events ($p < 0.04$) in the theophylline group was significantly greater than that found in oxitropium/theophylline combination and oxitropium group¹⁴⁷. **Ib**

Sixteen patients (67%) complained of gastrointestinal side effects while receiving ipratropium/salbutamol/theophylline and 10 patients (42%) reported similar effects during ipratropium/salbutamol administration¹⁴⁸. **Ib**

▷ Evidence statements on combinations of beta₂-agonists and inhaled steroids

In the study by Calverley et al.⁹⁸ the three active treatments increased pre-treatment **FEV₁** significantly compared with placebo (salmeterol/fluticasone $p < 0.0001$; salmeterol $p < 0.0001$; fluticasone $p = 0.0063$). This improvement was evident by week 2 and was sustained throughout treatment. The increase in FEV₁ associated with combination therapy was significantly greater than with either of its components separately. **Ib**

In the study by Szafranski et al.⁹⁷ all active treatments (formoterol/budesonide combination, budesonide alone and formoterol alone) increased **FEV₁** compared with placebo. Budesonide/formoterol also increased FEV₁ compared with budesonide. There was no significant difference for budesonide/formoterol versus formoterol for FEV₁. Improvements in FEV₁ were sustained with budesonide/formoterol throughout the study period compared with budesonide and placebo. All active treatments improved **FVC** compared with placebo: budesonide/formoterol by 9% ($p < 0.001$), budesonide by 4% ($p < 0.05$) and formoterol by 11% ($p < 0.001$). **Ib**

In the study by Mahler et al.⁹⁶ a significantly greater increase in **pre-dose FEV₁** at the endpoint was observed after treatment with salmeterol/fluticasone combination therapy (156 ml) compared with salmeterol (107 ml) $p = 0.012$ and placebo (-4 ml) ($p < 0.001$). A significantly greater increase in pre-dose FEV₁ was also observed for treatment with fluticasone vs placebo at the endpoint (109 vs -4 ml respectively $p < 0.001$). There was no significant difference between the combination and fluticasone. **Ib**

A significantly greater increase in 2 hour **post-dose FEV₁** at the endpoint was observed after treatment with salmeterol/fluticasone combination therapy (261 ml) compared with fluticasone (138 ml, $p < 0.001$) and placebo (28 ml, $p < 0.001$)⁹⁶. Significantly greater increases in 2 hour post-dose FEV₁ were observed at day 1 and throughout the study during treatment with salmeterol/fluticasone combination therapy compared with **Ib**

fluticasone. Significantly greater increases in 2-hour post-dose FEV₁ were observed for the salmeterol group versus placebo (233 vs 28 ml, respectively p<0.024) at the endpoint and at all assessment points throughout the study⁹⁶.

Budesonide/formoterol significantly reduced all **symptom scores** within the first week of treatment compared with budesonide, formoterol and placebo. This significant effect was sustained for 12 months for budesonide/formoterol compared with placebo, formoterol and budesonide.⁹⁷ **Ib**

Budesonide/formoterol increased **days free from shortness of breath** by 12% compared with placebo (p<0.001). Budesonide/formoterol compared to budesonide also demonstrated a statistically significant effect for shortness of breath sustained for 12 months, this was non significant for budesonide/formoterol versus formoterol⁹⁷. **Ib**

Budesonide/formoterol increased **awakening-free nights** by 14% compared with placebo (p<0.001). Awakening scores at 12 months were statistically significant for budesonide/formoterol versus placebo, budesonide alone and formoterol alone⁹⁷. **Ib**

Budesonide/formoterol improved and maintained morning and evening **PEFR** compared with placebo, budesonide and formoterol alone (p<0.001)⁹⁷. **Ib**

Increases in morning **PEFR** on day 2, approximately 24 hours after the initiation of treatment, were greater for salmeterol/fluticasone combination treatment compared with fluticasone, salmeterol and placebo (p<0.005)⁹⁶. **Ib**

Greater increases in morning PEF were observed throughout the 24 week treatment period with salmeterol/fluticasone combination treatment compared with fluticasone, salmeterol and placebo⁹⁶. **Ib**

The overall change from baseline in morning **PEF** with combination treatment (31.9 L/min) was greater than the sum of the mean changes from baseline observed with the individual components, 12.9 and 16.8 L/min for fluticasone (p<0.001) and salmeterol (p<0.001), respectively. Mean overall changes from baseline were also significantly greater for both fluticasone and salmeterol versus placebo (p<0.001)⁹⁶. **Ib**

Budesonide/formoterol reduced use of **rescue medication** by 1.3 and 0.7 inhalations per 24h compared with placebo and budesonide respectively (both p<0.001)⁹⁷. **Ib**

Significant reductions in **overall albuterol use** (number of inhalations per day and percentage of days without albuterol use) were observed during treatment with salmeterol/fluticasone combination compared with fluticasone and placebo. A significant reduction in overall albuterol use was also observed after treatment with salmeterol compared with placebo and with fluticasone compared with placebo⁹⁶. There was no difference between the combination and salmeterol groups. **Ib**

A significant increase in the overall percentage of **nights with no awakenings** requiring albuterol was observed for treatment with salmeterol/fluticasone combination, fluticasone and salmeterol compared with placebo (p<0.001)⁹⁶. **Ib**

At the endpoint, **breathlessness** was reduced in patients treated with the salmeterol/fluticasone combination (as assessed by the increase in the mean TDI score of 2.1). The reduction was greater than that after treatment with fluticasone (mean TDI score **Ib**

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1.3, $p=0.033$) and was significantly greater than that after treatment with salmeterol (mean TDI score 0.9, $p<0.001$) and placebo (mean TDI score 0.4, $p<0.001$). At the end point, there was a significantly greater reduction in breathlessness in patients treated with fluticasone (mean TDI score 1.3, $p=0.002$), but not salmeterol compared with placebo⁹⁶.

Calverley et al⁹⁸ demonstrated that combination treatment with salmeterol/fluticasone combination significantly reduced **breathlessness** scores (1.47) compared with placebo (1.66, $p=0.001$), salmeterol (1.59, $p=0.006$) and fluticasone (1.58, $p=0.01$). **Ib**

Calverley et al⁹⁸ showed a clinically significant improvement in **health status questionnaire** score by week 52. The raw mean changes in health status total score were -4.5 (12.9) at week 52. The change in SGRQ score in the combination group (salmeterol and fluticasone) over 52 weeks at the end of the study was significantly greater than that in both the placebo and fluticasone groups. **Ib**

In the study by Szanfranski et al.⁹⁷ compared with placebo, budesonide/formoterol showed clinically and statistically significant improvements in **SGRQ** symptoms score (mean difference 5.9, $p<0.001$) and impact score (mean difference 4.7, $p=0.006$) domains. **Ib**

In the study by Mahler et al.⁹⁶ after 6 months, treatment with salmeterol/fluticasone combination therapy resulted in a clinically important increase from baseline in mean overall **CRDQ** score (10) that was significantly greater compared with the placebo (5.0, $p = 0.007$) and fluticasone (4.8, $p = 0.017$) groups, but not with salmeterol (8.0). **Ib**

Clinically important increases in dyspnoea score (4.2), fatigue score (2.0) and physical summary score (6.1) were observed after treatment with salmeterol/fluticasone combination. These increases were also statistically significant versus the fluticasone and placebo treatment groups ($p<0.016$)⁹⁶. **Ib**

In the study by Calverley et al⁹⁸ compared with placebo, all active treatments (salmeterol/fluticasone combination, salmeterol alone and fluticasone alone) significantly reduced the number of **exacerbations** per patient per year and the number of exacerbations that needed treatment with oral corticosteroids. **Ib**

The rate of exacerbations fell by 25% in the combination group ($p<0.0001$) and by 20% ($p = 0.0027$) and 19% ($p = 0.0033$) in the salmeterol and fluticasone groups respectively compared with placebo⁹⁸. **Ib**

The treatment effect in relation to the number of exacerbations was more pronounced in patients with a baseline FEV₁ of <50% predicted who showed a 30% reduction with the combination compared with placebo, as against a 10% reduction in patients who had a baseline FEV₁ that was greater than 50% of that predicted⁹⁸. **Ib**

Acute episodes of symptom exacerbation that required oral corticosteroids were reduced by 39% in the combination group ($p<0.0001$), 29% in the salmeterol group ($p = 0.0003$) and 34% in the fluticasone group ($p = 0.0001$) compared with placebo⁹⁸. **Ib**

Szafranski et al⁹⁷ showed that compared with placebo, budesonide/formoterol combination significantly reduced the number of **severe exacerbations**. **Ib**

The mean number of severe exacerbations fell by 24% in the combination group (p=0.035) and by 15% (p=0.224) and 2% (p=0.895) in the budesonide and formoterol groups respectively versus placebo.

Budesonide/formoterol combination group also significantly reduced mean severe exacerbation rate versus formoterol (23% reduction; p=0.043).

Compared with placebo, the combination budesonide/formoterol and the budesonide group significantly reduced the number of oral steroid courses used in association with exacerbations (31%, p=0.027 and 29%, p=0.045 respectively).

In the study by Szafranski et al.⁹⁷ the **adverse event** profile was similar in each group (formoterol/budesonide combination, budesonide alone and formoterol alone). The frequency of discontinuations due to other adverse events was similar in all groups. **Ib**

In the study by Calverley et al⁹⁸ there were no differences between groups in the number of patients reporting an **adverse event** apart from an increased frequency of oropharyngeal candidiasis (placebo 2%, salmeterol 2%, fluticasone 7%, and combination 8%). **Ib**

In the study by Mahler et al⁹⁶ a greater percentage of patients in the fluticasone and the combination groups experienced candidiasis (mouth/throat) based on visual inspection compared with the placebo and salmeterol groups. **Ib**

▷ GDG consensus statements

When considering increasing therapy, adding a drug to existing therapy rather than increasing the dose of an existing therapy may reduce the risk of adverse events. **IV**

When combining therapies there may be advantages in terms of convenience, concordance and cost, if equivalent doses of the same drugs are available in single inhaler devices. **IV**

Although the GDG considered that the principal indication for inhaled corticosteroids is in patients with moderate or severe COPD who are experiencing two or more exacerbations per year (see section 7.6.1) the evidence from the studies combining inhaled steroids with long-acting beta₂-agonists suggests that adding inhaled steroids to long-acting beta₂-agonists may reduce breathlessness. This combination may be beneficial in patients who are still breathless despite monotherapy with long-acting beta₂-agonists. **IV**

RECOMMENDATIONS

R43	<p>If patients remain symptomatic on monotherapy, their treatment should be intensified by combining therapies from different drug classes. Effective combinations include:</p> <ul style="list-style-type: none"> ● beta₂-agonist and anticholinergic ● beta₂-agonist and theophylline ● anticholinergic and theophylline ● long-acting beta₂-agonist and inhaled corticosteroid. 	Grade A
R44	<p>The clinical effectiveness of combined treatments can be assessed by improvements in symptoms, activities of daily living, exercise capacity and lung function. Combination treatment should be discontinued if there is no benefit after 4 weeks.</p>	Grade D

7.8 Delivery systems used to treat patients with stable COPD

The devices used to deliver drugs to the lungs are, in many respects, as important as the drugs themselves. If the device is inefficient at delivering the drugs to the lungs or is difficult for patients to learn, or remember how to use then the effectiveness of the therapy will be reduced. This is a difficult area to conduct blinded studies in because the identity of the device cannot be concealed from patients and there are no standardised validated tools that can be used to assess ease of use or patient preference.

One Health Technology Assessment was found¹⁴⁹, one systematic review¹⁵⁰ two additional RCTs^{151,152} and one prospective study¹⁵³ that compared nebulisers, patient administered metered dose inhalers (pMDI) and or dry powered inhaler (DPI). Devices were all used to administer bronchodilators or saline placebo. The study by O'Driscoll et al.¹⁵³ was excluded due to methodological limitations.

Factors for consideration within this topic included small sample sizes (range of n=7 to n=47)¹⁵³, studies vary across settings (domiciliary, laboratory or clinic) raising the question of generalisability, duration of studies is extremely variable from 2 hours to 2 weeks, variable training in the use of devices (some devices require more manipulation and dexterity than others and hence may not be as user friendly in an elderly population), variable drop out rates, and differing drug doses in application to assessing clinical efficacy. Many of the studies were of a cross over design with variable washout periods (2 to 7 days) and variable age ranges (44 to 72 years)¹⁵⁰.

The recent BTS/SIGN guidelines for asthma²⁷ have also examined the evidence concerning the comparative effectiveness of different inhaler devices. They make several important observations about methodological difficulties with the evidence in this area:

- Studies comparing different inhaler devices recruit subjects who are competent using the devices involved. This is very unlike clinical practice where a patient's abilities may vary markedly between devices.

- Some studies of inhaler devices are of parallel design and some crossover. The data in these two types of studies are often not easy to combine in a meta-analysis. (This statement refers to evidence derived from the HTA¹⁴⁹ in which parallel and crossover studies were not combined). In addition, crossover studies may not allow a suitable washout period for drugs with a longer duration of action.
- Many studies use doses of medication at the upper end of the prescribing range. This may bias towards an underestimate of difference between inhalers, if one exists.
- Clinical trials tend to recruit patients with more stable and less severe disease. Whilst this may reflect the bulk of clinical practice it does make observation of a significant difference, especially with less frequently occurring outcomes, less likely, particularly in smaller studies, so a real difference may be missed.
- Studies of novel new inhaler devices are highly likely to be prone to bias when preference is expressed. Many inhaler device studies are designed with a null hypothesis of bio-equivalence to show the new is as good as the older, established comparator. These studies may be underpowered to detect differences, if they exist.
- Although most medications are available in the pressurised Metered Dose Inhaler (pMDI) the choice of Dry Powder Inhaler (DPI) will be determined by the choice of medication, as not all devices are available to deliver all drugs.
- The recommendations are often based on a comparison of pMDI with other devices as most of the available evidence comes from trials making the comparison between newer devices and the longer established pMDI.

It is perhaps surprising that assessment of inhaler technique is so often neglected, both in individual patient terms and in terms of phase 3 trials that include newly designed inhaler devices. Most patients whatever their age are able to acquire and maintain adequate inhaler technique given adequate instruction. The exception to this is that those with significant cognitive impairment (as a guideline, those with a Hodkinson Abbreviated Mental Test Score of 4 or less) are unable to use any form of inhaler device^{154,155}. In most patients however, a pragmatic approach guided by individual patient assessment is needed in choosing a device. It is also important to recognise that retention of inhaler technique is as important as its acquisition and many elderly patients who successfully acquire adequate technique with a particular device will demonstrate inadequate technique when assessed a month later¹⁵⁶. Regular reassessment and reinstruction is therefore essential, and this may explain why patients first prescribed inhalers in hospital have better technique than those first prescribed inhalers in primary care¹⁵⁷.

The standard metered dose inhaler (MDI), when used in isolation (i.e. without a large-volume spacer device) is rarely appropriate for elderly patients. Elderly patients are slower to learn adequate technique, many never acquire adequate technique, and those that do frequently fail to retain their knowledge when reassessed a month later^{154,156-158}. The MDI is particularly difficult for those with impaired handgrip strength (common in those with arthritic conditions)¹⁵⁸. The addition of a large-volume spacer improves both acquisition and retention of technique¹⁵⁶ and allows carers to assist with technique for those patients with cognitive impairment or physical disabilities affecting hand function. Large volume spacers have also been shown to reduce systemic absorption of inhaled corticosteroids¹⁵⁹.

The problems elderly patients have with MDIs have been recognised by the pharmaceutical industry with a resulting plethora of newer 'patient friendly' devices (including breath-

activated devices) developed over recent years. Unfortunately very few of these devices have been formally assessed in elderly patients. It is generally the case that breath actuated devices, such as the Turbohaler and Autohaler, are easier for an elderly person to use^{160;161}, but more data is needed on the retention of technique. There will however, always be a few patients who seem unable to acquire inhaler technique with any device. This may be due to praxis problems (dyspraxia) or to previously unrecognised cognitive impairment. They have further suggested that inability to acquire adequate technique in an elderly person should prompt screening for cognitive dysfunction^{161;162}.

Nebulised therapy involves the generation of respirable aqueous particles in a nebuliser chamber. The generation of the particles usually depends on compressed gas delivered from a cylinder or more commonly a compressor. The performance of both nebuliser chambers and compressors varies considerably and this can effect drug deposition and the efficacy of the therapy. European standards for nebuliser performance have been drawn up by the European Committee for Standardization (CEN) (EN 13544-1:2001) (www.cenorm.be) and manufacturers will be required to indicate if their products comply with these.

Nebulisers should not be seen as a panacea for those few patients unable to acquire and/or retain adequate inhaler technique. Nebuliser loading and operation requires manipulative and cognitive skill, and if lack of such skill is responsible for inadequate technique with inhaler devices it is likely that this may also be the case with a nebuliser. Nebulisers, like large volume spacers, do however have the advantage that carers can be trained in their use and provide useful support¹⁶³.

Recommendations on the use of nebulisers have been produced by the BTS¹⁶⁴ and the ERS¹⁶⁵ and these have informed some of the recommendations.

▷ Evidence statements

The systematic review¹⁵⁰ compared pMDI with any other handheld inhaler device. **Ia**
The Turbohaler vs. pMDI¹⁶⁶ (n=15) and Rotohaler vs. pMDI¹⁶⁷ (n=10) showed no significant differences in any **outcome**. However, the study¹⁶⁸ contained within the systematic review referred to above, using the Respimat vs. pMDI, (n=36, open label) showed significant increases in **FEV₁** (difference in change from baseline 70 ml, 95% CI; 10 to 130 ml). Respimat is unlicensed in the UK. The effect on change in **FVC** was of similar size. There were no differences observed between these two devices for any other reported outcomes.

Using **FEV₁** as a primary outcome, there is no clinical benefit of using nebulised medication in addition to or as an alternative to a pMDI, with or without a spacer, or a DPI in stable COPD¹⁴⁹. **Ia**

Cuvelier et al¹⁵¹ (DPI and MDI) and Eiser et al¹⁵² (MDI with a spacer vs. larger nebulised doses) found no significant differences between the two groups. **Ib**

Handling of DPI was considered easier than the MDI (p=0.014) and the DPI was preferred to the MDI (p<0.001)¹⁵¹. **Ib**

Patient **ease-of-use** scores and **preference** scores were significantly better for the DPI (p=0.014 and p <0.001) respectively and 56% of patients considered the DPI easier to use than the MDI¹⁵¹. **Ib**

There were no significant differences in **quality of life** scores from the St George's questionnaires and the HAD scores¹⁵². **Ib**

▷ GDG consensus statements

There is no evidence to dictate an order in which devices should be tested for those patients who cannot use pMDI. In the absence of evidence, the most important points to consider are patient preference and local cost. **IV**

Cognitive function and praxis are more important than age in determining the ability of an older patient to use hand held inhalers or nebulisers. **IV**

Older patients often soon forget correct inhaler technique. **IV**

Patients experiencing difficulties using hand held inhalers may also have difficulty using nebulisers. **IV**

Not all drugs are available in a formulation that can be used in a nebuliser. **IV**

Regular use of nebulised therapy involves considerable time and may impair patient's ability to undertake other activities and inhibit their ability to leave their home. **IV**

Regular use of high doses of bronchodilators via a nebuliser may produce significant side effects (e.g. tachycardia and tremor). **IV**

Nebulised bronchodilator therapy may lead to significant improvements in symptoms, exercise capacity or quality of life which are not reflected in changes in FEV₁. **IV**

Acute changes in lung function are not the most appropriate means of assessing the benefits of nebulised therapy. **IV**

RECOMMENDATIONS ABOUT INHALERS

R45	In most cases bronchodilator therapy is best administered using a hand held inhaler device (including a spacer device if appropriate).	Grade D
R46	If the patient is unable to use a particular device satisfactorily, it is not suitable for him or her and an alternative should be found.	Grade D
R47	Inhalers should be prescribed only after patients have received training in the use of the device and have demonstrated satisfactory technique.	Grade D
R48	Patients should have their ability to use an inhaler device regularly assessed by a competent healthcare professional and, if necessary, should be re-taught the correct technique.	Grade D
R49	To ensure optimum efficacy for each patient with COPD, the dose of medication should be titrated according to individual clinical response.	Grade D

RECOMMENDATIONS ABOUT SPACERS

R50	The spacer should be compatible with the patient's metered-dose inhaler.	Grade D
R51	It is recommended that spacers are used in the following way: <ul style="list-style-type: none"> the drug is administered by repeated single actuations of the metered dose inhaler into the spacer, with each followed by inhalation there should be minimal delay between inhaler actuation and inhalation tidal breathing can be used as it is as effective as single breaths. 	Grade D
R52	Spacers should be cleaned no more than monthly as more frequent cleaning affects their performance (due to build up of static). They should be cleaned with water and washing-up liquid and allowed to air dry. The mouthpiece should be wiped clean of detergent before use.	Grade D

RECOMMENDATIONS ABOUT NEBULISERS

R53	Patients with distressing or disabling breathlessness despite maximal therapy using inhalers should be considered for nebuliser therapy.	Grade D
R54	Nebulised therapy should not continue to be prescribed without assessing and confirming that one or more of the following occurs: <ul style="list-style-type: none"> a reduction in symptoms an increase in the ability to undertake activities of daily living an increase in exercise capacity an improvement in lung function. 	Grade D
R55	Nebulised therapy should not be prescribed without an assessment of the patient's and / or carer's ability to use it.	Grade D
R56	A nebuliser system, that is known to be efficient, should be used. Once available, Comité European de Normalisation (European Committee for Standardisation, CEN) data should be used to assess efficiency.	Grade D
R57	Patients should be offered a choice between a facemask and a mouthpiece to administer their nebulised therapy, unless the drug specifically requires a mouthpiece (for example, anticholinergic drugs).	Grade D
R58	If nebuliser therapy is prescribed, the patient should be provided with equipment, servicing, advice and support.	Grade D

7.9 Oxygen

As the COPD progresses patients often become hypoxaemic. Many patients tolerate mild hypoxaemia well, but once the resting PaO₂ falls below 8 kPa patients begin to develop signs of cor pulmonale, principally peripheral oedema. Once this occurs the prognosis is poor and if untreated the 5 year survival is less than 50%.

Some patients with COPD also become transiently hypoxaemic on exercise and oxygen has been used to try to improve exercise capacity and reduce disability in these individuals. Oxygen is also used to provide symptomatic relief of breathlessness.

Oxygen should be used with caution in patients with COPD as some patient's respiratory drive depends on their degree of hypoxia rather than the usual dependence on hypercapnia. Thus uncontrolled oxygen therapy can result in suppression of respiratory drive, carbon dioxide narcosis and ultimately respiratory arrest.

Thus, in stable COPD oxygen can be administered for long periods during the day and night (long term oxygen therapy (LTOT)), as ambulatory oxygen (either as part of LTOT or on its own to facilitate exercise) or as short burst therapy to relieve symptoms.

When considering the effects of oxygen therapy it is necessary to consider each of these uses separately. It is also necessary to consider the most effective form of supply. Oxygen can be supplied from cylinders, from tanks of liquid oxygen and can be purified from room air by electrically driven oxygen concentrators.

A rigorous literature search was not performed in this area as much of the evidence has been reviewed in the Department of Health sponsored report on oxygen therapy produced by the Royal College of Physicians¹⁶⁹. The statements and recommendations contained in this report were reviewed and inform some of the guideline recommendations.

As well as looking at the report, two systematic reviews were found looking at oxygen therapy^{170;171}.

The GDG is aware that the Department of Health and Welsh Assembly Government are reviewing the processes for assessing patients for oxygen therapy and its provision. These guidelines reflect the current position but they may need revision in the light of this review.

The total cost of oxygen therapy in England and Wales in 2002-3 was £34.8 million. This is made up of £19.8 million for oxygen cylinders and £15.0 million for oxygen concentrators.

7.9.1 Long term oxygen therapy (LTOT)

Long term oxygen therapy aims to improve survival in patients with COPD who have severe hypoxaemia ($\text{PaO}_2 < 8\text{kPa}$) as well as reducing the incidence of polycythaemia, reducing the progression of pulmonary hypertension and improving neuropsychological health.

There is more evidence about which patients require LTOT, its efficacy and its supply, than about the other forms of oxygen therapy.

The following evidence statements are derived from the RCP Report¹⁶⁹ and are therefore graded IV this does not necessarily reflect the strength of the underlying evidence.

▷ Evidence statements

“Although two randomised controlled trials showed survival benefit of LTOT in patients with COPD, when used for at least 15 h daily^{172;173} the precise mechanism of the improvement in survival with oxygen therapy is unknown.”

IV

Chronic Obstructive Pulmonary Disease: National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care

“Generally, the effects of LTOT on pulmonary artery pressure (PAP) have been small, and PAP may be of prognostic significance as a reflection of the severity of the disease. In the NOTT trial, survival after 8 years was related to the decrease in mean PAP during the first 6 months of treatment ¹⁷⁴. In the MRC trial, LTOT prevented a rise in PAP of 3 mmHg, seen in the control group, though a fall in PAP was not found.” **IV**

“In patients with COPD, airflow obstruction continues to deteriorate despite LTOT, and the level of the FEV₁ is the strongest predictor of survival in these patients ^{175,176}. A recent European study found that the majority of patients on LTOT died eventually as a result of respiratory failure ¹⁷⁷.” **IV**

“The UK MRC trial of LTOT showed benefits of oxygen therapy only in patients who were hypercapnic and who had had a previous documented episode of oedema indicating cor pulmonale ¹⁷². Data from the NOTT trial also showed that the benefits of LTOT were present in relatively normocapnic patients ¹⁷³. It is thus a reasonable assumption that improvements in survival are likely in the presence of chronic hypoxaemia, irrespective of chronic hypercapnia or previous episodes of oedema. This assumption is reflected in the advice of all current international guidelines on the prescription of LTOT.” **IV**

“In COPD patients considered for LTOT, the FEV₁ should normally be less than 1.5 litres, or less than 40% of predicted normal values. The presence of arterial hypoxaemia with a higher FEV₁ suggests that there may be another cause for the hypoxaemia, e.g. sleep apnoea, and further investigations will be required. Patients should be prescribed LTOT for at least 15 h per day, although survival improves when LTOT is used for more than 20 h per day. Thus the hours of LTOT use should not be restricted, especially in severe COPD. There is no benefit in the use of LTOT in COPD patients with a PaO₂ above 8 kPa.” **IV**

▷ Evidence statements on provision of LTOT

Oxygen concentrators are currently the most convenient and economical method of providing domiciliary long term oxygen therapy ¹⁷⁸. **IV**

The major disadvantage of liquid oxygen is that the oxygen evaporates and thus the cylinders have to be refilled, even if not used. Liquid oxygen for the provision of LTOT may also be more expensive to provide than oxygen concentrators in view of the costs of the deliveries. No formal costings comparing liquid oxygen and other modes of oxygen therapy delivery are currently available. There may be difficulties in supply of liquid-oxygen systems in isolated areas of the country where the distances between deliveries are greater ¹⁶⁹. **IV**

▷ Health economic evidence

One study was found which was a cost minimization analysis of providing oxygen by concentrator or cylinder in the home¹⁷⁹. No difference in efficacy or other resource use was assumed. Their conclusion is that as long as more than three cylinders a month are being used, independent of flow rate or duration of prescription, it is always cheaper to prescribe a concentrator. If the duration of prescription is likely to be 12 months or longer, it is always cheaper to prescribe a concentrator when two or more cylinders are bring used per month whatever the flow rate. Although this was based on data from Northern Ireland, they state that the cost of contracts for provision of concentrators are similar throughout the UK and are equivalent to other European countries.

RECOMMENDATIONS

R59	Clinicians should be aware that inappropriate oxygen therapy in people with COPD may cause respiratory depression.	Grade C
R60	LTOT is indicated in patients with COPD who have a PaO ₂ less than 7.3 kPa when stable or a PaO ₂ greater than 7.3 and less than 8 kPa when stable and one of: secondary polycythaemia, nocturnal hypoxaemia (oxygen saturation of arterial blood [SaO ₂] less than 90% for more than 30% of the time), peripheral oedema or pulmonary hypertension.	Grade A
R61	To get the benefits of LTOT patients should breathe supplemental oxygen for at least 15 hours per day. Greater benefits are seen in patients receiving oxygen for 20 hours per day.	Grade A
R62	The need for oxygen therapy should be assessed in: <ul style="list-style-type: none"> ● all patients with severe airflow obstruction (FEV₁ < 30% predicted) ● patients with cyanosis ● patients with polycythaemia ● patients with peripheral oedema ● patients with a raised jugular venous pressure ● patients with oxygen saturations ≤ 92% breathing air. <p>Assesment should also be considered in patients with moderate airflow obstruction (FEV₁ 30-49% predicted).</p>	Grade D
R63	To ensure all patients eligible for LTOT are identified, pulse oximetry should be available in all healthcare settings.	Grade D
R64	The assessment of patients for LTOT should comprise the measurement of arterial blood gases on 2 occasions at least 3 weeks apart in patients who have a confident diagnosis of COPD, who are receiving optimum medical management and whose COPD is stable.	Grade D
R65	Patients receiving LTOT should be reviewed at least once per year by practitioners familiar with LTOT and this review should include pulse oximetry.	Grade D

R66	Oxygen concentrators should be used to provide the fixed supply at home for long term oxygen therapy.	Grade D
R67	Patients should be warned about the risks of fire and explosion if they continue to smoke when prescribed oxygen.	Grade D

7.9.2 Ambulatory oxygen therapy

Ambulatory oxygen is defined as oxygen delivered by equipment that can be carried by most patients. It provides portable oxygen during exercise and activities of daily living. It may be used as part of continuous oxygen therapy in which case its benefits are those of long term oxygen therapy. But it is also used in isolation in the hope of improving exercise tolerance and quality of life.

The efficacy of ambulatory oxygen therapy is currently limited by the duration of oxygen supply from portable size PD cylinders even at low flow rates (see table 11).

Table 11 Duration of oxygen supply from a size DD portable oxygen cylinder at different flow rates

Used at a flow rate of	A portable cylinder without an oxygen conserving device will last
1 l/min	7 hours 40 minutes
2 l/min	3 hours 50 minutes
4 l/min	1 hour 55 minutes
6 l/min	57 minutes

(N.B. The usual regulator only delivers at 2 l/min and 4 l/min)

▷ Evidence statements

Oxygen conserving devices that provide oxygen with each breath are now available with very lightweight cylinders. These can last for a similar period of time to liquid-oxygen cylinders¹⁶⁹. **IV**

▷ GDG consensus statements

Ambulatory oxygen therapy can be used as a way of ensuring that patients who require long term oxygen therapy and who leave the home on a regular basis receive oxygen for sufficient hours to gain the benefits of LTOT. **IV**

In patients who do not meet the criteria for LTOT ambulatory oxygen therapy has been proposed as a means of improving exercise capacity and or health status:

- A recent cross over trial¹⁸⁰ (n=41) suggested benefits in health status. **Ib**

- In a small number of appropriately assessed patients who show desaturation on exercise, ambulatory oxygen therapy improves exercise capacity in patients with COPD. **IV**
- Overall, in patients who have not undergone such an assessment, evidence available to date^{171 181} does not allow any firm conclusions to be drawn concerning the effectiveness of ambulatory oxygen therapy in patients with COPD. **Ia**

Most of the devices for the provision of ambulatory oxygen therapy are not currently available on prescription. **IV**

Liquid oxygen is considerably more costly to provide for the patient. Liquid-oxygen portable systems can on average supply 8 hours of oxygen at 2 l/min, though they may be used in conjunction with oxygen-conserving devices. These liquid units must be filled from a large reservoir that is delivered to the patient's home. As liquid oxygen systems evaporate with time, the large home reservoir unit requires frequent filling or replacement. **IV**

The technology for the provision of ambulatory oxygen is developing rapidly. **IV**

▷ Health economic evidence

A cost utility analysis was found which compared oxygen supplied by a concentrator with cylinders for ambulation with liquid oxygen both at home and for ambulation. The total costs of using liquid oxygen were higher but liquid oxygen led to better quality of life assessed using the sickness impact profile. No significant difference was found by the EQ-5D however¹⁸².

RECOMMENDATIONS

R68	People who are already on LTOT who wish to continue with oxygen therapy outside the home, and who are prepared to use it, should have ambulatory oxygen prescribed.	Grade D
R69	Ambulatory oxygen therapy should be considered in patients who have exercise desaturation, are shown to have an improvement in exercise capacity and/or dyspnoea with oxygen, and have the motivation to use oxygen.	Grade D
R70	Ambulatory oxygen therapy is not recommended in COPD if PaO ₂ is greater than 7.3 kPa and there is no exercise desaturation.	Grade D
R71	Ambulatory oxygen therapy should only be prescribed after an appropriate assessment has been performed by a specialist. The purpose of the assessment is to assess the extent of desaturation, and the improvement in exercise capacity with supplemental oxygen, and the oxygen flow rate required to correct desaturation, aiming to keep the SaO ₂ above 90%.	Grade D
R72	Small light weight cylinders, oxygen-conserving devices and portable liquid oxygen systems should be available for the treatment of patients with COPD.	Grade D
R73	A choice about the nature of equipment prescribed should take account of the hours of ambulatory oxygen use required by the patient and the oxygen flow rate required (see table 12).	Grade D

Table 12 Appropriate equipment for ambulatory oxygen therapy

Usage	Equipment
For a duration of use of less than 90 minutes	Small cylinder
For a duration of use less than 4 hours but more than 90 min	Small cylinder with oxygen conserving device
For duration of use more than 4 hours	Liquid oxygen
For Flow rates greater than 2 l/min and duration of use more than 30 min	Liquid oxygen

7.9.3 Short burst oxygen therapy

Short-burst oxygen therapy is widely prescribed¹⁸³ and is one of the most expensive therapies used in the NHS. It has been claimed that it may simply be an expensive placebo and that some of its apparent benefits are due to a cooling effect of the oxygen on the face rather than a correction of hypoxia.

Short burst oxygen is commonly prescribed for use by patients who do not meet the criteria for LTOT but who remain breathless after minimal exertion despite other therapy. It is usually provided from cylinders.

▷ Evidence statements

Previous studies have shown variable results on the issue of short-burst oxygen therapy. Some improvement has been found in exercise capacity and dyspnoea, when using short-burst oxygen before exercise, though oxygen saturation was not measured¹⁸⁴. **IIb**

Patients report considerable symptomatic benefit and earlier recovery after exercise with short-burst oxygen, though there is little evidence to support this finding and effects may not be reproducible with time¹⁸⁵. **IIb**

One study showed that patients with chronic hypoxaemia due to COPD or interstitial lung disease show reduction in dyspnoea after 10 minutes of supplemental oxygen therapy, though normoxaemic patients were not studied¹⁸⁶. **IIb**

Some patients reporting improvements with short-burst oxygen may show exercise desaturation, though this has not been specifically studied in relation to short-burst intermittent oxygen use. **IV**

▷ Health economic evidence

No evidence was found on the cost effectiveness of short burst oxygen use in the home. However, it should be noted that this is an area with a high cost and relatively unknown benefit.

Although current recommendations are for conservative prescription by the specialist when all other treatments have shown no effect, it is recommended that research be carried out into the cost effectiveness.

RECOMMENDATIONS

R74	Short-burst oxygen therapy should only be considered for episodes of severe breathlessness in patients with COPD not relieved by other treatments.	Grade C
R75	Short-burst oxygen therapy should only continue to be prescribed if an improvement in breathlessness following therapy has been documented.	Grade D
R76	When indicated, short-burst oxygen should be provided from cylinders.	Grade D

7.10 Non-invasive ventilation

Non-invasive ventilation (NIV) is a method of providing ventilatory support that does not require the placement of an endotracheal tube. It is usually delivered via a mask that covers the nose, but occasionally a full face mask covering the nose and the mouth is required. The ventilators themselves are compact and portable and some can be run off car batteries as well as mains electricity.

NIV is most commonly used to treat acute respiratory failure during exacerbations of COPD (see section 8.13); however, interest has grown in using it as a treatment for chronic hypercapnic ventilatory failure in selected patients. In these patients it may be combined with LTOT.

There are a number of mechanisms by which NIV might benefit patients with stable COPD. NIV might rest the chronically fatigued respiratory muscles and allow recovery of the inspiratory muscle function¹⁸⁷. NIV may also improve sleep time and efficiency¹⁸⁸ by reducing episodes of hypoventilation associated with desaturation. Thirdly, by reducing nocturnal hypoventilation NIV may allow the respiratory centre to be reset thereby leading to improvements in daytime hypercapnia¹⁸⁹.

One systematic review was found¹⁹⁰ that compared NIV plus standard therapy with standard therapy alone. The review consisted of four RCTs. These studies all used different inclusion criteria and different ventilator settings with the result that it was felt that analysis of their pooled results was invalid.

One additional RCT was also identified¹⁹¹ (n=122), which compared NIV plus long-term oxygen therapy (LTOT) with LTOT alone. However, this study used lower inflation pressures than are normally used, relied on some historical control data and was not powered to detect differences in exacerbation rates. These issues make it difficult to draw firm conclusions from this study and further large scale, long-term studies are required in this important area.

▷ Evidence statements

The addition of NIV to LTOT in stable COPD patients with chronic ventilatory failure improved **daytime PaCO₂** during oxygen breathing¹⁹¹. **Ib**

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Resting dyspnoea improved over time in the NIV + LTOT group and at month 24 was better than in the LTOT alone group. Month 12 treatment effect 0.4, 95% CI 0.02 to 0.78 ($p = 0.048$). Month 24 treatment effect 0.6, 95% CI 0.15 to 1.05 ($p = 0.013$)¹⁹¹. **Ib**

After 2 years **quality of life** (measured by the MRF-28 total score) significantly improved in the NIV + LTOT group compared to the LTOT group. The SGRQ also showed a trend to improvement in both groups¹⁹¹. **Ib**

Hospital admissions were not significantly different between groups during follow-up¹⁹¹. **Ib**

The addition of non invasive ventilation (NIV) to long-term oxygen therapy (LTOT) in stable COPD patients with chronic ventilatory failure does not improve **lung function**¹⁹¹. **Ib**

▷ GDG consensus statements

There is additional inconsistent data from a small number of studies on small numbers of patients that NIV produces improvements in blood gases, dyspnoea, quality of life and exacerbation rates. **IV**

Patients with chronic hypercapnic respiratory failure who have been ventilated during an exacerbation or who are intolerant of LTOT may get improvements in blood gases, dyspnoea, quality of life and exacerbation rates when treated with NIV. **IV**

RECOMMENDATIONS

R77

Adequately treated patients with chronic hypercapnic ventilatory failure who have required assisted ventilation (whether invasive or non-invasive) during an exacerbation or who are hypercapnic or acidotic on LTOT should be referred to a specialist centre for consideration of long-term NIV.

Grade D

7.11 Management of pulmonary hypertension and cor pulmonale

Hypoxic patients with COPD develop pulmonary hypertension (i.e. pulmonary artery pressure > 20mmHg). Initially this is as a result of hypoxic vasoconstriction but structural changes also develop and these may be due to inflammatory processes. Pulmonary hypertension may be present for years without causing symptoms but in some patients it leads to the development of the clinical syndrome of cor pulmonale. For the purposes of this guideline, a clinical definition of cor pulmonale based on the pathological definition proposed by Behnke et al¹⁹² has been adopted: “*Alteration in the structure and function of the right ventricle resulting from diseases affecting the lungs except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart.*”

In the context of this guideline, the term “cor pulmonale” has been adopted to define a clinical condition that is identified and managed on the basis of clinical features. This clinical syndrome

of cor pulmonale includes patients who have right heart failure secondary to lung disease and those in whom the primary pathology is retention of salt and water leading to the development of peripheral oedema.

Cor pulmonale is defined as a clinical syndrome characterised by fluid retention, peripheral oedema and a raised venous pressure in patients with COPD who have no other cause of ventricular dysfunction.

Although the development of cor pulmonale and the diagnosis of pulmonary hypertension are significant events in the natural history of COPD and have implications for prognosis, a full literature search and critical appraisal process was not undertaken in this area, due to the time limitations within the guideline development process. However, a MEDLINE and Cochrane Database search, and a selective review of frequently cited papers and key review articles was undertaken as part of the development of a background paper for discussion by the guideline development group (as per section 2.4.1.).

7.11.1 Diagnosis of pulmonary hypertension & cor pulmonale

▷ Evidence statements

Pulmonary arterial hypertension is associated with widening of the descending pulmonary artery on a plain chest radiograph. A high hilar cardiothoracic ratio (>35) in patients with COPD was reported to be 95% sensitive and 100% specific for the presence of pulmonary hypertension¹⁹³, but could not predict the degree of hypertension and considerable inter observer variation in its measurement has been reported¹⁹⁴. III

Detection of right ventricular hypertrophy on ECG is specific but not sensitive¹⁹⁵. III

Echocardiography can be used to assess Ppa non-invasively¹⁹⁶. IV

Examinations are technically inadequate because of hyperinflation in up to 35% of patients^{197;198} and there is not always a good correlation between Ppa measured using echocardiography and the Ppa measured invasively in COPD. III

Two dimensional echocardiography can measure right ventricular dimensions and wall thickness but this is technically difficult and there is no gold standard for comparison^{197;199}. III

Doppler echocardiography measuring the tricuspid regurgitant jet is the best method of assessing Ppa non-invasively it cannot be used to accurately predict Ppa in individual patients. IV

MRI appears to be the most accurate method for measuring right ventricular dimensions non-invasively²⁰⁰. III

Radionuclide ventriculography is an accurate and reproducible non-invasive way of measuring **left** ventricular function but it is less good for right ventricular function because of overlap of RA and RV and presence of tricuspid regurgitation^{196;201}. III

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▷ GDG consensus statements

Pulmonary hypertension in COPD can be non-invasively assessed by echocardiography but examinations may be limited by hyperinflation and may not accurately assess the pulmonary artery pressure. **IV**

Pulmonary hypertension in COPD can only be quantified accurately by right heart catheterisation but this is rarely indicated. **IV**

The diagnosis of cor pulmonale is essentially clinical but depends on excluding other causes of peripheral oedema (including left ventricular failure and chronic thromboembolic disease). **IV**

The diagnosis of right heart failure can be supported by ECG changes or echocardiography and, in addition, these tests can exclude other causes of oedema and heart failure. **IV**

MRI scanning and radionuclide ventriculography are the most accurate ways of measuring right ventricular function in patients with COPD. **IV**

Chest radiography cannot be relied upon to identify pulmonary hypertension in COPD. **IV**

RECOMMENDATIONS

R78

A diagnosis of cor pulmonale should be considered if patients have:

Grade D

- peripheral oedema
- a raised venous pressure
- a systolic parasternal heave
- a loud pulmonary second heart sound.

R79

It is recommended that the diagnosis of cor pulmonale is made clinically and that this process should involve excluding other causes of peripheral oedema.

Grade D**7.11.2 Treatment of cor pulmonale**

Treatment of cor pulmonale aims to correct hypoxia and overcome salt and water retention.

Uncontrolled studies of ACE inhibitors have shown variable results and cannot be relied upon. ACE inhibitors may have benefits in reducing salt and water retention but these have not been shown to be clinically relevant in long term studies.

Diuretics are widely used but there are no trials in COPD to support their use. There are theoretical concerns that they may reduce cardiac output by reducing ventricular filling pressures. They may also cause a metabolic alkalosis thereby reducing ventilatory drive.

▷ Evidence statements

Oxygen

LTOT reduces the progressive rise in Ppa seen in hypoxic patients¹⁷². **Ib**

Oxygen reduces the abnormal rise in Ppa seen during exercise¹⁷⁴ and prevents the fall in right ventricular ejection fraction²⁰². **IIa**

ACE inhibitors

One study was found on the use of an ACE inhibitor²⁰³ and one study on the use of an angiotensin receptor antagonist²⁰⁴ in pulmonary hypertension but there were methodological limitations with these studies such that it was not possible to formulate any evidence statements.

Calcium channel blockers

Two studies, one of 18 months duration²⁰⁵ and one of 3 months duration²⁰⁶ failed to show benefits of nifedipine. **Ib**

Alpha-blockers

Alpha-blockers reduce Ppa in patients with COPD but their use is limited by their side-effects²⁰⁷⁻²⁰⁹. **IIb**

Digoxin

Studies of the effects of digoxin have failed to show any benefit in cor pulmonale unless there was co-existent left ventricular failure²¹⁰⁻²¹². **IIa**

▷ GDG consensus statements

Diuretics

There is insufficient evidence to recommend changing the current clinical practice of using diuretics to control peripheral oedema in patients with cor pulmonale. **IV**

RECOMMENDATIONS

R80	Patients presenting with cor pulmonale should be assessed for the need for long term oxygen therapy.	Grade A
R81	Oedema associated with cor pulmonale can usually be controlled symptomatically with diuretic therapy.	Grade D
R82	The following are not recommended for the treatment of cor pulmonale: <ul style="list-style-type: none"> ● angiotensin-converting enzyme inhibitors ● calcium channel blockers ● alpha-blockers ● digoxin (unless there is atrial fibrillation). 	Grade C

7.12 Pulmonary rehabilitation

Pulmonary rehabilitation can be defined as a multidisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimise each patient's physical and social performance and autonomy. It is widely used for patients with COPD²¹³.

Pulmonary rehabilitation is an increasingly popular and effective option for patients with moderate to severe COPD. Rehabilitation aims to prevent deconditioning and allow the patient to cope with their disease. Most programmes are hospital based and comprise individualised exercise programmes and educational talks.

Pulmonary rehabilitation has been available in North America and Europe for some years, but availability is still limited in the UK. Individual programmes differ in the precise exercises used, are of different duration, involve variable amounts of home exercise and have different referral criteria. There is growing interest in running rehabilitation in community settings which may make it easier for patients to attend.

When reviewing the evidence for pulmonary rehabilitation many papers were rejected due to small sample size, lack of methodological detail, no comparison group or because the paper had been included in a systematic review or meta analysis already reviewed. Pulmonary rehabilitation was compared to either usual care or education. The Cochrane Systematic Review by Lacasse²¹⁴, ACCP Evidence-Based Guidelines²¹⁵, BTS Statement²¹³ and a meta analysis²¹⁶ were reviewed.

7.12.1 Benefits of pulmonary rehabilitation

There is good evidence about the benefits that pulmonary rehabilitation can produce. There has been no direct comparison of the effects of a pulmonary rehabilitation course and the effects of pharmacotherapy, but most programmes require optimisation of medical therapy prior to, or as part of, enrolment.

▷ Evidence statements

Pulmonary rehabilitation leads to statistically significant and clinically meaningful improvements in **health related quality of life** (CRDQ), **functional exercise capacity** (WMD 49 meters 95% CI 26 to 72) and **maximum exercise capacity** (WMD 5.4 watts 95% CI 0.5 to 10.2)^{214;215}. **Ia**

Pulmonary rehabilitation reduces **dyspnoea**^{213;215}. **IV, Ia**

A single study (n=119) using the Centres for Epidemiologic Studies Depression Scale (CES-D) showed that there was no effect on **depression**²¹⁷. **Ib**

The ACCP evidence-based guideline²¹⁵ highlight that there is currently little information available from RCTs that evaluate the utilisation of health care resources for patients completing a comprehensive pulmonary rehabilitation programme. It has been shown in several non randomised and observational studies that there is a trend towards a decrease in the total number of **hospitalisation days** as well as the **total number of hospitalisations** **Ia**

required for a patient with COPD in the years following the completion of a comprehensive pulmonary rehabilitation programme compare to the year preceding rehabilitation.

The GDG was aware of one RCT²¹⁸ (n=200) contained within the Lacasse systematic review²¹⁴, which found no difference between the rehabilitation and control groups in the number of **hospitalisations**. **Ib**

There was conflicting evidence regarding the **number of days spent in hospital**.

Griffiths et al.²¹⁸ found that the number of days rehabilitation patients compared to control patients spent in hospital differed significantly (mean 10.4 days versus 21.0 days, p=0.022) in favour of the rehabilitation patients. **Ib**

However Ries et al.²¹⁹ in a smaller RCT (n=119) found that duration of hospital stay was non significant. **Ib**

In relation to the outcome of **primary care consultations**, Griffiths et al.²¹⁸ found that the rehabilitation group had more primary care consultations at the GP's premises than did the control group (p=0.033) but fewer home visits (p=0.037). **Ib**

A single centre RCT has shown that patients with more severe COPD undergoing a 8 week programme of pulmonary rehabilitation maintain improvements in exercise capacity and health status for up to 6 months however these were not sustained at one year²²⁰. **Ib**

▷ Health economic evidence

Fourteen papers of potential relevance were found. Some studies were not full economic evaluations and estimated the cost of providing a pulmonary rehabilitation service. Two studies estimated the cost effectiveness in the UK. The cost per QALY was estimated as between £2,000 and £8,000 based on a minimum of four weeks rehabilitations²²¹. Griffiths et al²²² undertook an economic evaluation alongside a clinical trial and estimated that pulmonary rehabilitation was cost saving and increased quality of life. The probability of the cost per QALY generated being below £0 was 0.64²²².

There is good evidence that pulmonary rehabilitation is **cost effective** in the outpatient setting compared to usual care²²². **Ib**

▷ GDG consensus statements

The magnitude of the effects of pulmonary rehabilitation on **exercise capacity**, **dyspnoea** and **health related quality of life** are significantly greater than the effects of bronchodilator drugs. **IV**

7.12.2 Course content, setting and duration

Traditionally pulmonary rehabilitation courses have been run in secondary care settings, usually on an out-patient basis but also on an in-patient basis in countries outside the UK. Recently community based programmes have also been developed. There is good evidence on

the content of the programme, but less information on the optimum duration or comparative efficacy in different settings.

▷ Evidence statements

The GDG found comprehensive evidence-based guidelines on pulmonary rehabilitation²¹⁵. These guidelines focus upon **course content** and included lower and upper extremity training, ventilatory muscle training and psychosocial, behavioural & educational components. The authors conclude that in patients with COPD, lower extremity training improves exercise tolerance whilst upper extremity training improves arm function. The evidence for ventilatory muscle training (VMT) currently does not support the routine use of VMT. **Ia**

The evidence to date does not support the benefits of short-term psychosocial single interventions however longer-term interventions may be beneficial. Scientific evidence in this area is lacking.

Two meta analyses were found of **respiratory muscle training**^{223;224}, which demonstrate conflicting findings. **Ia**

The Smith²²³ meta analysis of 17 RCTs demonstrated no significant findings for FEV₁ (8 trials), maximum inspiratory pressure respiratory muscle strength (11 trials), respiratory muscle endurance (9 trials), laboratory exercise capacity (9 trials), functional exercise capacity (9 trials) and functional status (QoL). The only significant effect was for respiratory muscle strength as measured by maximum voluntary ventilation. This equates to an 8.8L difference (p=0.02) (7 trials). Overall there is little evidence in support of respiratory muscle training. A disparity was noted by the GDG in the results published within the abstract and those of the body of the text for this meta analysis. Overall the results remain the same. **Ia**

Lotters²²⁴ updated the work in this area and includes five of the studies that had previously been included in the Smith²²³ meta analysis. **Ia**

Lotters²²⁴ demonstrated significant findings for inspiratory muscle strength (effect size 0.56, 95% CI 0.35 to 0.77) (15 studies), endurance (0.41, 95% CI 0.14 to 0.68) (7 studies) and dyspnoea (TDI) (2.3, 95% CI 1.44 to 3.15) (2 studies). From this recent meta analysis, it can be concluded that inspiratory muscle training significantly improves inspiratory muscle strength and endurance whilst the sensation of dyspnoea significantly decreases. **Ia**

A single centre study²²⁵ with small numbers of patients (n=47 between three arms) examined the effects of **strength, endurance or combined strength training**. At the end of the training period and at 12 weeks after training, all patients in the three groups showed significant increases in the duration of endurance testing as compared with pre training values. All training modalities showed significant improvements of the breathlessness score and the dyspnoea dimension of the chronic respiratory questionnaire. **III**

The BTS statement on pulmonary rehabilitation²¹³ provides an evidence update to the ACCP guidelines²¹⁵ and concludes that pulmonary rehabilitation is effective in all **settings** including hospital inpatient, hospital outpatient, the community, and possibly the home. **IV**

Puente-Maestu ²²⁶ undertook a small (n=41) RCT comparing the effects of **supervised versus self-monitored training programmes** in patients with COPD. Both types of training improved exercise tolerance, but the magnitude and the extent of physiological improvements were larger (p<0.05) in patients training under supervision. **Ib**

A single centre study²²⁷ compared **duration** of three versus with eighteen months of exercise training. There were small but statistically significant differences in favour of the eighteen-month programme for self reported physical disability using the Fitness Arthritis and Seniors Trial Functional Performance Inventory. There were statistically but not clinically significant improvements in six minute walk distance (6MWD). **Ib**

▷ GDG consensus statements

The majority of studies have been performed in a hospital outpatient setting. There is limited data on effectiveness in community or home studies and there have been no comparative studies. **IV**

The GDG concluded that the evidence regarding prolonged supervised outpatient programmes showed very modest benefits and that such programmes were unrealistic. **IV**

The COPD GDG augmented the BTS statement with the following italicised consensus addition:

In relation to **duration of the initial programme**, and taking in to account current evidence (cited in²¹³) the GDG believe that outpatient programmes should contain a minimum of 6 weeks *and a maximum of 12 weeks* of physical exercise, disease education, psychological and social interventions. **IV**

7.12.3 Referral criteria

No randomised trials were found looking at whether pre-determined factors influence a patient's response to pulmonary rehabilitation. Some data was found from retrospective analyses on which factors predicted concordance and response. The position statements of the BTS, ERS and ATS were considered in formulating the statements and recommendations.

▷ Evidence statements

One cross sectional study was found²²⁸ (n=91) that looked at whether people who declined or failed to complete COPD rehabilitation programmes differed in terms of demographics, physiological or psychological factors from those people who completed. **III**

The non-adherent group compared to the adherent group were more likely to be widowed or divorced and less likely to be currently married (p<0.001), more likely to live alone (39% vs. 14%, p<0.02), and more likely to live in rented accommodation (31 vs. 6%, p<0.002). They were also more likely to be current smokers (28 vs. 8%, p<0.02). Inadequate social support for COPD related problems (51 vs. 2%, p=0.001) was more common in the non-adherent group.

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The introduction of rehabilitation becomes appropriate when patients become aware of their disability ²¹³. **IV**

There is currently no justification for selection on the basis of **age, impairment, disability, smoking status or use of oxygen**. Some patients with serious co-morbidity such as cardiac or locomotor disability may not benefit as much ²¹³. **IV**

The only issues material to selection are poor motivation and the logistical factors of **geography, transport, equipment usage, and the group composition** ²¹³. **IV**

▷ GDG consensus statements

The COPD GDG augmented the BTS statement ²¹³ with the following italicised consensus addition:

Rehabilitation should be considered at all stages of disease progression when symptoms *and disability* are present and not at a predetermined level of impairment. The threshold for referral would usually be breathlessness equivalent to MRC dyspnoea grade 3 (see table 3). **IV**

7.12.4 Repeat programmes

The benefits of pulmonary rehabilitation appear to wane with time. There is limited evidence concerning the benefits of attendance at further pulmonary rehabilitation programmes.

▷ Evidence statements

There was evidence that repeated pulmonary rehabilitation led to further temporary improvements in breathlessness and exercise capacity and reduced exacerbations ²²⁹. The GDG was aware of methodological limitations of this study. The sample size was small, n=61, of which only 36 patients of the groups combined were available for evaluation. **Ib**

RECOMMENDATIONS ON PULMONARY REHABILITATION

R83	Pulmonary rehabilitation should be made available to all appropriate patients with COPD.	Grade A
R84	Pulmonary rehabilitation should be offered to all patients who consider themselves functionally disabled by COPD (usually MRC grade 3 and above). Pulmonary rehabilitation is not suitable for patients who are unable to walk, have unstable angina or who have had a recent myocardial infarction.	Grade D
R85	For pulmonary rehabilitation programmes to be effective, and to improve concordance, they should be held at times that suit patients, and in buildings that are easy for patients to get to and have good access for people with disabilities. Places should be available within a reasonable time of referral.	Grade D

R86	Pulmonary rehabilitation programmes should include multi-component, multi-disciplinary interventions, which are tailored to the individual patient's needs. The rehabilitation process should incorporate a programme of physical training, disease education, nutritional, psychological and behavioural intervention.	Grade A
R87	Patients should be made aware of the benefits of pulmonary rehabilitation and the commitment required to gain these.	Grade D

7.13 Vaccination and anti-viral therapy

Pneumococcal vaccination and annual influenza vaccination are recommended for patients with chronic respiratory disease by the Chief Medical Officer. The role of newer anti viral agents in preventing or treating influenza has been looked at separately by NICE²³⁰ but clinical experience with these drugs is limited.

Influenza

One systematic review was identified²³¹ relating to influenza vaccine for patients with COPD. This review included studies that compared live or inactivated virus vaccines (intramuscular or intranasal routes) with placebo either alone or with another vaccine. Nine trials were included but only four (n=215) were specific to a stable COPD population. These were all carried out some years ago and used vaccines that differ from those used now.

One additional retrospective cohort study was identified relating to influenza vaccine²³². Although this study included a heterogeneous population with chronic lung disease (n=1898) it was worthy of consideration as it included an elderly population.

Treatment of influenza

One NICE Technology Appraisal Guidance (TAG), No 58 (2003) 'Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza'²³⁰ was identified which replaces the NICE Technology Appraisal Guidance, No 15 (2000) 'Guidance on the use of zanamivir (Relenza) in the treatment of influenza'²³³.

A systematic review and economic decision modelling for the prevention and treatment of influenza A and B²³⁴ underpins the NICE TAG, No 58²³⁰.

The TAG and systematic review referred to above relate to Zanamivir, Oseltamivir and Amantadine. Zanamivir is a neuraminidase inhibitor and is taken using an inhaler (Diskhaler). It is licensed for the treatment of influenza A and B. Oseltamivir is also a neuraminidase inhibitor. It can be taken orally and is licensed for the treatment of influenza A and B. Amantadine is not currently recommended for the treatment of influenza²³⁰.

Pneumococcal vaccination

Two retrospective cohort studies were found^{235;236}, which appear to use the same population. These studies were included despite having a heterogeneous chronic lung disease population. The first study looks at the health benefits associated with pneumococcal vaccination of elderly patients with chronic lung disease. The second paper by Nichols et al.²³⁶ looks at the additive

benefits of influenza and pneumococcal vaccination during influenza seasons among elderly people.

It is important to note that due to the relevance of the three retrospective cohort studies by Nichols the GDG felt that the studies were worthy of inclusion. However, the study design, retrospective cohort, falls lower down the hierarchy of evidence and in addition to this, extrapolation meant that the study recommendations were down graded as per the current NICE grading system.

One Canadian RCT was found, n=189, that looked at the efficacy of Pneumococcal vaccine compared to placebo in severe COPD patients²³⁷. This was subsequently excluded by the GDG due to a heterogeneous population and the date of the study.

One RCT was identified²³⁸ relating to Haemophilus influenzae vaccine for prevention of exacerbation for chronic bronchitis. This was excluded as the population included bronchiectasis and chronic bronchial asthma.

▷ Evidence statements

Influenza vaccination

Nichols et al.²³² compared vaccinated to unvaccinated people in a cohort of n=1898 elderly persons with chronic lung disease (CLD) over three influenza seasons and demonstrated a 52% reduction in **hospitalisations** for both pneumonia and influenza (Adjusted risk ratio 0.48 p=0.008).

IIa

There was no difference in the number of hospitalisations for all respiratory conditions between the two groups²³².

There was a 70% reduction in risk for **death** (Adjusted odds ratio, 0.30; p<0.001) in the vaccinated patients²³².

During the influenza season, for **outpatient visits**, influenza vaccination was *not* associated with a lower risk for having at least one visit for either pneumonia or all respiratory conditions²³².

Treatment of influenza

Italics represent direct quotes from the Technology Appraisal Guidance No. 58²³⁰:

NICE

Amantadine

“Amantadine is not recommended for the treatment of influenza”.

Zanamivir

“The Assessment Report identifies five RCTs (unreferenced in the TAG) of zanamivir in elderly people and otherwise at-risk people (% of COPD patients not defined). A meta analysis of these trials, n=371 people were treated with zanamivir and n=392 received placebo. On an ITT basis, the median time to alleviation of symptoms was 0.93 days sooner with zanamivir (95% CI -0.05 to 1.90 days). For people who had confirmed influenza within these groups (n=236 treated with zanamivir and n=248 placebo), the median time to symptom alleviation was 1.99 days sooner with zanamivir compared with placebo (95% CI; 0.90 to 3.08 days). The median time to return to normal activities were 0.09 days sooner for the treatment group (95% CI; -0.78 to 0.95 days) on an ITT basis and 0.20 day (95% CI; -0.79 to 1.19 days) for the influenza positive subgroup.”

“There is some evidence that treatment with zanamivir for influenza reduces complications. An analysis of a set of trials including both otherwise healthy and at risk individuals (proportion of COPD not defined) found that in a pooled subgroup of 230 high risk adults and children with laboratory confirmed influenza, antibiotics were required by 24% in the placebo group and 13% in the zanamivir group; odds ratio 0.49, 95% CI; 0.23 to 1.04.”

“In clinical trials, zanamivir has not been extensively tested in people with chronic respiratory disease. In post licensing experience, there have been very rare reports of allergic reactions such as facial and oropharyngeal oedema, rash and urticaria”.

Oseltamivir

“The Assessment Report identifies five RCTs of oseltamivir in elderly people and otherwise at-risk adults (proportion of COPD not defined) that have been used in a meta analysis. The analysis involved 557 people treated with oseltamivir and 577 with placebo. On an ITT basis, the median time to alleviation of symptoms was 0.35 days sooner with oseltamivir (95% CI; -0.71 to 1.40 days). For people who had confirmed influenza within these groups (341 treated with oseltamivir and 387 who received placebo), the median time to symptom alleviation was 0.45 days sooner with oseltamivir compared with placebo (95% CI; -97 to 1.88 days). With oseltamivir, the median times to return to normal activities were 2.45 days sooner for the treatment group (95% CI; 0.05 to 4.86) on an ITT basis and 3.00 days (95% CI; 0.13 to 5.88 days) for the influenza positive subgroup.”

“There is some evidence that treatment with oseltamivir for influenza reduces complications. In an overlapping set of trials involving both otherwise healthy and at risk people (proportion of COPD not defined) who were diagnosed as influenza positive, 19 out of 1063 receiving placebo, developed pneumonia, compared with 9 out of 1350 receiving oseltamivir (odds ratio 0.37, CI 0.15 to 0.86).”

“Oseltamivir, in clinical trials, is generally well tolerated, but has been associated with a higher rate of nausea (3 to 7% higher) and vomiting (2% higher) compared with placebo.”

Pneumococcal vaccination

Nichol et al.²³⁵ over two influenza seasons looked at the health and economic benefits associated with pneumococcal vaccination of a cohort (n=1989) of elderly persons with chronic lung disease. Findings demonstrated that pneumococcal vaccination was associated with:

IIa

- a 43% reduction in the number of **hospitalisations** for pneumonia and influenza (Adjusted RR, 0.57; p=0.005)
- a 29% reduction in the risk for **death** from all causes (Adjusted RR, 0.71; p=0.008)²³⁵.

Influenza and pneumococcal vaccinations

Nichols et al.²³⁶ looked at the additive benefits of influenza and pneumococcal vaccinations among a cohort of n=1898 elderly persons with chronic lung disease over three influenza seasons. Results of the study indicate that for both influenza and pneumococcal vaccination there was:

IIb

- a 63% (95% CI 29 to 80) reduction in the risk for **hospitalisation** for pneumonia
- a 81% (95% CI 68 to 88) reduction in the risk of **death** (versus when neither vaccination had been received).

There was no evidence of an interaction between the vaccinations.

HEALTH ECONOMICS EVIDENCE STATEMENTS

Hak et al²³⁹ found that in the Netherlands, immunisation of elderly patients with chronic lung disease against influenza is effective and cost saving.

Guidance from the NICE technology appraisal no. 58²³⁰ recommends routine immunisation of people of any age with chronic respiratory disease, where it is known that either influenza A or influenza B is circulating in the community.

“Vaccination offers a very cost effective initial empirical treatment of defence against influenza.”

“The Committee concluded that the evidence indicated that, when influenza is circulating, it would be both clinically effective and cost effective for at-risk people with influenza-like illness to be treated with zanamivir or oseltamivir if they can begin their course of medication within 48 hours of the appearance of symptoms.”

People who have chronic respiratory disease (including COPD) are considered to be at risk.

RECOMMENDATIONS

National policy for 2003/2004 is that influenza immunisation should be offered to all patients with chronic obstructive pulmonary disease and pneumococcal vaccine should be offered to those with chronic lung disease²⁴⁰.

Detailed information regarding both the influenza and pneumococcal vaccine is available in the HMSO publication on Immunisation against Infectious Disease (1996) otherwise known as the “Green Book”²⁴¹. This publication includes a new (draft) pneumococcal replacement chapter (November 2003)²⁴².

R88

Pneumococcal vaccination and an annual influenza vaccination should be offered to all patients with COPD as recommended by the Chief Medical Officer.

HSC

R89

NICE Technology Appraisal Guidance No. 58²³⁰ makes the following recommendation:

Within their licensed indications, zanamivir and oseltamivir are recommended for the treatment of at-risk adults who present with influenza-like illness and who can start therapy within 48 hours of the onset of symptoms.

NICE

The technology appraisal also notes that zanamivir should be used with caution in people with COPD because of risk of bronchospasm. If people with COPD are prescribed zanamivir they should be made aware of the risks and have a fast-acting bronchodilator available.

7.14 Lung surgery

Bullectomy, lung volume reduction surgery (LVRS) and lung transplantation have all been used to treat patients with COPD. Bullectomy usually involves the removal of a single large bulla that leads to collapse of surrounding lung tissue. LVRS aims to improve breathlessness by removing areas of poorly functioning lung, thereby decreasing the intra-thoracic volume and reducing the mechanical disadvantage faced by the respiratory muscles.

LVRS and transplantation are usually only considered in advanced disease that is unresponsive to medical therapy and appropriate selection of patients is vital. This is a decision for individual surgeons and referral processes. The extent of investigations required prior to referral vary. Some investigations required to assess the appropriateness of surgery may only be available in specialist centres. The recommendations have been limited, regarding referral for surgery, to investigations that are generally available, but clinicians should be aware of local policies on investigation and referral.

Although lung surgery is an important option for some patients with COPD, a systematic literature search and formal critical appraisal process was not undertaken in this area, due to the time limitations within the guideline development process. However, a MEDLINE and Cochrane Database search and a selective review of frequently cited papers and key review articles was undertaken as part of the development of an expert opinion background paper (see section 2.4.1.). This was then discussed by the guideline development group.

Bullectomy

Most studies of the effectiveness of bullectomy were carried out some years ago and are not RCTs. The GDG conclusions were based on a recent review of the results of previous case series²⁴³. This was not a systematic review but it was based on an extensive search of *Index Medicus* and it included all studies published since 1950. Long-term follow-up of clinical and physiologic data were given in relatively few articles and these data were difficult to interpret because of the variable way in which they were presented.

Lung volume reduction surgery

One systematic review of LVRS in emphysema was found²⁴⁴.

This identified 2 RCTs and two additional RCTs were found^{245;246}. In addition interim results from the same 4 year RCT were published to highlight the high mortality rate in a subgroup of patients²⁴⁷.

There have been no RCTs comparing LVRS with lung transplantation but there have been reports of case series of the effectiveness of LVRS in patients on a transplant waiting list²⁴⁸. There are other case series comparing LVRS with transplantation^{249;250}.

Lung transplantation

There have been no RCTs of lung transplantation for COPD. COPD accounts for 47% of all 7204 single lung transplants reported to the International Society for Heart & Lung Transplant (ISHLT) Registry and 20.1% of all 5420 bilateral lung transplants²⁵¹. Outcomes from individual transplant centres have been reported as case series²⁵².

Latest figures show that there were only 117 lung transplants for all indications across all age groups, including children, in 2002-2003 (data from www.uktransplant.org). This compares with 1385 kidney transplants in the same period. This means that, in practice, lung transplantation is not a widely available therapeutic option for most patients with COPD.

International guidelines for selection of lung transplantation candidates have been published and these have been adopted by the GDG²⁵³. Patients under consideration for lung transplantation should be assessed in accordance with the International guidelines. The guidelines deal with general criteria e.g. renal function, nutritional status, presence of

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osteoporosis, and criteria specific to COPD. They also discuss the fact that older patients, even those with no co morbidities, have a significantly worse survival rate than younger patients and make recommendations about upper age limits for the procedure. All of these factors limit the usefulness of transplantation as a therapeutic option in many patients with COPD.

▷ Evidence statements

Bullectomy

Bullectomy is indicated for the relief of dyspnoea or for the management of complications of the bulla: **IV**

- recurrent or persistent pneumothorax
- infection with failure of medical treatment and evidence of abscess formation in bulla
- suspicion of carcinoma
- massive haemoptysis.

Study of serial chest radiographs is helpful in judging whether the collapse of normal lung surrounding bullae is responsible for the patient's functional state. **IV**

The size of bullae, the presence of emphysema in the non-bullous lung and the amount of collapse are best assessed by CT. **III**

Pulmonary function (FEV₁, VC, RV, and TLC and Dco) was better at 5 years than preoperatively in patients whose bullae occupied more than one third of a hemithorax. **III**

Other predictors of a successful outcome are a large volume of sequestered gas, a reasonably preserved T_LCO and a normal PaCO₂. **III**

Postoperative mortality was not always given in published reports and varied greatly, from 0 to 22.5% with a weighted mean in 262 patients of 8.0%. **III**

One third to one half of the patients appeared to maintain improvement in pulmonary function for about 5 years. **III**

Nine of 12 patients reviewed 5 to 10 years after surgery all reported a gradual return of **dyspnoea** with a mean fall of FEV₁ of 82 ml/yr; 5 of the 9 still maintained some of their postoperative improvement. **III**

Among 11 patients operated on for bullous disease 4 to 20 years earlier, FEV₁ (prebronchodilator) and T_LCO declined more rapidly in 6 smokers than in 5 ex-smokers (p<0.05), suggesting the great importance of smoking cessation after surgery. **III**

In general, resection of giant bullae does not seem to affect the size of other bullae. **III**

Lung volume reduction surgery (LVRS)

LVRS improves FEV₁^{246;254}. **Ib**

The effect seems to be maximal at 6 months and thereafter there is a variable but significant decline towards pre-surgical values^{246;254}.

LVRS improves **walking distance** ^{246;254}. **Ib**

LVRS improves **quality of life** ^{246;254}. **Ib**

Overall, LVRS does not appear to have any effect on long term **survival** (but see subgroup results below) ^{246;254}. **Ib**

LVRS results in an unacceptably high mortality in patients who have ^{246;247} : **Ib**

- a low forced expiratory volume in 1 second (<20% predicted)
- and either non-upper lobe predominant emphysema or a very low transfer factor (<20% predicted).

With the exclusion of patients at high risk for death from surgery according to the interim analysis, overall **mortality** in the surgery group was 0.09 death per person-year, as compared with 0.10 death per person-year in the medical-therapy group (risk ratio, 0.89; p=0.31); **exercise capacity** after 24 months had improved by more than 10 W in 16 percent of patients in the surgery group, as compared with 3 percent of patients in the medical-therapy group (p<0.001) ²⁴⁶. **Ib**

Among patients with predominantly upper-lobe emphysema and low exercise capacity (40W in men and < 25W in women), mortality was lower in the surgery group than in the medical-therapy group (risk ratio for death, 0.47; p=0.005). Among patients with non-upper-lobe emphysema and high exercise capacity, mortality was higher in the surgery group than in the medical-therapy group (risk ratio, 2.06; p=0.02) ²⁴⁶. **Ib**

Clinically and statistically significant benefits of LVRS on **mortality, exercise capacity** and **SGRQ** were seen in patients with upper lobe emphysema and low exercise capacity (<40W in men and < 25W in women). LVRS led to increased mortality and deterioration in exercise capacity in patients with non-upper lobe emphysema and high exercise capacity. Some benefits were seen in patients with upper lobe emphysema and high exercise capacity and in patients with non- upper lobe emphysema and low exercise capacity but these were less marked ²⁴⁶. **Ib**

	Low exercise capacity	High exercise capacity
Upper lobe emphysema	↓ Mortality (RR 0.47) ↑ Exercise (OR ∞) ↑ SGRQ (OR 8.38)	→ Mortality (RR 0.98) ↑ Exercise (OR 5.81) ↑ SGRQ (OR 5.67)
Non-upper lobe emphysema	→ Mortality (RR 0.81) → Exercise (OR 1.77) ↑ SGRQ (OR 7.35)	↑ Mortality (RR 2.06) ↓ Exercise (OR 0.90) → SGRQ (OR 1.35)

Transplantation

COPD patients are considered potentially to be in the transplant window if they meet the following criteria ²⁵³: **IV**

- FEV₁ < 25% of predicted (without reversibility)
- and/or PaCO₂ ≤ 55mmHg (7.3kPa) and/or elevated pulmonary artery pressures with progressive deterioration, e.g. cor pulmonale
- preference should be given to those patients with elevated PaCO₂ with progressive deterioration who require long-term oxygen therapy, as they have the poorest prognosis.

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Older patients have significantly worse survival rates following transplantation and the following age limits are suggested ²⁵³: **IV**

- single lung transplants ~ 65 years
- bilateral lung transplants ~ 60 years.

In a case series of 306 consecutive lung transplants for emphysema **hospital mortality** was 3.9%, overall **five year survival** was 58.6%±4.4%, and there was no difference in alpha1-antitrypsin deficient patients. Better 5 yr survival rates were achieved by bilateral compared to single lung transplants 66.7%±4.0% vs 44.9%±6.0%)²⁵². **III**

Lung transplantation leads to improvements in **FEV₁, exercise capacity and quality of life** ²⁵⁵. **III**

Bilateral lung transplantation results in a greater improvement in FEV₁, but improvements in exercise capacity are not always significantly greater ²⁵⁵. **III**

LVRS vs Transplantation

▷ GDG consensus statements

LVRS is an alternative to lung transplantation in selected patients. **IV**

LVRS offers an earlier treatment option as a bridge to lung transplantation. **IV**

LVRS provides treatment for patients with COPD who are not otherwise candidates for lung transplantation. **IV**

▷ Health economics evidence statements

One paper was identified, however it was deemed irrelevant as it was a comparison of techniques and did not look at the cost effectiveness of lung surgery per se. This is outside the scope of the guideline.

RECOMMENDATIONS**R90**

Patients who are breathless, and have a single large bulla on a CT scan and an FEV₁ less than 50% predicted should be referred for consideration of bullectomy.

Grade C**R91**

Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living despite maximal medical therapy (including rehabilitation), should be referred for consideration of lung volume reduction surgery if they meet all of the following criteria:

Grade A

- FEV₁ more than 20% predicted
- PaCO₂ less than 7.3kPa
- upper lobe predominant emphysema
- T_LCO more than 20% predicted.

R92	<p>Patients with severe COPD who remain breathless with marked restrictions of their activities of daily living despite maximal medical therapy should be considered for referral for assessment for lung transplantation bearing in mind comorbidities and local surgical protocols. Considerations include:</p> <ul style="list-style-type: none"> ● age ● FEV₁ ● PaCO₂ ● homogeneously distributed emphysema on CT scan ● elevated pulmonary artery pressures with progressive deterioration. 	Grade C
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7.15 Alpha-1 antitrypsin replacement therapy

Alpha-1 antitrypsin deficiency is an uncommon cause of COPD, accounting for around 2% of cases of COPD. There is considerable variability in the clinical manifestations it produces: some patients having minimal or no symptoms and others developing severe emphysema at an early age. Smoking is the major factor influencing the development of emphysema but some non-smokers develop airflow limitation in later life and this appears to be associated with a history of asthma or pneumonia²⁵⁶. Recombinant alpha-1 antitrypsin is now available and replacement therapy has been proposed as a way of treating patients with alpha-1 antitrypsin deficiency.

No systematic reviews were identified on the role of alpha-1 antitrypsin replacement therapy. Dirksen²⁵⁷ was the only RCT. This was powered to detect a 50% difference in decline in FEV₁ over 3 years but there is no information about completeness of follow-up and it was underpowered to detect changes in the secondary outcome measure of changes in lung density on CT. Consideration was also given to data from the alpha-1 antitrypsin deficiency register study group²⁵⁸ (n=1129, 36 clinical centres in USA and 1 in Canada). The authors state that the results cannot be generalised, as the cohort was not a representative sample. Decisions about treatment were made by the referring physician and may be subject to bias.

An uncontrolled cohort study was identified²⁵⁹ comparing a treated German population with an untreated Danish population but this was excluded due to methodological limitations.

The GDG was aware of the difficulties in attempting an RCT in this area (large sample size required, timing of intervention, long term-follow up difficult to achieve and expensive augmentation treatment required).

▷ Evidence statements

Both Dirksen²⁵⁷ and the Registry study²⁵⁸ found no significant effect of alpha-1 antitrypsin replacement therapy on the rate of decline in FEV₁. **Ib, III**

The Registry study was the only study to examine mortality. It found that patients receiving alpha-1 antitrypsin replacement therapy had a lower **mortality** (RR 0.64 95% CI 0.43 to 0.94, p=0.02) but this may have been affected by the biases referred to above²⁵⁸. **III**

Dirksen highlighted a trend towards a reduced rate of **loss of lung tissue** assessed by CT scanning in patients receiving alpha-1 antitrypsin replacement therapy²⁵⁷. **Ib**

▷ Health economics evidence statements

Only one economic study was found²⁶⁰. This model is 12 years old and was very uncertain around efficacy, had many assumptions, is US based and the costs of therapy and treatment may now be outdated.

The guideline developers were unable to derive any evidence statements based on this health economic evidence and felt that none of this economic evidence was useful for contributing to the formulation of the recommendations.

RECOMMENDATIONS

R93

Alpha-1 antitrypsin replacement therapy is not recommended in the management of patients with alpha-1 antitrypsin deficiency (see also recommendation 11). **Grade D**

7.16 Mucolytic therapy

Many patients with COPD cough up sputum². Mucolytics are agents which are believed to increase the expectoration of sputum by reducing its viscosity. Some of these drugs, particularly N-acetylcysteine, may also have antioxidant effects which may contribute to their clinical effects.

In some European countries mucolytics are widely prescribed in the belief that they reduce the frequency of exacerbations and / or reduce symptoms in patients with chronic bronchitis. In contrast, in the U.K. mucolytics have not been recommended in previous guidelines and until recently were black listed and could not be prescribed on the NHS.

Three systematic reviews were found²⁶¹⁻²⁶³. The studies included in these systematic reviews tended to be the same trials although the systematic review by Poole et al²⁶¹ did include additional papers. In addition to the trials included in the systematic reviews there were two other papers, an RCT²⁶⁴ that compared mucolytic agents to placebo and a retrospective cohort study²⁶⁵ that looked at the risk of re-hospitalisation among COPD patients using N-acetylcysteine compared to non-users.

Stey et al²⁶³ looked at the effect of oral N-acetylcysteine compared to placebo in chronic bronchitis (11 RCTs, n=2011) with treatment durations of 12 to 24 weeks.

Grandjean et al²⁶² determined the efficacy of oral N-acetylcysteine compared to placebo in chronic bronchopulmonary disease (8 RCTs, n=1408) with a treatment duration ranging from three to six months.

Poole et al²⁶¹ undertook a meta analysis of mucolytics compared to placebo in the treatment of chronic bronchitis (22 RCTs, n=6 415) with a treatment duration of 2 to 24 months. The mucolytics included within this systematic review and meta analysis include N-acetylcysteine (NAC), ambroxol, sobrerol, carbocysteine lysine, carbocysteine sobrerol, letosteine, cithiolone,

iodinated glycerol, N-isobutyrylcysteine (NIC) and myrtol.

Most of the study participants in the three systematic reviews²⁶¹⁻²⁶³ had mild COPD, only McGavin 1995 and Petty 1990 included patients with an FEV₁ of <50% predicted. Most of the studies were carried out at least 10 years ago. There are differences between the studies in the definition of exacerbation that has been used but almost all used generally accepted definitions. This, together with the short duration of the studies makes it difficult to draw firm conclusions about effects on exacerbation rates.

The efficacy of mucolytic treatment needs to be considered in relation to the severity of COPD and duration of treatment.

Confounders not consistently accounted for in the studies include concomitant use of antibiotic therapy, drug concordance and drug type and dosage, except for the systematic review by Poole et al²⁶¹ which excluded combination mucolytics and antibiotics.

Other considerations include the degree of benefit that may be conferred for those who are repeatedly admitted to hospital with exacerbations of their COPD or those patients who have frequent or prolonged exacerbations. Poole et al.²⁶¹ highlighted that none of the studies reported the effect of treatment with mucolytics on hospitalisation due to COPD.

Oral mucolytic therapy was removed from schedules 10 and 11 (the so called “black” and “selected” lists) from 1st February 2003 and can now be prescribed. Carbocisteine is available in the UK.

▷ Evidence statements

All three systematic reviews²⁶¹⁻²⁶³ demonstrate that compared to placebo, mucolytic therapy was associated with a significant reduction in the **number of exacerbations**. **Ia**

The systematic review by Poole et al²⁶¹ also demonstrated that the odds ratio for having **no exacerbations** in the study period on a mucolytic compared to placebo was 2.22 (p<0.0001).

In addition there was a significant reduction in the **number of days of COPD illness**, a benefit of 0.56 day per month 95% CI -0.77 to -0.35, (p<0.0001) and a reduction in the **number of days on prescribed antibiotics** of 0.53 days per month (p<0.0001); however both of these analyses relied on a smaller number of primary studies where these outcomes were reported.

N-acetylcysteine (NAC) was significantly associated with a lower risk of **re-hospitalisation**, RR=0.67 (95% CI 0.53 to 0.85)²⁶⁵. **I Ib**

There were no significant differences for **lung function** parameters (FEV₁ or % predicted or PEFr) between the treatment and placebo groups (meta-analysis of 10 RCTs²⁶¹). **Ia**

Improvement of their **symptoms** was reported by 61% of patients receiving NAC compared to 35% receiving placebo (relative benefit 1.78 (95% CI 1.54 to 2.05), NNT 3.7)²⁶³. **Ia**

Cattaneo²⁶⁴ in an Italian RCT (n=60) found that there was a statistically significant **Ib**

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improvement in dyspnoea ($p < 0.02$), cough ($p < 0.02$), and difficulty in expectorating ($p < 0.02$) in patients treated with neltenequine (smokers and non smokers) compared with placebo. There was also a statistically significant improvement in sputum characteristics ($p < 0.02$) and volume ($p < 0.01$) in neltenequine treated patients when compared with placebo treated patients.

Petty et al.²⁶⁷ in an eight-week study compared iodinated glycerol to placebo in patients ($n = 361$) with severe COPD. Primary outcomes were based upon **symptom efficacy** parameters (cough frequency, severity, chest discomfort, ease in expectorating) and these were statistically significant ($p < 0.05$) in favour of iodinated glycerol. There were no statistically significant differences between treatment groups for frequency of aerosol **bronchodilator use** or frequency of **concomitant medications**.

Ib

There were no significant serious **adverse events** reported²⁶¹⁻²⁶³.

Ia

▷ Health economic evidence statements

One paper by Grandjean et al.²⁶⁸ was found on the cost effectiveness of oral NAC.

The results of the cost effectiveness analysis model show that mucolytic therapy is a cost effective treatment compared to placebo as it reduces the rate of exacerbations, leading to a reduction in hospitalisation and resource use. It is also associated with a reduction in days off sick, leading to a decrease in indirect costs.

The cost effectiveness of mucolytic therapy is mainly dependent on reducing the number of exacerbations in patients with mild disease. Six of the nine studies used to calculate the effectiveness were also included in the Cochrane review²⁶¹.

RECOMMENDATIONS

R94

Mucolytic drug therapy should be considered in patients with a chronic cough productive of sputum.

Grade B

(N.B. The recommendation has been down graded from A to B due to extrapolation. The studies were designed to look at a population of people with chronic bronchitis rather than COPD specifically).

R95

Mucolytic therapy should be continued if there is symptomatic improvement (e.g. reduction in frequency of cough and sputum production).

Grade D

7.17 Anti-oxidant therapy

There is now very good evidence for the presence of oxidative stress in people with COPD. This is critical to the inflammatory response and leads to proinflammatory gene expression²⁶⁹. Various attempts have been made to enhance the lung antioxidant activity, including administering antioxidants such as vitamin C and vitamin E. Attempts have also been made to supplement lung glutathione using glutathione itself or its precursors, particularly N-acetylcysteine (NAC)²⁷⁰. NAC also acts as a mucolytic and is considered in section 7.16, but at least some of its effects in reducing exacerbation rates may be due to the antioxidant properties of this drug.

There was a large cross over in studies found from the literature search for mucolytics and antioxidant therapy in patients with stable COPD. Papers found upon literature searching in this area were primarily focused upon epidemiology, pathophysiology or populations non specific to COPD (acute bronchitis and bronchopneumonia). Two papers were identified that were ultimately critically appraised.

Rautalahti et al ²⁷¹ undertook a long term (5 to 8 years) double blind placebo controlled RCT in Finland to look at the effect of alpha-tocopherol and beta₂-carotene supplementation (ATBC) on COPD symptoms. n=10284 for symptom follow-up.

The ATBC Cancer Prevention Study Group 1994 published a separate paper highlighting the design, methods, participant characteristics and concordance to the alpha tocopherol and beta₂-carotene lung cancer prevention study²⁷². This paper provided quality appraisal information.

Epidemiological studies have looked at the relationship between dietary antioxidant intake, lung function impairment and the effects of smoking. These studies do not allow conclusions to be drawn about causality but may indicate areas for future research.

▷ Evidence statements

During the follow up the supplementations did not affect the recurrence or incidence of **chronic cough, phlegm or dyspnoea**. The authors conclude that the results indicate **no** benefit from supplementation with alpha tocopherol or beta₂-carotene on the symptoms of COPD but support the beneficial effect of dietary intake of fruit and vegetables ²⁷¹. **Ib**

Neither of the antioxidant supplements had a statistically significant effect on the risk of being **admitted to hospital** due to a COPD diagnosis ²⁷¹. **Ib**

RECOMMENDATIONS

R96

Treatment with alpha-tocopherol and beta-carotene supplements, alone or in combination, is not recommended.

Grade A

7.18 Anti-tussive therapy

Cough is the most common symptom of COPD but anti-tussive therapy is not used in the UK. This may be because of a lack of data to support their efficacy. When considering studies in this area it is important to note the difficulty in demonstrating effectiveness with objective criteria.

No systematic reviews of anti-tussive therapy were found. Four RCTs were identified ²⁷³⁻²⁷⁶ and 1 Polish observational study ²⁷⁷.

All 5 studies had methodological limitations which included a range of issues such as under-powering, small sample sizes, potential systematic biases and confounders, short duration of studies, variability in measuring compliancy and variability in reporting outcomes as either intention to treat or per protocol analysis. In some cases a heterogeneous group of respiratory disorders was reported.

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Drugs included Helicidine vs. placebo ²⁷⁶, Mogueisteine vs. codeine ²⁷⁴, Mogueisteine vs. Dextromethorphan ²⁷⁵ and Mogueisteine vs. placebo ²⁷³.

Due to the methodological limitations apparent in these trials all results should be treated with caution and hence the GDG felt it inappropriate to present evidence statements based on these data.

RECOMMENDATION

R97

Antitussive therapy should not be used in the management of stable COPD.

Grade D

7.19 Prophylactic antibiotic therapy

Prophylactic antibiotic therapy was used some years ago in an attempt to prevent exacerbations and there has been renewed interest in this area recently.

One systematic review²⁷⁸ was identified which was relevant to the use of prophylactic antibiotic therapy in chronic bronchitis. Although the methodology of the systematic review was of good quality the nine studies²⁷⁹⁻²⁸⁷ (n=1055) contained within the review suffered from the methodological issues referred to below.

6 RCTs were found with situation specific populations relevant to COPD ^{282;286;288-291}. With all of these papers methodological limitations were evident that precluded the relevance of the results. Many of the papers pre dated the Consort Statement ²⁹² and hence lacked detail. The GDG were also mindful of the change in COPD definition and the prevalence of other causes of chronic cough at this time and hence the relevance or otherwise of papers identified from the 1950s and 60s.

Methodological limitations included under-powering, small sample sizes, lack of operational definitions, systematic bias, potential confounders, lack of standardisation or technical details and heterogeneity of results.

A further 9 papers of varying research design were excluded due to heterogeneity of the study population ^{279;293-300}.

The results of all of these trials should be treated with caution due to the inherent methodological limitations and in light of these the GDG felt it inappropriate to present evidence statements based on these data.

RECOMMENDATION

R98

There is insufficient evidence to recommend prophylactic antibiotic therapy in the management of stable COPD.

Grade D

7.20 Multi-disciplinary management

Doctors, nurses and physiotherapists are essential members of the multi-disciplinary team managing patients with COPD. In more severe COPD the multidisciplinary team will also include an occupational therapist, dietician, social worker, mental health trained worker, behaviour nurse therapist, clinical psychologist or liaison psychiatrist. These individuals may fulfil a variety of roles including those listed below.

Many of these activities may be undertaken in the clinic or in the practice as part of routine care by the practitioner seeing the patient but in certain circumstances the patient may need to be referred to a specialist department e.g. physiotherapy. Multi-disciplinary working is breaking down historic demarcation of roles and many of the activities in managing COPD can be undertaken by individuals from different professional backgrounds. Competencies are more important than professional boundaries.

RECOMMENDATION

R99 R100	COPD care should be delivered by a multidisciplinary team.	Grade D
	<p>The following functions should be considered when defining the activity of the multidisciplinary team:</p> <ul style="list-style-type: none"> ● assessing patients (including performing spirometry, assessing the need for oxygen, the need for aids for daily living and the appropriateness of delivery systems for inhaled therapy) ● managing patients (including non-invasive ventilation, pulmonary rehabilitation, hospital-at-home / early discharge schemes, providing palliative care, identifying and managing anxiety and depression, advising patients on relaxation techniques, dietary issues, exercise, social security benefits and travel) ● advising patients on self-management strategies ● identifying and monitoring patients at high risk of exacerbations and undertaking activities which aim to avoid emergency admissions. ● advising patients on exercise ● education of patients and other health professionals. 	Grade D

7.20.1 Respiratory nurse specialists

Research on the role of the clinical nurse specialist (CNS) in COPD is scarce. Unlike the role of the CNS in asthma, where the role is established in the BTS / SIGN guidelines for asthma²⁷, and where structured review of the patient by nurses has a clearer evidence base.

COPD specialist nurses are found both in the primary and secondary care settings.

Their role varies from place to place depending on local circumstances. But there are some common themes.

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Education of patients and their carers is a key component of their work. Nurses often have more time to spend with patients and their carers than doctors and patients may feel less inhibited about asking questions or showing their lack of understanding. In their work with patients, nurses will cover many of the topics discussed in Appendix C.

Support and education for other professionals caring for COPD patients, through formal and informal education sessions. Sessions on use of spirometry and early detection of COPD and on the topics covered above.

Co-ordination of care: The nurse is usually the main point of contact for the patients and their families and as such provides them with a link to the multidisciplinary team.

Through this they may pre-empt or prevent hospital admission by early intervention.

Through needs assessment they can refer patients to other professionals e.g. dietician, social services.

Assessing and monitoring stable COPD over time: through use of spirometry, oxygen saturation and symptom measurements e.g. the BORG breathlessness scale.

They provide **psychological and emotional support** for the patient and their family. Through advice on anxiety management, helping them deal with issues of loss of role in the family.

Nurse prescribing, an increasing number of nurses can now prescribe, allowing them to adjust treatments according to patient's needs.

Home care provision. Nurses play a pivotal role in home care provision both in the stable COPD and during exacerbation.

Oxygen Assessment, Nurses are often involved in oxygen assessments. They monitor patients on LTOT through home assessment of oxygen saturation levels, spirometry and symptom measurement, and for evidence of heart failure.

Monitoring of patients on **home ventilation**.

Hospital-at-home: Other nurses are involved in "hospital-at-home" for COPD patients. They assess and monitor patients at home who would otherwise have required hospitalisation due to their exacerbation.

Role of the Respiratory Nurse Consultant: Can be seen as evolving COPD nursing further, not just in drug management but also in other therapeutic and supportive interventions.

Due to the time limitations within the guideline development process a systematic literature search and formal critical appraisal process was not undertaken in this area, see section 2.4.1. However, a MEDLINE and Cochrane Database search, and a selective review of frequently cited papers and key review articles was undertaken. The authors of a systematic review on the role of respiratory nurse specialists which is under development³⁰¹ were also contacted and they provided a database of relevant papers which included the grey literature. These studies were reviewed as part of the development of an expert opinion background paper which was then discussed by the guideline development group.

There is little robust evidence relating to the role of respiratory nurses in COPD. One systematic review was identified³⁰² of home care by outreach nursing. Some of the studies related to specific

aspects of COPD care (e.g. hospital-at-home schemes) which are covered elsewhere in the guideline.

▷ GDG consensus statements

Respiratory nurse specialists form an important part of the multidisciplinary team managing patients with COPD. **IV**

Their role within the multidisciplinary team will vary depending on local circumstances and individual competencies. **IV**

RECOMMENDATIONS

R101

It is recommended that respiratory nurse specialists form part of the multidisciplinary COPD team.

Grade D

7.20.2 Physiotherapy

Respiratory physiotherapy is a specialised area of care which has three main aims:

- to help reduce the work of breathing associated with respiratory disease
- to help restore patients' maximal function
- to help improve peripheral and respiratory muscle weakness.

Core treatments delivered by physiotherapists include techniques to reduce the work of breathing using for example relaxed breathing control in combination with positioning to maximise the function of the respiratory muscles and enhance diaphragmatic displacement. In chronic asthma, the use of diaphragmatic breathing where an element of dysfunctional breathing was identified, has shown a significant benefit on health related quality of life³⁰³. Pursed lip breathing techniques may also be effective in helping patients manage breathlessness although data is limited.

Physiotherapeutic management of dyspnoea may include sputum clearance techniques where copious secretions cause distress. Therapists commonly use the active cycle of breathing technique (ACBT) with forced expirations to enhance expectoration. The use of the forced expiration technique (FET) appears to enhance peripheral mucus transport in patients with normal or high elastic recoil. Where secretions are basal and particularly tenacious gravity assisted drainage with manual chest percussion may aid clearance.

An extensive literature search was undertaken in this area and yielded a hit rate of 314 studies. 286 of these were excluded, as they did not focus upon the area for address, papers tended to focus on rehabilitation and / or exacerbations (addressed elsewhere in the guideline) and inspiratory muscle training.

No systematic reviews were found and overall there was generally limited research in this area. Most of the studies identified were of small sample sizes (range 7 to 44 participants). None of the identified trials were UK based. Six of the eight identified randomised controlled studies were excluded due to methodological limitations and also because short-term interventions

only were considered³⁰⁴⁻³⁰⁹. A cohort study by Kolaczowski et al.³¹⁰ was also excluded due to limited methodological details being available.

One randomised controlled trial was identified³¹¹ and one quasi-experimental study³¹² that met quality appraisal criteria.

Christensen et al.³¹¹ 1990 in a Danish RCT looked at the long term treatment of chronic bronchitis (n=44) with positive expiratory pressure mask and chest physiotherapy. Diaphragmatic breathing performed through a PEP mask followed by forced expirations and cough was compared to self-administered diaphragmatic breathing followed by forced expirations and cough.

Casciari et al.³¹² undertook a quasi-experimental study (controlled study without randomisation) in an American population, with a sample size of n=22. Effects of breathing retraining in patients with COPD were compared. The intervention group received exercise and breathing training and a comparison group received exercise reconditioning alone.

▷ Evidence statements

Casciari et al.³¹² found that the respiratory rate in the group receiving breathing retraining at rest decreased from 17.4 breaths per minute (bpm) to 15 bpm after the exercise component (not significant) to 9.7 bpm after the breathing retraining (p<0.01). During maximal exercise, the respiratory rate decreased from 32.6 bpm (baseline) to 30.3 bpm after exercise (non significant) to 23.8 bpm after breathing retraining (p<0.05).

IIa

Tidal volume during exercise increased from 800ml at baseline to 910ml after exercise (not significant) to 1320ml after breathing retraining (p<0.05)³¹².

During exercise, PaO₂ increased between exercising and breathing retraining (p<0.01)³¹².

After 9 weeks, PaO₂ and base excess differed significantly between the two groups in favour of the breathing retraining group; PaO₂ breathing retraining 77.5 compared to the control group 60.0 (mmHg)³¹².

There were no significant differences in exercising respiratory rates or the tidal volume and arterial blood gases during rest and exercise for the group receiving exercise reconditioning only³¹².

“The increment in work performance during the final three weeks of the program was significantly higher in the group that received breathing retraining (p<0.002). Data indicate that compared with controls, exercise performance increased significantly in the group of COPD subjects who received breathing retraining compared to those who received exercise only”³¹².

Christensen et al.³¹¹ compared diaphragmatic breathing performed through a PEP mask followed by forced expirations to self-administered diaphragmatic breathing followed by forced expirations. The PEP group reported significantly less **cough** (p=0.025), less **mucus production** (p=0.013) fewer **exacerbations** compared to the control group (6 vs. 28).

Ib

There was a significantly lower rate of **antibiotic** use in the PEP group compared to the control ($p < 0.05$). The use of **mucolytics** was also significantly lower in the PEP group compared to the control group ($p < 0.05$)³¹¹.

There was a statistically significant difference in the FEV₁ at one year in favour of the PEP group ($p = 0.039$)³¹¹.

RECOMMENDATIONS

R102

If patients have excessive sputum, they should be taught:

- the use of Positive Expiratory Pressure masks
- active cycle of breathing techniques.

Grade B
Grade D

7.20.3 Identifying and managing anxiety and depression

COPD leads to disabling and distressing symptoms. Patients often become socially isolated and have to give up activities that they enjoy. These factors may lead to the development of anxiety and or depression. The symptoms and signs of these may be similar to those of COPD itself and may be overlooked. Depression is also relatively common and the two conditions may simply co-exist; however, the presence of depression or anxiety may significantly worsen patients' quality of life. A concurrent depressive disorder may bring the patient into a vicious circle: the depressed mood reduces the patient's ability to cope with the physical symptoms, which become less tolerable. The psychosocial effects of the disease may be enforced by the depressed mood.

Two systematic reviews were identified^{313;314}. One³¹³ examined the prevalence of depression in COPD, the other³¹⁴ examined psychologically-based interventions to reduce anxiety and panic in patients with COPD. Two additional RCTs were critically appraised one with $n = 36$ ³¹⁵ and the other with $n = 56$ ³¹⁶ but this was rejected because of methodological limitations. One randomised self-controlled crossover trial was critically appraised³¹⁷ and 3 case-controlled studies³¹⁸⁻³²⁰, 2 uncontrolled cross-sectional cohort studies^{321;322} and 4 uncontrolled longitudinal cohort studies³²³⁻³²⁶ were critically appraised. One of the case controlled studies³¹⁸ and two of the cohort studies^{324;325} were rejected because of methodological limitations.

Factors for consideration within this topic include:

- considerable pre-screening of patients
- the majority of studies are cohort studies with poor methodology
- small patient populations in some studies
- studies are in a number of different settings; outpatient, inpatient, community
- a number of different rating scales with different thresholds for depression are used in studies (see identification of depression section below)
- the majority of studies are uncontrolled
- subjects baseline FEV₁ varies considerably i.e. patients have different severity of COPD.

▷ Evidence statements

Overall prevalence of anxiety and depression

In the systematic review of 10 case-control and uncontrolled trials³¹³ the methodologically best-rated studies did not find a statistically significant difference in the **prevalence** of depression between patients with COPD and controls. **III**

A striking difference in prevalence of depression was seen between studies (between 6% and 42%).

Van Manen et al³¹⁹ (case-control (n=521)) found, 21.6% of COPD patients had a score of 16 or more on the CES-D scale compared with 25% of patients with severe COPD (FEV₁ <50%), 19.6% of those with mild to moderate COPD (FEV₁ 50-80%), and 17.5% of the controls. **I Ib**

Results were adjusted to account for demographic variables and co morbidity. In the multivariate analysis there appeared to be no risk for depression in the total group of COPD patients (OR 1.5, 95% CI 0.8 to 2.6) or in the subgroup of patients with mild to moderate COPD (OR 1.1, 95% CI 0.5 to 2.1).

Patients with severe COPD had a 2.5 times greater risk for depression than controls (OR 2.5, 95% CI 1.2 to 5.4).

Lacasse et al³²² in a cross-sectional cohort (n = 109) found that 62 (57%; 95% CI 47 to 66) patients with COPD presented significant **depressive symptoms** (GDS score: 11-19). **III**

In addition, 20 patients (18%; 95% CI 12 to 27) were severely depressed (GDS > 20/30).

Yohannes et al³²¹(cross-sectional cohort (n = 137)) found that 25 (18%) of patients were **clinically anxious** and 57 (42%) were **clinically depressed**. Twenty-one of the 57 depressed COPD subjects (37%) had a clinical anxiety score > 3 whereas four of the 80 non-depressed COPD subjects (5%) had a clinical anxiety score > 3 (p<0.001). **III**

In the depressed elderly COPD population, 17 (30%) were mildly depressed (MADRS score 7-19); 39 (68%) were moderately depressed (MADRS score 20-34) and one (2%) was severely depressed (MADRS score 35-60)³²¹.

The most powerful predictor of severity of anxiety was MADRS (the more depressed patients being more likely to suffer anxiety)³²¹.

Relationship of depression to severity of COPD

Van Manenet et al³¹⁹ (case-control (n = 521)) found that 21.6 compared with 25% of patients with **severe** COPD (FEV <50%) had a score of 16 or more on the CES-D scale, compared with 19.6% of those with **mild to moderate** COPD (FEV 50-80%), and 17.5% of the controls. **I Ib**

Results were adjusted to account for demographic variables and co morbidity. In the multivariate analysis there appeared to be no risk for depression in the total group of COPD patients (OR 1.5, 95% CI 0.8 to 2.6) or in the subgroup of patients with mild to moderate COPD (OR 1.1, 95% CI 0.5 to 2.1)³¹⁹.

Patients with severe COPD had a 2.5 times greater risk for depression than controls (OR 2.5, 95% CI 1.2 to 5.4)³¹⁹.

The risk of depression was significantly increased in patients with a reversibility FEV₁ of < 1.1% predicted (OR 3.7, 95% CI 1.3 to 11)³¹⁹.

Lacasse et al³²² (cross-sectional cohort (n = 109)) found that depression scores correlated with 7 of the 8 domains of the **SF-36**. Depression was associated with a substantial impairment in psychological and physical functioning. **III**

Yohannes et al³²¹ cross sectional cohort (n = 137) found that the most powerful predictor of severity of depression was the MRADL score which accounted for 22% of the variance in MADRS (the more disabled patients being more likely to suffer depression). **III**

Depressed COPD patients (identified by GMS) had poorer **quality of life** scores compared with non-depressed patients (54 ± 1.8 vs. 36 ± 1.2 , $p = 0.04$)³²¹.

Depressed COPD patients (identified by GMS) had lower mean **MRADL** scores compared with non-depressed patients (9.9 ± 0.7 vs. 14.4 ± 0.5 , $p = 0.05$)³²¹.

Van Manen et al³¹⁹ (case-control (n = 521)) found that the risk of depression was significantly increased in patients with COPD with severe impaired physical functioning (OR 5.6, 95% CI 1.6 to 19.9). **IIb**

Yohannes et al³²¹ cross sectional cohort (n = 137) found that depressed COPD patients (identified by GMS) had higher prevalence of hospital admission episodes within the previous 12 months compared with non-depressed patients (34/57 (60%) vs. 28/80 (35%), $p = 0.007$). **III**

Mean inpatient days of hospitalisation for depressed patients was 9.8 ± 1.7 and non-depressed was 2.3 ± 0.6 days ($p < 0.0001$)³²¹.

Yohannes et al³²⁶ (uncontrolled longitudinal cohort study (n = 137)) found that depression scores and QOL scores do not predict **mortality**. **IIb**

Identification of depression and anxiety in COPD patients

The Brief Assessment Schedule Depression Cards (BASDEC) has been validated in patients with COPD including those over 60 years of age^{320;321;326}. **IIa**

Other scales that have been used are: **III**

- Hospital Anxiety and Depression Scale (HADS)³²⁷
- Geriatric Depression Scale³²²
- Geriatric Mental State Schedule³²¹
- Montgomery Asberg Depression Rating Scale³²¹
- Centre for Epidemiological Studies Depression Scale (CES-D)³¹⁹
- Clinical Global Improvement Scale³¹⁵
- Hamilton Depression Rating Scale (HAM-D)³¹⁵
- Patient Related Anxiety Scale.³¹⁵

Management (pharmacological/non-pharmacological) of anxiety and depression in COPD patients

There is a lack of evidence that **psychologically based interventions** reduce anxiety in COPD ³¹⁴. **Ia**

Borson et al. ³¹⁵ (RCT (n = 36)) found that **Nortriptyline** treatment was superior to placebo for treatment of depression. **Ib**

CGI rating showed that 10/13 (77%) patients receiving active drug experienced a sustained improvement in mood disorder compared with 2 out of 17 (12%) patients taking placebo ³¹⁵.

Scores on the HAM-D improved by 60% in the nortriptyline group (29.6 ± 7.6 to 12.6 ± 6.9) compared with 17% (29.5 ± 6.4 to 22.8 ± 11.3) in the placebo group ($p = 0.01$)³¹⁵.

Nortriptyline treatment was accompanied by marked improvements in anxiety. Anxiolytic effects of nortriptyline were reflected by a 45% reduction in mean score on the pRAS (54.3 ± 17 to 29.9 ± 11.4) compared with only 4% improvement (47.4 ± 21.5 to 45.3 ± 28.6) in patients receiving placebo ($p < 0.005$)³¹⁵.

Oxygen therapy improved anxiety but not depression in a small subgroup of patients who were hypoxic ³²⁸. **IIa**

Yohannes et al ³²⁹ found that patient uptake of fluoxetine was poor (14 out of 57 patients aged 60-89 years). The reasons for refusing treatment varied but were largely due to misapprehension by the patient. **III**

▷ GDG consensus statements

The presence of depression or anxiety may be overlooked in patients with COPD because of the overlap of many of the symptoms of these conditions and COPD. **IV**

A number of assessment tools have been used to identify anxiety and depression in patients with COPD. Many of these were not designed to be used in, and have not been validated for use in patients with chronic disease. **IV**

Depression and anxiety are more common in patients with severe COPD and particularly in those who are hypoxic or severely dyspnoeic than in normal individuals. **IV**

The patient's acceptance of treatment may be influenced by the way in which the diagnosis is presented to the patient and by a discussion about the reasons for their concern about starting treatment. **IV**

RECOMMENDATIONS

R103	Health care professionals should be alert to the presence of depression in patients with COPD. The presence of anxiety and depression should be considered in patients: <ul style="list-style-type: none"> ● who are hypoxic (SaO₂ less than 92%) ● who have severe dyspnoea ● who have been seen at or admitted to a hospital with an exacerbation of COPD. 	Grade D
R104	The presence of anxiety and depression in patients with COPD can be identified using validated assessment tools.	Grade D
R105	Patients found to be depressed or anxious should be treated with conventional pharmacotherapy.	Grade A
R106	For antidepressant treatment to be successful, it needs to be supplemented by spending time with the patient explaining why depression needs to be treated alongside the physical disorder.	Grade C

7.20.4 Nutritional factors

Many patients with COPD lose weight as a consequence of decreased food intake as a result of breathlessness, altered absorption as a result of hypoxia and increased resting energy expenditure as a result of the increased work of breathing³³⁰. The mechanisms of this remain unclear but probably relate to systemic effects of cytokines, particularly TNF- α ³³¹.

There has been some interest in the consequences of this weight loss, particularly whether it is an independent predictor of outcome, and whether interventions are effective both at increasing weight and influencing outcome.

One systematic review was identified³³² that compared oral, enteral or parenteral nutritional support (nutritional support was defined as any caloric supplementation given for more than two weeks) with placebo or usual diet or other treatment regimens such as anabolic substances.

Two additional randomised controlled trials were critically appraised^{333;334} and 14 cohort studies were critically appraised³³⁵⁻³⁴⁸, all but two of these^{347;348} had methodological limitations and hence were subsequently excluded.

Factors for consideration within this topic include:

- considerable pre-screening of patients
- the majority of studies are cohort studies with poor methodolog
- small patient populations in some studies
- studies are in a number of different settings; outpatient, inpatient, community
- not yet established which outcome best predicts nutritional status (weight, BMI, fat free mass etc)
- the majority of studies are uncontrolled
- some studies rely on patient recall of diet and weight.

▷ Evidence statements

Landbo et al ³³⁸ (uncontrolled cohort study n = 2132) found that there was an independent effect of Body Mass Index (BMI) on **survival**, with significantly higher mortality seen in underweight subjects than in those of normal weight. **I Ia**

The effect of BMI on **all-cause mortality** is dependent on the stage of COPD. A significant effect of BMI on all-cause mortality was present only in subjects with severe COPD (FEV₁ % pred <50) in whom mortality was lowest in the obese and increased with decreasing BMI (p<0.001)³³⁸.

COPD mortality was highest in underweight subjects and decreased for increasing BMI in both men and women (p<0.001). The impact of BMI on COPD mortality was stronger than that on all-cause mortality, with RRs between the lowest and highest BMI of 5.56 (range 2.47 to 12.54) and 7.17 (range 2.45 to 21) in men and women respectively³³⁸.

Schols et al ³⁴⁶ (retrospective survival analysis n = 400) found that **survival** was significantly decreased in both underweight and normal weight patients as compared with overweight and obese patients (p<0.0001). **I Ib**

Marquis et al ³³⁹ (uncontrolled cohort n = 142) found that a midthigh muscle cross-sectional area obtained by CT scan (MTCSAct) <70 cm² was associated with a fourfold increase (95% CI 1.52 to 8.09) in **mortality** rate, independently of any other variables (p = 0.004). **I Ib**

Compared with patients with an FEV₁ >50% predicted and a MTCSAct > 70 cm², those with an FEV₁ < 50% predicted and a MTCSAct > 70cm² had a **mortality** odds ratio of 3.37 (95% CI 0.41 to 28), whereas patients with an FEV₁ <50% predicted and a MTCSAct < 70cm² had a mortality odds ratio of 13.16 (95% CI 1.74 to 99.20)³³⁹.

In all three stages of COPD the highest mortality was found in underweight subjects. In subjects with severe COPD mortality continued to decrease with increasing BMI, with an RR of 7.11 (range 2.97 to 17.05) in underweight compared with obese subjects. A similar but weaker association was found in subjects with mild and moderate COPD³³⁹.

Schol et al ³⁴⁶ (post hoc analysis of prospective study) found that a history of weight loss was significantly related to decreased **survival** (p<0.005). **I Ib**

Weight gain (>2kg/8wk) in depleted and non-depleted patients with COPD was significantly associated with decreased mortality risk³⁴⁶.

Prescott et al ³⁴⁰ (uncontrolled cohort study n = 1612) found that among subjects with COPD, **all-cause mortality** was increased in subjects who lost > 1 BMI unit. An excess mortality was seen in subjects who lost >3 BMI units (~10 kg). Mortality in subjects who gained weight did not differ significantly from those with a stable weight. **I Ib**

Effect of weight change on mortality did not differ with severity of COPD. The effect of baseline BMI was U shaped with excess mortality associated with both under and overweight. In subjects with mild or moderate COPD and in subjects without COPD, no modification of the effect of baseline BMI was found; however, among patients with severe COPD (FEV % pred <50), effect of weight change differed with baseline weight³⁴⁰.

In all groups, weight loss was associated with increased mortality; however, normal and underweight subjects (BMI <25) with severe COPD differed from the remaining in experiencing increased survival after weight gain. The reverse was found in the overweight and obese (BMI > 25), among whom the best survival was seen in subjects who had stable weight or who had decreased their weight³⁴⁰.

The highest risks were found in subjects who lost weight between examinations, whereas weight increase did not seem to increase risk of **COPD-related death**. Unlike all-cause mortality, the risk function for baseline BMI was linear with the lowest risk seen in patients who increased their weight³⁴⁰.

Sahebji et al³⁴¹ (uncontrolled cohort study n = 126) found that:

I Ib

- BMI is significantly correlated with diffusing capacity for carbon monoxide (**DLCO**), **FEV₁** and the **FEV₁/FVC** ratio (p<0.001).
- Underweight patients (BMI < 20) are significantly more likely to have abnormally low levels of DLCO compared with normal weight (BMI = 20-27) and overweight patients (BMI>27) (p<0.001).
- Underweight patients (BMI < 20) are significantly more likely to have lower FEV₁ and FEV₁/FVC compared with normal weight (BMI = 20-27) and overweight patients (BMI>27) (p<0.001).
- Underweight (BMI < 21 kg/m²) patients with COPD are more **dyspnoeic** than normal weight (BMI 21-28 kg/m²) (p = 0.03). Dyspnoea scale normal weight 2.5 ± 1.2 vs. underweight 3.1 ± 0.9.
- Carbon monoxide diffusing capacity (DLCO) was significantly lower in underweight compared with normal weight patients. DLCO % predicted normal weight 57 ± 17 vs. underweight 36 ± 11 (p<0.001).

Maximum inspiratory pressure (Pimax) was significantly lower in underweight patients compared with normal weight patients. Pimax cmH₂O normal weight 66 ± 19 vs. underweight 55 ± 18 (p = 0.02). Pimax % predicted normal weight 62 ± 17 vs. underweight 52 ± 17 (p = 0.03).

Gray-Donald et al³⁴³ (uncontrolled cohort study n = 135) found that in underweight COPD subjects **peak exercise performance** and **ventilatory muscle strength** are decreased.

I Ib

Submaximal exercise performance, dyspnoea and overall quality of life are not affected³⁴³.

Schols et al³⁴⁴ (uncontrolled cohort study n = 255) after stepwise analysis on total group of patients (normal weight and underweight) established that the functional measures Pimax, maximal expiratory pressure (Pemax) and 12 minute walking distance were better predicted by FFMPiBW (fat-free mass as a percentage of ideal body weight) than PiBW (percent ideal body weight).

I Ib

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Baarends et al ³³⁶ (uncontrolled cohort study n = 62) found that peak VO₂ correlated significantly with the FFM index (kg/m²; r = 0.57, p<0.001) BMI (kg/m²; r = 0.56, p<0.001) and intracellular water (kg/m²; r = 0.54, p<0.001). **I Ib**

Depletion of FFM contributes to a blunted tidal volume and decreased peak oxygen pulse in response to peak exercise (multiple regression analysis)³³⁶.

Stepwise analysis demonstrated that the fat free mass index and transfer factor for carbon monoxide (T_LCO) explained 53% of the variation in peak VO₂³³⁶.

Marquis et al ³³⁹ (uncontrolled cohort n = 142) also found that a midhigh muscle cross-sectional area obtained by CT scan (MTCSAct) <70 cm² was associated with a fourfold increase (95% CI, 1.52 to 8.09) in mortality rate, independently of any other variables (p = 0.004). **I Ib**

Engelen et al ³³⁷ (uncontrolled cohort n = 72) found that depleted patients are more likely to exhibit lower values for respiratory and peripheral skeletal muscle strength than nondepleted patients. **I Ib**

Measures of muscle strength were lower in the depleted group, but only the difference in handgrip strength reached statistical significance (p<0.01)³³⁷.

Sahebji et al ³⁴¹ (uncontrolled cohort study n = 126) found that 46.8% of COPD patients (n = 126) had nutritional abnormalities (i.e. underweight BMI <20kg/m² = 23% and overweight BMI >27 kg/m² = 23.8%). **I Ib**

Schols et al ³⁴⁴ (uncontrolled cohort study n = 255) found that depletion of body weight, fat-free mass and muscle mass is most pronounced in patients suffering from chronic hypoxemia and in normoxic patients with severe airflow obstruction (FEV₁<35%) but also occurred in ± 25% of patients with moderate airflow obstruction. **I Ib**

Prescott et al ³⁴⁰ (uncontrolled cohort study n = 1612) found that in females, baseline BMI was lower in people with impaired lung function (p = 0.009) whereas no difference was found in males. **I Ib**

In both females and males, weight changes differed with lung function with mean weight loss seen in subjects with poorest lung function and mean weight gain seen in subjects without airways obstruction (p<0.001)³⁴⁰.

The proportion of subjects that lost > 1 BMI unit (~3.8kg) increased with decreasing lung function reaching 35.3% and 27.4%, respectively in females and males with severe COPD (p<0.001)³⁴⁰.

Gray-Donald et al ³⁴³(uncontrolled cohort study n = 135) found that 24.4% of COPD subjects had % IBW of <90%. **I Ib**

86% of those with a weight of <80% IBW and 60% of those with weight < 90% had an abnormally low triceps skin fold thickness (TSF) (< 60% standard)³⁴³.

Among underweight subjects (IBW <90% predicted), 32% reported weight loss of >5% in the last year³⁴³.

When compared with their usual weight, 81% of underweight subjects had lost > 10%

body weight, with self-reported weight losses of as much as 43%³⁴³.

The mean weight loss from usual weight in the underweight group was 17% ($\pm 13\%$)³⁴³.

The systematic review / meta analysis³³² (n = 277 subjects) found that there was no evidence from this analysis that simple nutritional support had any significant effect on anthropometric measures, lung function or exercise capacity in patients with stable COPD.

Ia

Otte et al³³³ (RCT n = 28) found that nutritional supplementation produced weight gain (fed mean 1.5kg vs. 0.16kg control p<0.01) in malnourished patients with pulmonary emphysema, but it did not change other indices of well-being.

Ib

Schols et al³⁴⁶ (survival analysis n = 603) found that nutritional intervention resulted in a significant increase in weight, fat-free mass and fat-mass whereas no significant changes in any of these parameters were seen in the placebo group.

IIb

Relative to a similar body weight gain as the group receiving nutritional support only, the anabolic steroids group showed a larger increase in fat-free mass and maximal inspiratory mouth pressure without causing adverse side effects³⁴⁶.

On the basis of weight change > 2kg/8wk, 50% of the treated patients were characterised as responders, including 24% of placebo group³⁴⁶.

In 62% of the patients an improvement in Pimax was shown³⁴⁶.

Weight gain in depleted and non-depleted patients with COPD was significantly associated with decreased mortality risk³⁴⁶.

▷ GDG consensus statements

BMI may be less reliable as an index of nutritional status in older patients because of age-related changes in height, posture and ratio of fat to muscle. In these patients changes in weight, particularly if greater than 3kg should be noted and acted upon.

IV

Exercise may augment the effects of nutritional supplementation on weight gain.

IV

RECOMMENDATIONS

R107

BMI should be calculated in patients with COPD (See section 6.6):

Grade D

- the normal range for BMI is 20 to less than 25³⁴⁹
- if the BMI is abnormal (high or low), or changing over time, the patient should be referred for dietetic advice
- if the BMI is low, patients should also be given nutritional supplements to increase their total calorific intake, and be encouraged to take exercise to augment the effects of nutritional supplementation.

The NICE guideline *Nutritional support in adults: oral supplements, enteral and parenteral feeding*, can be referred to when it is available (scheduled for publication in December 2005).

R108

In older patients attention should also be paid to changes in weight, particularly if the change is more than 3 kg.

Grade D

7.20.5 Palliative care

Palliative care is the active total care of patients and their families by a multiprofessional team when the patient's disease is no longer responsive to curative treatment. It is similar, but distinct from terminal care. Although traditionally linked to cancer, it is increasingly recognized that palliative care has a role for patients dying from non-cancer conditions including COPD.

The management of severe COPD has a large palliative element and focuses on symptom control and optimising quality of life.

Among its principles, palliative care promotes open communication between doctor and patient, which includes access to information about diagnosis and prognosis where appropriate. The prognosis for some patients with COPD can be very poor: a recent audit of 1400 patients admitted to hospital with an exacerbation of COPD showed that 14% had died within 3 months^{347,350}. However, for most patients with COPD, the interval from diagnosis to death may be many years, so that choosing the right moment to discuss the prognosis of the disease and the patients views on issues such as ventilatory support or advance directives can be difficult.

There was limited evidence about palliative care approaches in COPD. One Cochrane systematic review was identified³⁵¹ and four qualitative studies³⁵²⁻³⁵⁵.

The systematic review³⁵¹ looked at opioids for the palliation of breathlessness in terminal illness. Although 14 RCTs were specifically related to a COPD population, there were limitations with these studies: including small sample sizes varying from 6 to 18 patients and variable time durations to drug interventions ranging from one off dose of drug through to 2 week periods. All of the COPD studies utilised a cross over design but were subject to variable washout periods.

The GDG acknowledge that palliative care is a difficult area in which to conduct research.

▷ Evidence statements

A statistically significant effect of opioids was demonstrated for **breathlessness** using non-nebulised opioids, SMD -0.40 (95% CI -0.63 to -0.17), $p=0.0006$. However this was a heterogeneous population that was inclusive of both COPD and cancer patients³⁵¹. **Ia**

There was no statistically significant effect for breathlessness in the studies using nebulised opioids.

In a subgroup analysis of nine COPD studies there was no statistically significant difference for breathlessness between the treatment and control group, SMD -0.26 (95% CI -0.44 to 0.08) $p=0.0042$ ³⁵¹. **Ia**

The four other identified studies were of a qualitative nature in their design.

Heffner³⁵⁵ used a cross sectional descriptive questionnaire in the USA to assess the attitudes of n=105 patients in a pulmonary rehabilitation program with chronic lung conditions about end-of-life decision-making. 87% of the sample constituted people with COPD.

Sullivan³⁵³ interviewed fifteen respirologists in a Canadian study to elicit what physicians told end-stage patients with COPD about intubation and mechanical ventilation.

Rhodes³⁵⁴ in a UK study interviewed nine relatives of end-stage COPD deceased patients and although this represents a small sample size it does provide useful insights derived from narrative thematic experiences. The potential limitation of this study is that due to the limited sample size it may be unrealistic to generalise the experiences outside of the one UK Health Authority area from which it was derived.

Elkington³⁵² conducted a questionnaire survey of General Practitioners of one inner London Health Authority (n=389) to establish the role that discussions of prognosis play in GP's management of patients with severe COPD.

It was not possible to derive the same type of evidence statements from these qualitative studies as from RCTs but several important themes were identified.

Emergent Themes

Areas identified by Heffner³⁵⁵ in a USA population included: patient interest in Advance Directives (AD), patient-doctor discussion about end-of-life issues and patient's interest in decision-making.

III

Patient interest in Advanced Directives (ADs)

89% of patients stated that they would be interested in learning more about ADs whilst 69% wanted to learn more explicit details about intubation and mechanical ventilation.

Patient doctor discussions about end-of-life issues

99% of patients stated that they would find discussions with physicians about ADs, intubation and mechanical ventilation acceptable. Despite their stated interests, only 19% had already discussed ADs with physicians and only 15% had had discussion about life support interventions.

There was a 50:50 split regarding whether patients thought physicians should initiate discussions or wait until patients initiated these discussion about ADs. However the data showed that waiting for the physician to initiate the discussion was an ineffective strategy; of the 20 patients who already had discussions about ADs, 19 of these had initiated these discussions themselves.

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Patient interest in decision making

Most patients wished to actively participate in decisions about life support. In the circumstances of being hospitalised with a serious illness 72% stated that they would want to decide themselves about life support.

Sullivan ³⁵³ highlighted emergent themes from a population of Canadian physicians which included; timing of the discussion, importance of “knowing” the patient, content of the discussion, framing the information, decision difficulty, style and delivery of discussion.

III

Timing of the discussion

There was agreement that an intubation and mechanical ventilation (MV) discussion should be initiated when a patient is in a stable condition.

Importance of “knowing” the patient

Knowing the patient allowed physicians to determine the patient’s perceptions of their quality of life, satisfaction with current functioning and expectations in life. All of the 15 physicians interviewed used a combination of these factors in their decisions making.

Content of the discussion

Discussions included a tube being placed down the patient throat with emphasis on discomfort and inability to eat or speak. Regardless of whether the patient chose to be intubated the availability of analgesia was discussed. Content of discussion also included that following intubation and mechanical ventilation the best a patient may hope for was return to their pre exacerbation state of health. “Death” was not stressed by name in initial discussions.

Framing the information

Information was usually framed according to the physician’s clinical judgement. The physician would take into account how successful the mechanical ventilation outcome was likely to be including eventual quality of life. A negatively framed physician discussion included palliative care.

Decision difficulty

80% of physicians highlighted the importance of family in facilitating the decision making process.

Style and delivery of discussion

Content of the narrative was similar although the style and delivery of the information varied between physicians.

Rhodes³⁵⁴ identified the following themes; quality of life, services in the community, adaptations and equipment, informal care, after death support and meeting needs.

III

Relatives reported that **quality of life** in the year before death was often very low.

Regarding **services in the community**, there was little contact with the community nursing service or social workers, none had been offered or used day care.

Those transferring home from hospital were assessed for **home adaptations**, aids and equipment, similar assessments for those who had not had a hospital admission were patchy. The central role of the GP in gaining access to services was reiterated. Often services were provided too late to be of benefit.

Many of the **informal caregivers** were elderly persons themselves and had their own health problems. None of those interviewed seemed to realise that their relative's illness had been terminal.

After death support was identified as a theme. Bereaved people within the sample as a whole valued being able to talk to their GP, ask questions and talk through the illness and death. Those who received a post-death visit or letter appreciated it. A follow-up from a district nurse was also appreciated.

In relation to **meeting needs** much of the care for this group was described as being through crisis intervention and hospital admission.

Elkington³⁵⁶ highlighted descriptive percentages from 214 UK GPs relating to discussions of prognosis in severe COPD.

III

82% of respondents agreed that GPs have an important role in discussions of prognosis. 37% of GPs agreed that they found it hard to start the discussions about prognosis with patients (and 30% of GPs stated that they left it for patients or their relative to raise the subject of prognosis).

67% stated that they found it difficult to predict prognosis for individual cases (45% of GPs stated that there was insufficient information about COPD patients in the GP records to discuss prognosis with them).

▷ GDG Consensus statement

Opioids, benzodiazepines, tricyclic anti-depressants and major tranquilizers are useful in palliating symptoms in patients in the end stages of COPD.

IV

Oxygen may also be used to palliate breathlessness not relieved by other therapies (see section 7.9).

IV

Patients dying with COPD can benefit from the services of multidisciplinary palliative care teams, including admission to hospices.

IV

RECOMMENDATIONS

R109	Opioids should be used when appropriate to palliate breathlessness in patients with end-stage COPD which is unresponsive to other medical therapy.	Grade D
R110	Benzodiazepines, tricyclic antidepressants, major tranquillisers and oxygen should also be used when appropriate for breathlessness in patients with end stage COPD unresponsive to other medical therapy.	Grade D
R111	Patients with end stage COPD and their family and carers should have access to the full range of services offered by multidisciplinary palliative care teams, including admission to hospices.	Grade D

7.20.6 Assessment for occupational therapy

The prevalence of respiratory disability in moderate and severe COPD is high. Respiratory disease has been recognised for many years as the second commonest cause of major disability in elderly people³⁵⁷, and the vast majority of respiratory disability is due to COPD. Despite this the level of community support provided to patients disabled by COPD is low. It compares unfavourably with that provided to patients with similar or even lower levels of disability caused by musculoskeletal or neurological problems^{357,358}. This may be in part the result of a lack of recognition of disability by healthcare professionals. Patients with respiratory disability do not carry an obvious 'badge' of disability such as a walking frame or a hemiparesis that marks them out (at rest) as someone in potential need of support. Until recently there has been a lack of appropriate assessment tools validated for the measurement of activities of daily living (ADL) (as opposed to quality of life) in patients with respiratory disease. Two such tools have recently been devised and validated independently³⁵⁹⁻³⁶² and can be used for the global assessment of patients. An assessment tool has been developed to assess patients needs for occupational therapy³⁶³ but this has not been validated specifically in patients with COPD.

ADL assessment, whether by questionnaire or formal occupational therapy review may take place in the outpatient setting, but commonly occurs towards the end of an inpatient stay during an exacerbation. Even when assessment has previously been performed in the stable outpatient situation it should be repeated in inpatients, particularly if patients have previously demonstrated borderline coping abilities when clinically stable. Such patients may need temporary or even permanent domiciliary support on discharge. It is well recognised that disability level is a predictor of recurrent hospital admission for COPD, though it remains unclear whether alleviation of disability or provision of appropriate support reduces admission frequency.

Occupational therapy may be relevant across the spectrum of COPD, including:

- recently diagnosed patients
- during exacerbations
- during pulmonary rehabilitation
- as part of palliative care.

▷ GDG consensus statements

Assessment tools such as the Manchester Respiratory Activities of Daily Living (MRADL) questionnaire³⁵⁹, the London Chest Activity of Daily Living scale (LCADL)³⁶² or the Canadian Occupational Performance Measure (COPM)^{363;364}, can be used to formally assess patients need for occupational therapy. **IV**

Occupational therapy assessment of patients needs may take place as part of a programme of respiratory rehabilitation, and should certainly form part of a multidisciplinary assessment and planning package prior to discharge from hospital. **IV**

RECOMMENDATIONS

R112	Patients should be regularly asked about their ability to undertake activities of daily living and how breathless they become when doing these.	Grade D
R113	Clinicians managing patients with COPD should assess their need for occupational therapy using validated tools.	Grade D

7.20.7 Social services

Patients and their carers may be entitled to claim benefits including benefits for people who cannot work and benefits for the extra costs of disability. It may be possible to receive more than one benefit at a time. As well as benefits, patients may be entitled to disabled person's tax credit (DPTC), which is not a benefit: it is a payment from the Inland Revenue for disabled people who work. DPTC is payable in addition to benefits, for example, disability living allowance, but it depends on a person's income.

Information on benefits can be obtained from The Benefits Agency telephone help line which provides information on benefits for sick and disabled people and carers. The help line can also arrange for a person to ring a claimant adviser to help them with forms completion for disability living allowance and attendance allowance.

Benefits Enquiry Line: 0800 882200

Minicom: 0800 243355

Website: www.dwp.gov.uk

Patients and their carer can also obtain advice from the Citizens Advice Bureau and The British Lung Foundation also produces a leaflet describing the benefits that may be available for patients with COPD.

▷ GDG consensus statements

There is a greater access to financial benefits for patients aged under 65 years. **IV**

The processing time for many applications for financial and social assistance reduces the potential benefits for many patients. **IV**

RECOMMENDATIONS

R114

Patients disabled by COPD should be considered for referral for assessment by a social services department.

Grade D**7.20.8 Advice on travel**

Recommendations for patients planning air travel are contained in BTS guidelines³⁶⁵. Information about other modes of transport and details about specific airlines policies are available from the British Lung Foundation and are summarised in their leaflet “Going on holiday with a lung condition”. The four general points contained in this leaflet are included below and the BTS recommendations on assessment of fitness to fly have been adopted. See section 2.4.1. for the methodology underpinning this section.

Modern aircraft are pressurised to cabin altitudes up to 2438 m (8000 ft) and at this altitude the partial pressure of oxygen will have dropped to the equivalent of breathing 15.1 % oxygen at sea level. Arterial oxygen tensions fall in healthy passengers and altitude exposure will exacerbate hypoxaemia in patients with COPD, particularly those who are hypoxaemic at sea level. The physiological compensations for acute hypoxaemia at rest are mild to moderate hyperventilation (lowering of arterial carbon dioxide tension (PaCO₂) moderates the hyperventilation) and a moderate tachycardia but the clinical significance of temporary altitude induced hypoxaemia in patients with COPD is unclear. The BTS Working Party concluded, “The available controlled studies involve relatively small numbers of patients with stable disease and no co-existing medical problems. Simulated altitude exposure did not generally exceed 1 hour. These studies also largely excluded additional stressors such as exercise, dehydration, sleep, and active smoking. The only report to study exercise suggested that FEV₁ <50% predicted is a risk factor for desaturation.”

The BTS Working Party also noted “COPD patients with large bullae are theoretically at increased risk of pneumothorax as a result of volume expansion at reduced cabin pressures. The volume of gas in a non-communicating bulla will increase by 30% on ascent from sea level to 2438 m (8000 ft). There is one case report of fatal air embolism in a patient with a giant intrapulmonary bronchogenic cyst³⁶⁶. However, there are no data to state with any confidence what the maximum volume of a bulla should be before it reaches an unacceptable level of risk of rupture leading to tension pneumothorax, pneumomediastinum, or air embolism.”

▷ GDG consensus statements

The following points are important for patients with COPD who are considering travel:

IV

- plan in advance
- be realistic
- shop around because of variability in the cost and availability of support (especially oxygen) and the regulations of different airlines, train, coach and ferry companies.
- ask questions

- travel with all necessary medication
- ensure necessary medication is accessible during journeys.

Fitness to fly can be assessed by an initial measurement of arterial oxygen saturation using a pulse oximeter, combined with history and examination (with particular reference to cardiorespiratory disease, dyspnoea, and previous flying experience) and the results of spirometry. **IV**

Depending on the results of the initial assessment a hypoxic challenge test may be necessary (see table 13). **IV**

Table 13 Results of initial assessment

Screening result	Recommendation
Sea level Sao ₂ >95%	Oxygen not required [B]
Sea level Sao ₂ 92-95% and no risk factor*	Oxygen not required [C]
Sea level Sao ₂ 92-95% and additional risk factor*	Perform hypoxic challenge test with arterial or capillary measurements [B]
Sea level Sao ₂ <92%	In-flight oxygen [B]
Receiving supplemental oxygen at sea level	Increase the flow while at cruising altitude [B]

*Additional risk factors: hypercapnia; FEV₁ <50% predicted; lung cancer; restrictive lung disease involving the parenchyma (fibrosis), chest wall (kyphoscoliosis) or respiratory muscles; ventilator support; cerebrovascular or cardiac disease; within 6 weeks of discharge for an exacerbation of chronic lung or cardiac disease.

RECOMMENDATIONS

R115	All patients on LTOT planning air travel should be assessed in line with the BTS recommendations ³⁶⁵ .	Grade D
R116	All patients with an FEV ₁ < 50% predicted who are planning air travel should be assessed in line with the BTS recommendations.	Grade D
R117	All patients known to have bullous disease should be warned that they are at a theoretically increased risk of developing a pneumothorax during air travel.	Grade D
R118	Scuba diving is not recommended for patients with COPD.	Grade D

7.20.9 Education

When reviewing the evidence in this area it was apparent that education is usually offered as part of a comprehensive pulmonary rehabilitation programme. Few studies have evaluated the effects of education alone on patient outcomes.

There is little robust evidence relating to COPD patient education. Many of the papers identified were excluded due to poor sample size and quality appraisal issues. Abstracts were also excluded due to lack of information upon which to quality appraise the study.

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Four studies were identified that met the quality criteria³⁶⁷⁻³⁷⁰. In addition the Guideline Development Group was aware that both the ACCP Pulmonary Rehabilitation Guidelines²¹⁵ and the BTS Pulmonary Rehabilitation Statement²¹³ contribute information to the area of education although their primary focus is towards pulmonary rehabilitation.

One meta analysis was found of psycho education³⁷¹, which was rejected because of quality appraisal issues.

▷ Evidence statements

Sassi-Dambron³⁶⁷ compared dyspnoea management strategies to general health education (not directly related to lung disease) in patients with COPD. At the end of the six-week treatment, there were no significant differences between the treatment and control groups on any outcome measure. Outcomes included eight dyspnoea measures, exercise tolerance, quality of life, anxiety, depression, FEV₁ and FVC. **Ib**

Gallefoss^{369;370} examined whether patient education affected medication concordance and quality of life in a combined population of asthmatics and COPD patients. The results for both of these trials were analysed as separate populations (the groups were also educated separately). The intervention group received a short education program whilst the comparison group were “followed by their GPs” only. **Ib**

There were significant differences in the response to education between patients with COPD and asthma.

The educated patients with COPD received less than half the amount of **rescue medication** compared with the control group (p=0.03). More of the educated patients with COPD reported oral steroid courses but this was not statistically significant (69% vs. 44%) (p=0.07).

For **HRQL**, there were no statistically significant HRQL scores or **FEV₁** results in the educated patient with COPD compared with the control group. (Patient education did increase the HRQL and FEV₁ among asthmatics but not among patients with COPD).

Howland³⁶⁸ compared education to a control group in a quasi-experimental design. In patients with mild to severe COPD the only significant finding in favour of the education group was for health locus control (p=0.003), one of five measures used to assess general health perception. There were no other significant differences on any measure of **health or symptom status, physical function, mental health or social function**. **IIa**

▷ Health economic evidence

Education varies in its content and there is extremely limited economic data about this area. What there is does suggest that patient education is reasonably cost effective, due to the change in behaviour and consequent reduction in resource use. There is not enough evidence to be confident in this however.

RECOMMENDATIONS

R119	There are significant differences in the response of patients with COPD and asthma to education programmes. Programmes designed for asthma should not be used in COPD.	Grade A
R120	Specific educational packages should be developed for patients with COPD. <ul style="list-style-type: none"> ● suggested topics for inclusion are listed in Appendix C ● the packages should take account of the different needs of patients at different stages of their disease. 	Grade D
R121	Patients with moderate and severe COPD should be made aware of the technique of NIV. Its benefits and limitations should be explained so that, if it is ever necessary in the future, they will be aware of these issues. (See section 8.13).	Grade D

7.20.10 Self-management

Self-management plans have been used successfully for many years for patients with asthma, although very few patients have actually been given a written self-management plan. These plans are concerned with guiding responses to subtle day-to-day variations in symptoms and lung function. Self-management plans in COPD on the other hand are designed to enable patients to respond appropriately to the first signs of an exacerbation and are not concerned with minor day-to-day variations in symptoms. If used correctly they will often lead to patients starting courses of antibiotics or oral steroids that they have been given to keep at home and may lead to reduced hospital admissions. Self-management plans need to be structured in a way that takes into account the age and mental state of patients with COPD.

One systematic review was identified³⁷² and one additional RCT (n=191)³⁷³.

The main aim of self-management is to prevent exacerbations by life style adaption and to allow patients to acquire the skills to treat their exacerbation at an early stage³⁷². This can be achieved either by self-management education and/or self-management plans. A self-management plan was defined as a plan (either written or verbal) designed with the primary purpose of patient self-management of COPD exacerbations. The plan advised patients in the event of a COPD exacerbation about starting or adjusting medication.

It was noted that a variety of interventions and comparisons were evident when looking at the research in this area. In summary, Monninkhof³⁷² cites seven studies with self-management education components^{368;374-379}. Two additional studies have a self-management education component augmented with a self-management action plan^{369;380}, however of the management plans, only one was aimed specifically at self-treatment of exacerbations. The systematic review excludes studies that are primarily focused on pulmonary rehabilitation. Interventions were compared to usual care.

The Bourbeau³⁷³ study combined a COPD specific self-management program consisting of teaching and exercise with a customised action plan for exacerbations compared to usual care. The exercise component comprised of a training program with supervised home sessions (including an exercise bicycle) of at least 3 times per week for 30 to 45 minutes per session. In

light of this exercise component and in order to be congruent with the exclusion cited by the systematic review³⁷² the Bourbeau study was excluded.

There were varying degrees of detail when operationally defining COPD and importantly Monninkhof et al.³⁷² highlights that the time span over which the trials were conducted (1986 to 2003) means that changes in both the educational content and method of delivery together with background changes to treatment will have an impact on the trial outcomes. Follow up periods ranged from 2 months to one year.

▷ Evidence statements

Monninkhof³⁷² in a meta analysis of Gallefoss and Littlejohns^{370;376}, showed a statistically significant increase in the use of **oral steroid** courses in the educated patients compared to the control group, relative risk 1.30 (95% CI 1.02 to 1.91). **Ia**

Within the Monninkhof systematic review³⁷², two studies, Watson and Littlejohns^{376;380} assessed the use of **antibiotics** for respiratory problems. Littlejohns reported that 79% in the intervention group compared to 52% in the control group were prescribed antibiotics. Watson examined days on antibiotics via symptom diaries and found that 10% vs. 4% in the intervention and control group respectively were prescribed antibiotic therapy³⁷². **Ia**

Use of **rescue medication** (short-acting beta₂-agonist) was assessed by Gallefoss³⁷⁰ as cited in the systematic review³⁷². The original paper by Gallefoss³⁷⁰ highlights that the educated patients received less than half the amount of rescue medication (median 125 defined daily dosage (DDD) compared with the control group (median 290 DDD) p=0.03. **Ib**

Monninkhof³⁷² reported four studies^{376-378;381} (overall sample size n=417) that looked at COPD related **hospitalisations** and found no statistically significant overall differences. **Ia**

Monninkhof³⁷² highlights that meta analysis of two studies^{376;381} which report data about the number of patients with **one of more admissions**, demonstrated a non-significant reduction of hospitalisations in favour of the treatment group. Relative risk 0.80, (95% CI 0.43 to 1.50). **Ia**

There were no statistically significant differences between the groups for **emergency room visits, use of other health care facilities, days lost from work**³⁷². **Ia**

Gallefoss and Watson^{369;380} (total sample size n=131) measured SGRQ outcomes. SGRQ total scores and domain scores were all lower (indicating a better HRQL) in the self-management education groups but these differences did not reach clinical significance. Although the **SGRQ** demonstrated a statistically significant result for the **activity component** only in favour of the intervention group, WMD -10.2 (95% CI -18.5 to -2.0) there was significant **heterogeneity** between the results p<0.05³⁷². **Ia**

There were no statistically significant differences between the groups for **lung function**³⁷². **Ia**

There were no statistically significant differences between the groups for **symptom scores**³⁷². **Ia**

▷ GDG consensus statements

The GDG believed that the effects of self management look promising but further studies are required to refine the content of self management plans. **IV**

There is no evidence that self management plans similar to those used in asthma are of value in COPD. **IV**

Self management plans need to be refined and the key components identified. **IV**

RECOMMENDATIONS

R122	Patients at risk of having an exacerbation of COPD should be given self-management advice that encourages them to respond promptly to the symptoms of an exacerbation.	Grade A
R123	Patients should be encouraged to respond promptly to the symptoms of an exacerbation by: <ul style="list-style-type: none"> ● starting oral corticosteroid therapy if their increased breathlessness interferes with activities of daily living (unless contraindicated) ● starting antibiotic therapy if their sputum is purulent ● adjusting their bronchodilator therapy to control their symptoms. 	Grade D
R124	Patients at risk of having an exacerbation of COPD should be given a course of antibiotic and corticosteroid tablets to keep at home for use as part of a self management strategy (see recommendation 150).	Grade D
R125	The appropriate use of these tablets should be monitored.	Grade D
R126	Patients given self management plans should be advised to contact a health care professional if they do not improve.	Grade D

7.21 Fitness for general surgery

Due to the time limitations within the guideline development process and the fact that these questions address a topic at the periphery of the guideline a full literature search and critical appraisal process was not undertaken in this area. However, a MEDLINE search, a selective review of frequently cited papers and key review articles were undertaken as part of the development of a background paper for discussion by the guideline development group. See section 2.4.1 for the methodology.

Patients with COPD appear to have an increased risk of post-operative pulmonary complications (3.0 fold for unselected surgery and 4.7 fold for thoracic or abdominal surgery³⁸²). The risk may increase with increasing “severity” of COPD, but it also depends on duration of anaesthesia and nature of surgery. The GDG were aware of the conclusions of the

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National Confidential Enquiry into Perioperative Deaths (NCEPOD), particularly their report and recommendations relating to deaths in elderly patients ³⁸³.

▷ GDG consensus statements

Pulmonary risk factors alone do not predict the risk of post-operative pulmonary complications. **IV**

FEV₁ on its own has little clinical usefulness in predicting post-operative pulmonary complications ³⁸⁴⁻³⁸⁶. **III**

Composite assessment tools such as the widely used ASA scoring system ³⁸⁷ can be used to assess operative risk and plan patients' management. **IV**

RECOMMENDATIONS

R127	The ultimate clinical decision about whether or not to proceed with surgery should rest with a consultant anaesthetist and consultant surgeon taking account of the presence of comorbidities, the functional status of the patient and the necessity of the surgery.	Grade D
R128	It is recommended that lung function should not be the only criterion used to assess patients with COPD before surgery. Composite assessment tools such as the ASA scoring system are the best predictors of risk.	Grade D
R129	If time permits, the medical management of the patient should be optimised prior to surgery and this might include undertaking a course of pulmonary rehabilitation.	Grade D

7.22 Follow-up of patients with COPD

Throughout the course of the disease, the management of COPD is likely to be shared between health care professionals in both primary and secondary care. Most patients with mild and moderate symptoms and those who are not experiencing frequent exacerbations will be managed predominately in primary care. Follow-up of patients with more severe disease will also be predominantly in primary care but there will also be a need for access to secondary care services. Patients with severe COPD are likely to have frequent exacerbations leading to hospital admissions. They often have complex problems with co-morbidities, may be on high levels of treatment, and need monitoring for LTOT.

Clinicians in primary care have the skills to assess patients symptoms and the adequacy of their control, monitor the progression of their disease, identify the development of complications and the need for referral to secondary care or other specialists (see section 6.10 on referral for specialist advice). There are no data to guide decisions on how frequently patients should be reviewed but clearly this will vary according to individual circumstances and the severity of the patient's disease. Some patients with COPD deteriorate faster than others and it is important to identify these individuals as they need specialist input. Reasons for referral to hospital services are dealt with in section 6.10.

Many of the recommendations in this section of the guideline are based on expert opinion rather than on the result of research studies, due to the paucity of evidence and difficulty of conducting studies in this area. See section 2.4.1. for the methodology underpinning this section. This does not undermine the value or importance of these recommendations, which may have a large impact on the quality of care and outcome for the person with COPD and their carers. The GDG's consensus statements are broadly based on statements contained in the BTS COPD Guidelines ²⁵.

▷ GDG consensus statements

Follow up of patients with mild or moderate COPD will usually take place in primary care. **IV**

For patients with severe disease, shared care between the hospital and primary care team is the usual pattern although there are no data to show how care should be provided to achieve the best combination of clinical and cost effectiveness. **IV**

Patients with severe disease requiring interventions such as non-invasive ventilation should be reviewed regularly by specialists. **IV**

RECOMMENDATIONS

R130	<p>Follow up of all patients with COPD should include:</p> <ul style="list-style-type: none"> ● highlighting the diagnosis of COPD in the case record and recording this using Read codes on a computer database ● recording the values of spirometric tests performed at diagnosis, (both absolute and percent predicted) ● offering smoking cessation advice ● recording the opportunistic measurement of spirometric parameters (a loss of 500 ml or more over five years will select out those patients with rapidly progressing disease who may need specialist referral and investigation). 	Grade D
R131	<p>Patients with mild or moderate COPD should be reviewed at least once per year, or more frequently if indicated, and the review should cover the issues listed in table 14.</p>	Grade D
R132	<p>For most patients with stable severe disease regular hospital review is not necessary, but there should be locally agreed mechanisms to allow rapid access to hospital assessment when necessary.</p>	Grade D
R133	<p>When patients with severe COPD are reviewed in primary care, they should be seen at least twice a year, and specific attention should be paid to the issues listed in table 14:</p>	Grade D
R134	<p>Patients with severe disease requiring interventions such as long term non-invasive ventilation should be reviewed regularly by specialists.</p>	Grade D

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Table 14 Summary of follow up of patients with COPD in primary care

	Mild/Moderate	Severe
Frequency	At least annual	At least twice per year
Clinical assessment	<ul style="list-style-type: none"> ● smoking status & desire to quit ● adequacy of symptom control: <ul style="list-style-type: none"> – breathlessness – exercise tolerance – estimated exacerbation frequency ● presence of complications ● effects of each drug treatment ● inhaler technique ● need for referral to specialist and therapy services ● need for pulmonary rehabilitation 	<ul style="list-style-type: none"> ● smoking status & desire to quit ● adequacy of symptom control: <ul style="list-style-type: none"> – breathlessness – exercise tolerance – estimated exacerbation frequency ● presence of cor pulmonale ● need for long-term oxygen therapy ● patient's nutritional state ● presence of depression ● effects of each drug treatment ● inhaler technique ● need for Social Services & Occupational Therapy input ● need for referral to specialist and therapy services ● need for pulmonary rehabilitation
Measurements to make	<ul style="list-style-type: none"> ● FEV₁ & FVC ● calculate BMI ● MRC dyspnoea score 	<ul style="list-style-type: none"> ● FEV₁ & FVC ● calculate BMI ● MRC dyspnoea score ● Sao₂



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Updated information and services can be found at:
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These include:

Data Supplement

"Supplementary Evidence Tables"

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