Chronic obstructive pulmonary disease:
Evidence Update February 2012

A summary of selected new evidence relevant to NICE clinical guideline 101 'Management of chronic obstructive pulmonary disease in adults in primary and secondary care' (2010)

Evidence Update 5

Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might reinforce or generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE guidance development centres. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.evidence.nhs.uk/topic/chronic-obstructive-pulmonary-disease). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

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Contents

Introduction

This Evidence Update identifies new evidence that might reinforce or generate future change to the practice laid out in the following reference guidance:

 [1]**Chronic obstructive pulmonary disease. NICE clinical guideline 101 (2010). Available from www.nice.org.uk/guidance/CG101**

Over 4000 pieces of evidence were identified and assessed, of which 27 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group (EUAG), comprised of subject experts, reviewed the prioritised evidence (with additional input from internal experts) and provided a commentary.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other NICE guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update also makes reference to the following guidance:

 [1]Roflumilast for the management of severe chronic obstructive pulmonary disease. NICE technology appraisal 244 (2012). Available from www.nice.org.uk/guidance/TA244

- [2]Varenicline for smoking cessation. NICE technology appraisal 123 (2007). Available from www.nice.org.uk/guidance/TA123

Other relevant guidance

The following guidance is also of relevance to UK chronic obstructive pulmonary disease (COPD) practice, however the Evidence Update does not discuss any potential effect the new evidence may have on their recommendations:

- British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation (2001) Pulmonary rehabilitation guideline. Thorax 56: 827–34
  Available from www.brit-thoracic.org.uk/guidelines/pulmonary-rehabilitation-guidelines.aspx

- O'Driscoll BR, Howard LS, Davison AG (2008) British Thoracic Society Guideline for emergency oxygen use in adult patients. Thorax 63 (suppl 6): 1–68
  Available from www.brit-thoracic.org.uk/guidelines/emergency-oxygen-use-in-adult-patients.aspx

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

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[1] NICE-accredited guidance is denoted by the accreditation symbol 

[2] Guidance published prior to NICE accreditation

Key messages

The following table summarises what the EUAG decided were the key messages from the Evidence Update. It also indicates the EUAG's opinion on whether new evidence identified by the Evidence Update reinforces or has potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence, which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance that may be affected, please see the full commentaries.

	Effect on guidance	
Key message	**Potential change**	**No change**
Managing stable COPD		
Smoking cessation		
• The potential health benefits of smoking cessation in people with chronic obstructive pulmonary disease (COPD) appear to be confirmed by current evidence, and benefits may extend to those with more severe COPD.		✓
• Smoking cessation counselling plus either nicotine replacement therapy or an antidepressant are effective ways to help patients to stop smoking.		✓
Inhaled therapy		
• Current evidence suggests that long-acting beta-agonists plus inhaled corticosteroids (ICS) reduce moderate exacerbations, and confirms that ICS may be associated with a risk of pneumonia. Whether mortality is reduced remains unclear.		✓
• A combined regimen of tiotropium plus formoterol may be of greater benefit to lung function and symptoms versus tiotropium alone, but evidence to suggest a reduction in mortality or exacerbations appears to be inconclusive.		✓
• Tiotropium may be more effective than salmeterol in terms of exacerbations but the evidence is currently unclear.		✓
• Dry-powder delivery of tiotropium appears to be safe but there may be safety concerns with delivery via mist inhaler.	✓	
• Indacaterol is more effective than placebo and has shown non-inferiority to tiotropium. Evidence suggests it is superior to salmeterol and to formoterol, although mean differences did not meet the clinical significance criteria stated in the full version of NICE clinical guideline 101. Indacaterol is a potential consideration for future NICE guidance reviews.	✓	
• A NICE technology appraisal has recently recommended roflumilast only in the context of research as part of a clinical trial for adults with severe COPD.		✓
Pulmonary rehabilitation		
• The benefits of longer versus shorter pulmonary rehabilitation programmes appear to be inconclusive. Current evidence seems unable to define an optimal programme length.		✓

Key message	Effect on guidance	
	Potential change	No change
Pulmonary rehabilitation (continued)		
• Evidence suggests that there appears to be no clinical or cost benefit of community-based over hospital-based rehabilitation, and that the venue may be best determined by local access preferences and transport links.		✓
• Inspiratory muscle training (IMT) appears to show empirical benefits when used as the sole physical training modality. However more evidence is needed, particularly concerning the most suitable subgroups of patients, and whether IMT adds usefully to standard pulmonary rehabilitation programmes is unclear.		✓
• Pulmonary rehabilitation offers potential benefits even in patients with the most severe COPD.		✓
• Preliminary evidence suggests that Nordic walking may be a useful addition to current pulmonary rehabilitation strategies but larger, longer-term studies are needed.		✓
Vaccination and anti-viral therapy		
• Recent evidence appears to suggest that pneumococcal vaccination in patients with COPD may not reduce the risk of pneumonia, exacerbations or mortality. Large, well-designed trials of newer polyvalent vaccines are needed.		✓
Multidisciplinary management		
• Current evidence of the efficacy of home care by outreach nursing for COPD appears to be inconclusive. Large, well-designed studies with clearly defined populations and interventions are needed.		✓
• Complex patient education programmes may be more effective than simpler interventions particularly in patients with more severe COPD. Further investigation of long-term outcomes in wider patient groups may be useful.	✓	
Management of exacerbations of COPD		
• Evidence suggests that for oxygen therapy during exacerbations, titration to an appropriate target is associated with better outcomes than administering high flow oxygen.		✓
• Current evidence indicates a potentially high risk of death around the time of an acute exacerbation, and that the critical period may extend beyond the period of hospitalisation.		✓
• Pulmonary rehabilitation in patients who have recently experienced an exacerbation may reduce hospital admissions and possibly mortality.	✓	
Areas not currently covered by NICE guidance		
Risk factors		
• Evidence suggests that residential dampness and mould may be associated with lung health problems but further research is needed.		✓

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided.

Definitions of clinically important effects

Interpretation of the new evidence should take into account that the full version of NICE clinical guideline (CG) 101 considered the following differences in outcomes to be the minimum that is clinically important:

- 15% relative risk reduction (RRR) in mortality
- 20% RRR in exacerbations
- 20% RRR in hospitalisations
- 4 point improvement (indicated by a negative difference) in St. George's Respiratory Questionnaire (SGRQ)
- 1 unit improvement in transitional dyspnoea index (TDI)
- 100 ml difference in forced expiratory volume in 1 second (FEV_1).

1.1 Diagnosing COPD

No new key evidence was found for this section.

1.2 Managing stable COPD

Smoking cessation

In a meta-analysis of 47 studies, **Lee and Fry (2010)** examined decline in FEV_1 among never smokers, continued smokers, ex-smokers and quitters (those who discontinued smoking between recruitment and follow up).

Never smokers had a lower rate of FEV_1 decline than continued smokers (10.8 ml/year less; 95% confidence interval [CI] 8.9 to 12.8), and the rate of decline of FEV_1 of continued smokers was significantly more than in the other three groups ($p < 0.001$). Among the three non-smoking groups there was no statistically significant difference in FEV1 decline, suggesting that disease progression in ex-smokers and quitters was more closely aligned with non-smokers than smokers.

The limitations of the review were; only one database was searched, many of the included studies were solely in men, and a third of the studies were from before 1970.

Although the review was unable to confirm the benefits (or otherwise) of smoking cessation at different stages of COPD severity, a recent study by Vestbo et al. (2011) examined data in 2163 patients from a previously reported prospective observational study (the ECLIPSE trial). This study found that patients continuing to smoke were at greater risk of marked disease progression irrespective of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage.

Together, these two studies strengthen the strong messages on smoking cessation in NICE CG101, and indicate that even in severe COPD, stopping smoking may be of benefit. The established link between smoking and death from cardiovascular disease (Anthonisen et al. 2005) adds further weight to this argument.

Strassman et al. (2009) performed a network meta-analysis (involving comparison of treatments that were not compared directly in a trial setting) of 7372 patients from six studies of smoking cessation interventions in COPD. In an efficacy ranking system (versus no intervention/usual care), smoking cessation counselling (SCC) plus nicotine replacement therapy (NRT) was deemed most effective (odds ratio [OR] = 5.08; 95% CI 4.32 to 5.97; $p < 0.001$), with SCC plus antidepressant in second place (OR = 3.32; 95% CI 1.53 to 7.21; $p = 0.002$). However, a direct comparison of these two regimens found no significant difference in efficacy ($p = 0.28$). High-intensity and low-intensity counselling had the same effect when combined with antidepressant, but high-intensity counselling was more effective in the presence of NRT (OR = 1.81; 95% CI 1.04 to 3.15; $p = 0.04$).

Although a large number of databases were searched, the network meta-analysis results were not based on direct experimental comparison of interventions and only involved a small number of studies. The evidence suggests that SCC plus either NRT or antidepressant both are equally effective smoking cessation interventions to offer patients, and there is little evidence for the superiority of high-intensity over low-intensity counselling. The recommendations in NICE CG101 to offer pharmacological therapy with appropriate support are unlikely to be affected by this evidence.

Notably, varenicline was not included in the interventions looked at by Strassman et al. (2009). Varenicline is a further smoking cessation treatment option and should be used in accordance with 'Varenicline for smoking cessation' (NICE technology appraisal guidance 123). The European Medicines Agency recently confirmed that the benefits of varenicline as a smoking-cessation medicine outweigh a slight reported increase in cardiovascular events.

The evidence overall suggests that stopping smoking is of benefit, even in people with severe COPD, and there are a number of ways patients may be helped to do so.

Key references

Lee PN, Fry JS (2010) Systematic review of the evidence relating FEV1 decline to giving up smoking. BMC Medicine 8: 84
Full text: www.biomedcentral.com/content/pdf/1741-7015-8-84.pdf

Strassmann R, Bausch B, Spaar A et al. (2009) Smoking cessation interventions in COPD: a network meta-analysis of randomised trials. European Respiratory Journal 34: 634–40
Full text: www.erj.ersjournals.com/content/34/3/634.full.pdf+html

Supporting references

Anthonisen NR, Skeans MA, Wise RA et al. (2005) The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Annals of Internal Medicine 142: 233–9
Full text: www.annals.org/content/142/4/233.full

Vestbo J, Edwards LD, Scanlon PD et al. (2011) Changes in forced expiratory volume in 1 second over time in COPD. New England Journal of Medicine 365: 1184–92
Full text: www.nejm.org/doi/full/10.1056/NEJMoa1105482

Inhaled therapy

Combination therapy

In a meta-analysis of 18 randomised controlled trials (RCT) of 12,446 patients, **Rodrigo et al. (2009)** investigated the safety and efficacy of combined long-acting beta$_2$-agonists (LABA) plus inhaled corticosteroids (ICS) versus LABA monotherapy in stable COPD. Compared with LABA monotherapy, LABA plus ICS did not significantly reduce severe exacerbations (that is, those needing hospitalisation or withdrawal; RR = 0.91; 95% CI 0.82 to 1.01) or all-cause mortality (RR = 0.90; 95% CI 0.76 to 1.06). Potential limitations to the review were; the included studies were as short as 8 weeks, the mortality event rate in most studies was very low, and many studies were not designed or powered to look at mortality.

The review also analysed less severe exacerbations and found that in this subgroup a LABA plus ICS regimen was associated with a significantly lower risk of moderate exacerbations (that is, needing systemic corticosteroids) compared with LABA monotherapy (RR = 0.84; 95% CI 0.74 to 0.96; p = 0.008 – although the reduction in RR was less than the minimum clinically important difference [MCID] of 20% indicated by the full version of NICE CG101). There was however some evidence of heterogeneity between trials for this outcome. The safety analysis revealed an increased risk of pneumonia with LABA plus ICS (RR = 1.63; 95% CI 1.35 to 1.98).

These findings largely agree with the TORCH study of LABA plus ICS (Calverley et al. 2007), which did not establish a clear link between the combination regimen and reduced mortality versus LABA alone but did find that exacerbations were reduced.

Overall, the evidence suggests that LABA plus ICS reduce moderate exacerbations, in line with the intent of this regimen in NICE CG101, and are associated with a known risk of pneumonia as already stated in current guidance. However it remains unclear if mortality is reduced. This evidence is unlikely to affect current guideline recommendations.

Wang et al. (2011) performed a meta-analysis of eight RCTs (1868 patients; trial duration ranged from 2 weeks up to 24 weeks) comparing a combined regimen of the long-acting muscarinic antagonist (LAMA) tiotropium plus a LABA (formoterol) with tiotropium alone in stable COPD. Tiotropium plus formoterol significantly improved average FEV_1 (weighted mean difference [WMD] = 105 ml; 95% CI 69 to 142 ml; p < 0.0001), average FVC (WMD 135 ml; 95% CI 96 to 174; p < 0.0001) and trough FEV_1 (WMD = 53 ml; 95% CI 30 to 76; p < 0.0001 – although this improvement was less than the MCID of 100 ml indicated by the full version of NICE CG101) compared with tiotropium alone. The mean change in TDI was also greater with tiotropium plus formoterol compared with tiotropium alone (WMD = 1.50; 95% CI 1.01 to 1.99; p < 0.0001). There were insufficient data for SGRQ to perform a meta-analysis. Adverse events and exacerbations tended to be fewer with the combined regimen, but this was not statistically significant.

These results suggest that lung function and symptoms (based on data for TDI only) may be improved with a combined regimen of tiotropium plus formoterol over tiotropium alone, but there was not enough evidence to suggest a reduction in mortality or exacerbations.

Key references

Rodrigo GJ, Castro-Rodriguez JA, Plaza V (2009) Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting beta-agonists monotherapy for stable COPD: a systematic review. CHEST 136: 1029–38
Full text: www.chestjournal.chestpubs.org/content/136/4/1029.full.pdf+html

Wang J, Jin D, Zuo P et al. (2011) Comparison of tiotropium plus formoterol to tiotropium alone in stable chronic obstructive pulmonary disease: a meta-analysis. Respirology 16: 350–8
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1440-1843.2010.01912.x/abstract

Supporting references

Calverley PMA, Anderson JA, Celli B (2007) Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. New England Journal of Medicine 356: 775–89
Full text: www.nejm.org/doi/full/10.1056/NEJMoa063070

Tiotropium

In an RCT of 7376 patients, **Vogelmeier et al. (2011)** compared tiotropium (18 micrograms once daily) with salmeterol (50 micrograms twice daily) and found that time to the first exacerbation was greater with tiotropium (187 days) versus salmeterol (145 days), corresponding to a 17% risk reduction (hazard ratio [HR] = 0.83; 95% CI 0.77 to 0.90; p < 0.001).

Interpretation of this evidence in the context of NICE guidance is complicated by the fact that patients were allowed to continue treatment with inhaled corticosteroids during the study; tiotropium plus ICS is not a regimen recommended in NICE CG101 and therefore any potential effect of this evidence on current recommendations may not be clear. Further information on this evidence can be found in the National Prescribing Centre's (NPC) MeRec Rapid Review 3501.

Two recent meta-analyses have examined the safety of dry-powder inhalers and mist inhalers for the delivery of tiotropium.

Dry-powder delivery of tiotropium was investigated in a meta-analysis of 19 RCTs (18,111 patients; trial duration ranged from 6 weeks to 48 months) by **Rodrigo et al. (2009),** who found no increased risk of a composite of major adverse cardiovascular events compared with controls (RR=0.96; 95% CI 0.82 to 1.12). Of the individual components of the composite, there was no increased risk of cardiovascular death and non-fatal stroke, however the trials were not set up to study this in detail. There was also no significant increase in the risk of all-cause mortality (RR = 0.97; 95% CI 0.86 to 1.09). A 4-year RCT of tiotropium in COPD (the UPLIFT study; Tashkin et al. 2008) was included in the meta-analysis, which in fact found that the risk of serious cardiac events may be lower with tiotropium than with placebo. The new evidence suggests that tiotropium via dry-powder inhaler does not appear to increase risk of cardiovascular events or mortality, and current recommendations in NICE CG101 regarding its use are unlikely to be affected.

There may, however, be evidence to suggest safety issues with tiotropium when delivered via mist inhaler (Spiriva Respimat). In a meta-analysis of five RCTs (6522 patients), **Singh et al. (2011)** found that mist inhaler delivery of tiotropium was associated with a significantly greater risk of mortality compared with placebo (RR = 1.52; 95% CI 1.06 to 2.16; p = 0.02). The risk was greater with a 10 microgram dose (RR = 2.15; 95% CI 1.03 to 4.51; p = 0.04) but the 5 microgram dose was also associated with elevated risk (RR = 1.46; 95% CI 1.01 to 2.10; p = 0.04). There also appeared to be an elevated risk of cardiovascular death (RR = 2.05; 95% CI 1.06 to 3.99; p = 0.03) but low event rates for this outcome prevent definitive conclusions.

The potential safety issues with tiotropium via mist inhaler may be a consideration for future reviews of NICE CG101, particularly for patients with cardiovascular disease. Further information about the evidence for these potential concerns can be found in the NPC's MeReC Rapid Review 4012.

A safety trial by Boehringer Ingelheim Pharmaceuticals is currently underway to investigate concerns with tiotropium delivery via mist inhaler.

Key references

Rodrigo GJ, Castro-Rodriguez JA, Nannini LJ et al. (2009) Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis. Respiratory medicine 103: 1421–9
Abstract: www.resmedjournal.com/article/S0954-6111(09)00162-0/abstract

Singh S, Loke YK, Enright PL et al. (2011) Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: Systematic review and meta-analysis of randomised controlled trials. British Medical Journal 342: d3215
Full text: www.bmj.com/content/342/bmj.d3215.full.pdf

Vogelmeier C, Hederer B, Glaab T (2011) Tiotropium versus salmeterol for the prevention of exacerbations of COPD. New England Journal of Medicine 364: 1093–103
Full text: www.nejm.org/doi/full/10.1056/NEJMoa1008378

Supporting references

Tashkin DP, Celli B, Senn S et al. (2008) A 4-year trial of tiotropium in chronic obstructive pulmonary disease. New England Journal of Medicine 359: 1543–54
Full text: www.nejm.org/doi/full/10.1056/NEJMoa0805800

Boehringer Ingelheim Pharmaceuticals. Comparison of tiotropium in the HandhiHaler versus the respimat in chronic obstructive pulmonary disease (NCT01126437).
Further details available from: www.clinicaltrials.gov/ct2/show/NCT01126437

Indacaterol

INVOLVE (**Dahl et al. 2010)** was a 1-year RCT of 1732 patients which compared indacaterol 300 and 600 micrograms once daily, formoterol 12 micrograms twice daily and placebo for 52-weeks. At 12 weeks, both indacaterol groups showed a mean increase in trough FEV_1 of 170 ml (95% CI 130 to 200 ml; $p < 0.001$) versus placebo (primary outcome), exceeding the trial's pre-defined clinically important difference of 120 ml (note that 600 micrograms daily is double the maximum dose of indacaterol licensed in the UK). Both doses of indacaterol produced increases in FEV_1 over placebo 100 ml greater than that produced by formoterol ($p < 0.001$), but the clinical relevance of this difference was questioned by the European Medicines Agency (see EMA Assessment Report). In addition this comparison was not a predefined primary or secondary endpoint, but a predefined exploratory objective of the study. A range of clinical outcomes were reported as secondary endpoints (all versus placebo). These are discussed further in the NPC's On The Horizon Rapid Review 1828. All active treatments were statistically significantly superior to placebo.

INHANCE (**Donohue et al. 2010**) was a 26-week RCT including 1683 patients who received indacaterol 150 or 300 micrograms or placebo daily (double blind), or open-label tiotropium 18 micrograms once daily. At week 12, both doses of indacaterol improved trough FEV_1 compared to placebo (primary outcome) by 180 ml (98.75% CI 140 to 220 ml; $p < 0.001$). Tiotropium improved trough FEV_1 compared with placebo by 140 ml (98.75% CI 100 to 180 ml). Both indacaterol doses were stated to be statistically significant for non-inferiority to tiotropium for trough FEV_1 at 12 weeks ($p < 0.001$) and for superiority ($p \leq 0.01$). However, insufficient data are provided in the published report to evaluate this fully. The 40 ml difference in improvement in mean trough FEV_1 over placebo between tiotropium and indacaterol is substantially less than than MCID of 100 ml indicated by the full version of NICE CG101. INHANCE is discussed further in the NPC's On The Horizon Rapid Review 1828.

INTENSITY, a 3-month non-inferiority RCT of 1598 patients by **Buhl et al. (2011)** compared indacaterol 150 micrograms and tiotropium 18 micrograms, both once daily. The rounded treatment difference for trough FEV_1 (0 ml; 95% CI −20 ml to 20 ml) met the predefined non-inferiority margin of 55 ml ($p < 0.001$ for non-inferiority) but superiority was not demonstrated (coprimary outcomes). Secondary outcomes included TDI and SGRQ. The mean difference in TDI score between the two treatments was 0.58 ($p < 0.001$; 95% CI not stated). This is less than the MCID of 1 point indicated by the full version of NICE CG101, but more patients assigned to indacaterol showed 1 point or greater improvement from baseline (57.9% vs 50.1%; OR = 1.49; 95% CI 1.19 to 1.85; $p < 0.001$). The mean difference between the two treatments in improvement in SGRQ from baseline was 2.1 ($p < 0.001$; 95% CI not stated). This is also less than the MCID of 4 points indicated by the full version of NICE CG101, but more patients assigned to indacaterol showed 4 points or more of improvement (50.5% vs 42.5%; OR = 1.43; 95% CI 1.15 to 1.78).

Indacaterol 150 micrograms daily was compared with salmeterol 50 micrograms twice daily in INSIST, a 12-week RCT of 1123 patients by **Korn et al. (2011)**. The primary efficacy outcome was time-standardised area under the curve of FEV_1 values between 5 minutes and 11 hours 45 minutes after the morning dose at week 12. Indacaterol was statistically superior to salmeterol in this outcome (adjusted mean difference 57 ml; 95% CI 35 to 79 ml; $p < 0.001$). The key secondary efficacy variable was trough FEV_1 at 12 weeks. Indacaterol was statistically superior to salmeterol (adjusted mean difference 60 ml; 95% CI 37 to 83 ml; $p < 0.001$). This is less than the MCID of 100 ml indicated by the full version of NICE CG101. Indacaterol produced a statistically superior improvement in TDI (adjusted mean difference

0.63; 95% CI 0.30 to 0.97; p < 0.01) This is also less than the MCID of 1 point indicated by the full version of NICE CG101, but more patients assigned to indacaterol showed 1 point or more improvement from baseline (69.4% vs 62.7%; OR = 1.41; 95% CI 1.07 to 1.85; p < 0.05).

Indacaterol 150 micrograms daily was compared with salmeterol 50 micrograms twice daily and placebo in INLIGHT-2, a 6-month RCT of 1002 patients by **Kornmann et al. (2011)**. Indacaterol improved trough FEV_1 compared with placebo at 12 weeks (p < 0.001; primary outcome, value not stated). The difference versus placebo in trough FEV_1 in the indacaterol group was 60 ml greater than that in the salmeterol group at 12 weeks and 70 ml greater at 26 weeks (secondary outcomes, both p < 0.001; 95% CI not stated). These results are less than the MCID of 100 ml indicated in the full version of NICE CG101. The between-group difference in SGRQ score at 12 weeks was significantly different in favour of indacaterol (p < 0.05). The absolute difference was not stated, but appears from a figure to be less than the MCID of 4 points indicated by the full version of NICE CG101. More patients assigned to indacaterol showed 4 points or more improvement from baseline (57.9% vs 46.8%; OR = 1.59; 95% CI 1.12 to 2.25; p < 0.01). Indacaterol produced a statistically superior improvement in TDI at 4 weeks and 12 weeks, but not at 26 weeks. The adjusted mean difference at 12 weeks was 0.55 (p < 0.05; 95% CI not stated). This is also less than the MCID of 1 point indicated in the full version of NICE CG101. Statistical analysis of differences between active groups in the proportion of patients who showed 1 point or more improvement from baseline was not presented.

Chapman et al. (2011) conducted INDORSE, a 26-week extension to INHANCE, among 415 of the patients randomised to either dose of indacaterol or to placebo in that trial. The primary objective was to evaluate the 52-week safety of indacaterol (that is, over the combined period of INDORSE and INHANCE). Among the secondary evaluations the two key efficacy endpoints were trough FEV_1 at 52 weeks and time to first moderate or severe exacerbation. The incidence and type of adverse events were stated to be generally comparable across study groups, but no statistical analysis was presented. Distinct from cough as an adverse event, cough that occurred within 5 minutes of participants inhaling the study drug at clinic visits was recorded. This was observed in an average of 18.3% of patients receiving indacaterol 150 micrograms, 23.6% of those receiving indacaterol 300 micrograms and 1.9% of those receiving placebo (no statistical analysis presented). Difference in trough FEV_1 from placebo at 52 weeks was 170 ml (95% CI 110 to 230 ml) for patients receiving indacaterol 150 micrograms and 180 ml (95% CI 120 to 240 ml) for patients receiving indacaterol 300 micrograms (p < 0.001 for both). Hazard ratios for time to first exacerbation were not statistically significantly different from placebo, although exacerbation rates were lower in the indacaterol 150 micrograms and 300 micrograms groups (0.39 and 0.38 exacerbations per year respectively) than in the placebo group (0.54 exacerbations per year; p < 0.05). Improvements in total SGRQ scores were greater than 4 points in all three arms at all time-points after 8 weeks (except for placebo at week 44). Mean scores with both indacaterol doses were statistically significantly better than placebo at week 26 and week 44 but not at other time points (absolute differences not stated).

A safety meta-analysis by Donohue et al. (2011) pooled data from all published and unpublished studies of indacaterol in COPD of at least 12 weeks duration completed at the time of this analysis (some lasted up to 12 months), but did not employ a systematic review methodology. Indacaterol doses studied were 75, 150, 300 and 600 micrograms daily (total number of patients exposed to indacaterol = 4764). Other active treatments included in the review were salmeterol 50 micrograms and formoterol 12 micrograms (both twice daily) and tiotropium 18 micrograms once daily. The most common adverse events with indacaterol were COPD worsening, nasopharyngitis, and headache; most cases were mild or moderate and incidence was generally similar to placebo and other active treatments. The risks of acute

respiratory serious adverse events (leading to hospitalisation, intubation, or death), and major adverse cardiovascular events were not significantly different from placebo with any of the active treatments. The mean percentage of attended visits at which patients experienced cough after inhalation of indacaterol ranged from 14.1% to 18.4% across the indacaterol dose groups (specific data not presented), compared with 2% in the placebo group (no statistical analysis presented). This suggests a number needed to harm of six to eight versus placebo. Although broadly reassuring regarding safety (but note the incidence of cough after inhalation), the limitations of this study should be noted; it was based on a relatively small patient population taken from controlled trials, in which safety was not the primary endpoint.

Indacaterol therapy is a potential consideration for future reviews of NICE CG101.

Key references

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Abstract: www.erj.ersjournals.com/content/early/2011/05/26/09031936.00191810.abstract

Chapman KR, Rennard SI, Dogra A et al. (2011) Long-term safety and efficacy of indacaterol, a long-acting beta2-agonist, in subjects with COPD: a randomized, placebo-controlled study. Chest 140: 68–75
Abstract: www.chestjournal.chestpubs.org/content/140/1/68.abstract

Dahl R, Chung KF, Buhl R et al. (2010) Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax 65: 473–9
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Full text: www.ajrccm.atsjournals.org/content/182/2/155.full.pdf+html

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Abstract: www.erj.ersjournals.com/content/early/2010/08/06/09031936.00045810.abstract

Supporting reference

Donohue JF, Singh D, Kornmann O et al. (2011) Safety of indacaterol in the treatment of patients with COPD. International Journal of Chronic Obstructive Pulmonary Disease 6: 477–92
Full text: www.dovepress.com/safety-of-indacaterol-in-the-treatment-of-patients-with-copd-a8339

Roflumilast

NICE technology appraisal 244 has recently recommended roflumilast only in the context of research as part of a clinical trial for adults with severe COPD (for the purposes of this technology appraisal guidance defined as forced expiratory volume in 1 second [FEV_1] post-bronchodilator less than 50% predicted) associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment. This should be referred to as the latest guidance.

Pulmonary rehabilitation

Optimal duration

In a systematic review of five RCTs (451 patients) looking at optimal duration of pulmonary rehabilitation in people with COPD, **Beauchamp et al. (2011)** found limited evidence to suggest that longer duration rehabilitation programmes are of greater benefit than those of a shorter length. The authors were unable to conduct a meta-analysis due to considerable

heterogeneity of outcomes and particularly the way programme length was defined across the included studies (the definition of a 'short' programme ranged from 4 weeks to 3 months duration, and the 'long' programmes ranged from 7 weeks to 18 months).

Of the four studies that considered health-related quality of life (HRQOL), three found evidence that longer programmes were more beneficial. Two of these used the Chronic Respiratory Questionnaire (CRQ), in which a difference of 0.5 was deemed clinically significant by the authors. In one trial of 44 patients, the mean difference in total CRQ was 0.61 (95% CI −0.15 to −1.08); and in a second trial of 140 patients, significant improvement in CRQ was noted for all domains but only dyspnoea showed clinical significance (a difference of 0.53). The third trial (140 patients) noted a significant difference in disability of 12% with longer versus shorter trials (1.53 vs1.71) using the Fitness Arthritis and Seniors Trial functional importance inventory.

For exercise capacity, only two of four studies looking at this outcome found that patients were more improved in longer programmes. One trial of 140 patients noted those in longer programmes walked 30.5 m farther in a 6-minute walking distance (6MWD) than patients in shorter programmes (although not achieving the 54 m stated by the authors to indicate clinical significance). In a second trial of 27 patients, the longer programme led to a difference in 12-minute walking distance (12MWD) of 60 m at 26 weeks, and an increase of 92 m at 52 weeks (versus a decline of 47 m with the short programme). The authors were unable to define an optimum programme length.

Although some of the evidence appears to suggest greater benefit of longer rehabilitation programmes, limitations of the review including the absence of a meta-analysis, and lack of clinical significance with some outcomes, mean that current recommendations in NICE CG101 are unlikely to be affected. Detailed information on pulmonary rehabilitation can be found in the British Thoracic Society's pulmonary rehabilitation guideline (British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation 2001).

Key reference

Beauchamp MK, Janaudis-Ferreira T, Goldstein RS et al. (2011) Optimal duration of pulmonary rehabilitation for individuals with chronic obstructive pulmonary disease - a systematic review. Chronic respiratory disease 8: 129–40
Abstract: www.crd.sagepub.com/content/8/2/129.abstract

Hospital versus community

Waterhouse et al. (2010) conducted a powered, randomised 2 x 2 trial of 240 patients (mean age ~69 years) comparing pulmonary rehabilitation in a hospital versus community setting, followed by telephone or conventional follow-up. They found no significant difference in the percentage change in the distance walked during an Endurance Shuttle Walk Test (designed to walk people without encouragement at a predetermined speed to ensure they are at 85% of their maximum oxygen capacity [VO_2 max]) relative to baseline between the hospital (108.7%) and the community (90.95%) rehabilitation groups (mean difference 17.8%; 95% CI −24.3 to 59.9; p = 0.405). There was also no significant difference between the groups in terms of the increase in the time that they were able to walk for post-rehabilitation. The absence of any significant differences in these outcomes continued at 6-month 12-month and 18-month post-rehabilitation follow-ups, at which times there also appeared to be no indication of an effect of telephone versus conventional follow-up. An economic analysis also conducted by the authors indicated no cost advantage to either of the rehabilitation settings or to telephone follow up. A post-hoc analysis found a strong trend (falling marginally short of statistical significance) towards an effect on rehabilitation outcomes depending on the rehabilitation team, which may warrant further investigation.

The evidence suggests that there seems to be no clinical or cost benefit of community-based over hospital-based rehabilitation, and the venue may be best determined by local access preferences and transport links. This evidence therefore reinforces current recommendations in NICE CG101.

Key reference

Waterhouse JC, Walters SJ, Oluboyede Y et al. (2010) A randomised 2 x 2 trial of community versus hospital pulmonary rehabilitation for chronic obstructive pulmonary disease followed by telephone or conventional follow-up. Health Technology Assessment 14: 1–164
Full text: www.hta.ac.uk/project/1316.asp

Inspiratory muscle training

In a meta-analysis of 32 RCTs (830 patients), **Gosselink et al. (2011)** looked at the effect of inspiratory muscle training (IMT) in patients with COPD. Significant improvements were found in a number of outcomes including maximal inspiratory muscle strength (+13 cm H_2O; $p < 0.001$), respiratory muscle endurance time (+261 seconds; $p < 0.001$), 6MWD or 12MWD (+32 m and +85 m respectively; $p < 0.001$), TDI (+2.8; $p < 0.001$) and quality of life measured by CRQ (+3.8 units; $p < 0.01$). For inspiratory muscle strength and exercise capacity, individuals with inspiratory muscle weakness (maximal inspiratory pressure < 60 cm H_2O) were more likely to improve.

This evidence suggests the potential of IMT in pulmonary rehabilitation, but may not yet provide definitive answers as to whether IMT should be added to other forms of rehabilitation, and especially as to whether there is a subgroup of patients with inspiratory muscle weakness who may benefit. Further research is needed to evaluate IMT and whether those with muscle weakness can feasibly be identified and treated effectively with this intervention.

Thomas et al. (2010) also investigated IMT as part of a systematic review of home-based physiotherapy interventions. In a meta-analysis of the three RCTs (34 patients) included in the review examining the use of IMT in the home setting, they found that IMT significantly improved breathlessness score measured by TDI by 2.36 (95% CI 0.76 to 3.96) compared with controls. Although this analysis suggests that home-based IMT may be effective, because of potential limitations of the evidence (limited numbers of patients and treatment heterogeneity between studies), more research is needed to determine whether IMT can be added to or substituted for standard pulmonary rehabilitation techniques, before firm recommendations can be made.

Overall, there may not yet be enough robust and conclusive evidence to consider including IMT in future updates of NICE CG101.

Key references

Gosselink R, De Vos J, van den Heuvel SP et al. (2011) Impact of inspiratory muscle training in patients with COPD: what is the evidence? European Respiratory Journal 37: 416–25
Abstract: www.erj.ersjournals.com/content/37/2/416.abstract

Thomas MJ, Simpson J, Riley R et al. (2010) The impact of home-based physiotherapy interventions on breathlessness during activities of daily living in severe COPD: a systematic review. Physiotherapy 96: 108–19
Abstract: www.sciencedirect.com/science/article/pii/S0031940609001205

Severe COPD

Fernandez et al. (2009) conducted an RCT of 42 male patients (mean age 66 years in the intervention group, 70 years in the control group) to examine the safety and efficacy of a home-based pulmonary rehabilitation programme for patients with very severe COPD on long-term oxygen therapy (LTOT). Although baseline characteristics were largely balanced between the groups, some appeared to be outside of expected ranges for patients of this

disease severity (for example, medical research council dyspnoea scores of 2.6 in the treatment arm and 2.3 in the control arm; body mass index [BMI] ~29; and 6MWD ~60% of predicted), which potentially reduces the external validity of findings.

The rehabilitation programme included a simple set of home exercises and low-intensity supervision comprising two hospital visits and four home visits over 2 months. Those receiving rehabilitation showed a significant increase in 6MWD (313 ± 72 m vs 392 ± 82 m; p = 0.0001 [exceeding the 54 m difference stated by the authors to indicate clinical significance]) and a significant improvement in HRQOL indicated by a reduction in the SGRQ score (55.3 ± 15.0 vs 40.5 ± 13.8; p = 0.0001). No complications arose from performing the exercises. This study appears to reinforce the recommendation in NICE CG101 that pulmonary rehabilitation should be offered to all patients who consider themselves functionally disabled by COPD, and serves as a reminder that this may extend to those even with the most severe disease on LTOT.

Key reference
Fernandez AM, Pascual J, Ferrando C et al. (2009) Home-based pulmonary rehabilitation in very severe COPD: Is it safe and useful? Journal of cardiopulmonary rehabilitation and prevention 29: 325–31
Abstract: www.journals.lww.com/jcrjournal/Abstract/2009/09000/Home_Based_Pulmonary_Rehabilitation_in_Very_Severe.10.aspx

Nordic walking

Breyer et al (2009) performed an RCT of 60 patients (mean age ~60 years) with COPD investigating the effect of Nordic walking (a walking technique involving specialised poles) on daily physical activities (measured by a tri-axial accelerometer) and functional exercise capacity (measured by 6MWD). After a 3-month training period, patients in the Nordic walking group spent more time walking (14.9 ± 1.9 minutes/day) and standing (129 ± 26 minutes/day) and their intensity of walking also increased (0.40 ± 14 m/s^2) compared with baseline as well as with controls (all $p < 0.01$). 6MWD also increased (79 ± 28 m) compared with baseline and controls (both $p < 0.01$). These improvements remained at 6-month and 9-month follow-up.

A number of issues may prevent definitive conclusions including the limited number of patients and a lack of details about the intervention (whether Nordic walking continued during follow up; what type of terrain was used; and the time of year). Data for pulmonary function, BMI, HRQOL and GOLD status were not reported, and no long-term survival information was given. A lack of previous studies of this intervention in COPD also meant that the trial could not be powered appropriately.

This preliminary evidence suggests that Nordic walking may be a useful addition to current pulmonary rehabilitation strategies and larger studies are now needed comparing the intervention with other techniques, and looking at additional, longer term outcomes such as survival, resource usage and patient satisfaction. There are no current implications for NICE CG101.

Key reference
Breyer MK, Breyer-Kohansal R, Funk GC et al. (2010) Nordic Walking improves daily physical activities in COPD: A randomised controlled trial. Respiratory research 11: 112
Full text: www.respiratory-research.com/content/pdf/1465-9921-11-112.pdf

Vaccination and anti-viral therapy

A Cochrane review of seven studies (1709 patients) by **Walters et al (2010)** examined the use of injectable vaccines against pneumococcal infections in patients with COPD. From an analysis of six studies (1372 patients) it was found that pneumococcal vaccination did not significantly reduce the likelihood of developing pneumonia compared with controls

(OR = 0.72; 95% CI 0.51 to 1.01). A further analysis of two studies (216 patients) found that reduction in likelihood of acute COPD exacerbations was also not significant (OR = 0.58; 95% CI 0.30 to 1.13). For secondary outcomes, pooled results of three studies (888 patients) did not show a significant reduction in all-cause mortality or death from cardio-respiratory causes.

These conclusions appear to be counter to the recommendations in NICE CG101 that pneumococcal vaccination should be offered to all patients with COPD. However any potential impact on current guidance may be limited by the quality of the evidence; two included studies were abstracts from which only the published abstract data were used, and two studies were from the 1980s, when only 14-valent vaccines were used (modern vaccines are 23-valent). Larger, well designed clinical trials are therefore needed of the newer polyvalent vaccines in COPD (although this may be difficult in the UK where the 5-yearly pneumococcal vaccine has become standard practice).

Key reference
Walters JAE, Smith S, Poole P et al. (2010) Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews issue 11: CD001390
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD001390.pub3/pdf

Multidisciplinary management

Hospital at home

Wong et al. (2011) performed a Cochrane systematic review of nine RCTs (1498 patients) investigating home care by outreach nursing for COPD. A pooled analysis of eight studies found mortality was not significantly reduced at 12 months (OR = 0.72; 95% CI 0.45 to 1.15) and from pooling five studies found no significant difference in hospitalisations (OR = 1.01; 95% CI 0.71 to 1.44). A further pooled analysis of four studies did however find a significant improvement in HRQOL (mean difference [MD] = −2.61; 95% CI −4.82 to −0.40).

There was considerable heterogeneity between the included studies in terms of the inclusion criteria (ranging from patients on LTOT with life expectancy < 2 years through to patients with one respiratory symptom, an FEV_1 < 80% and FEV_1/FVC < 70%) and the interventions (ranging from two home visits by a respiratory nurse through to 1 hour/week home teaching for 8 weeks followed by weekly phone calls for 8 weeks and monthly calls for the remainder of the year). The heterogeneity between studies may limit any conclusions and there is unlikely to be an impact on current recommendations in NICE CG101. To further investigate the movement of long-term follow-up services into the community, longer and larger well-designed studies are needed looking at clearly defined populations and intervention types.

Key reference
Wong CX, Carson KV, Smith BJ (2011) Home care by outreach nursing for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews issue 3: CD000994
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD000994.pub2/pdf

Education and self-management

In a Cochrane review of 5 studies (574 patients) **Walters et al. (2010)** investigated the effect of action plans involving limited patient education only for exacerbations of COPD. The intervention consisted of an educational session with the patient lasting up to 1 hour only, with a resulting personal action plan. Participants receiving the intervention had greater use of corticosteroids (mean difference [MD] 0.74; 95% CI 0.14 to 1.35) and antibiotics (OR 1.65; 95% CI 1.01 to 2.69) but this did not result in reduced hospital admissions (MD 0.23; 95% CI –0.03 to 0.49). There was no mortality benefit, other benefits were minor and HRQOL was

largely unchanged. The evidence suggests that a single, short educational session is unlikely to benefit health outcomes.

Rice et al. (2010) examined a more complex programme in a multicentre RCT of 743 patients (mean age ~70 years) with severe COPD. Although the authors refer to the intervention as a 'relatively simple disease management programme' it was more intensive than those looked at by Walters et al. (2010). Patients in the treatment arm received a single 1–1.5 hour education session, an action plan for self-treatment of exacerbations, and monthly follow-up calls from a case manager.

After 1 year, among those receiving disease management the mean cumulative frequency of hospitalisations and emergency department visits was 0.48 per patient compared with 0.82 in usual care (difference 0.34; 95% CI 0.15 to 0.52; $p < 0.001$). The trial involved almost entirely male and relatively high-risk patients, and was based in the USA. This evidence in terms of the incorporation of case management and structured action plans, particularly for higher risk patients, may be a consideration for future reviews of NICE CG101.

Further research may now be needed to investigate multidimensional and more intensive educational programmes and action plans, looking at effects in wider patient groups on long-term outcomes such as exacerbations and utilisation of healthcare resources.

Key references

Rice KL, Dewan N, Bloomfield HE et al. (2010) Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. American journal of respiratory and critical care medicine 182: 890–896
Full text: www.ajrccm.atsjournals.org/cgi/content/full/182/7/890

Walters JAE, Turnock AC, Walters EH et al. (2010) Action plans with limited patient education only for exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews issue 5: CD005074
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD005074.pub3/pdf

1.3 Management of exacerbations of COPD

Oxygen therapy during exacerbations

In an RCT of 405 patients (mean age 69 years) examining titrated versus high flow oxygen treatment in the prehospital (ambulance/paramedic) setting, **Austin et al. (2010)** found that in a sub-group analysis of patients with confirmed COPD (titrated, n = 97; high flow, n = 117), mortality was reduced by 78% in patients receiving titrated oxygen treatment compared with those who received high flow oxygen (relative risk = 0.22; 95% CI 0.05 to 0.91; $p = 0.04$). Mortality in the confirmed COPD subgroup was 9% (11 deaths) in the high flow arm and 2% (2 deaths) in the titrated oxygen arm ($p = 0.04$). Patients with COPD who received titrated oxygen were also less likely to have respiratory acidosis ($p = 0.01$) and hypercapnia ($p = 0.02$). There were some compliance issues in the study, particularly related to off-protocol use of high flow oxygen at some point in the titration arm.

This evidence appears to support the assertion in the British Thoracic Society's guideline for emergency oxygen use in adult patients (O'Driscoll et al. 2008) that 'oxygen is a treatment for hypoxaemia, not breathlessness' and 'oxygen (should) be prescribed according to a target saturation range'. The evidence also appears to agree with current recommendations in NICE CG101 that oxygen should be given to keep the saturation level within the individualised target range.

A recent comment piece by Beasley et al. (2011) summarising the latest evidence on high-concentration oxygen therapy in COPD (including Austin et al. 2010) affirmed that the preferred initial treatment in acute exacerbations of COPD is oxygen titration.

Key reference
Austin MA, Wills KE, Blizzard L et al. (2010) Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. British Medical Journal 341: c5462
Full text: www.bmj.com/content/341/bmj.c5462.full.pdf

Supporting reference
Beasley R, Patel M, Perrin K et al. (2011) High-concentration oxygen therapy in COPD. Lancet 10: 969–70
Abstract: www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)61431-1/fulltext

Prognosis following an exacerbation

Hoogendoorn et al. (2011) performed a meta-analysis of six cohort studies (57,144 patients) and found that a severe exacerbation needing hospitalisation resulted in a weighted mean case-fatality rate of 15.6% (95% CI 10.9 to 20.3%) with an average in-hospital mortality rate of 6.7%. There were some potential methodological concerns with the review; no discussion about which study types to include was apparent, no reports of quality assessment of the studies were provided, and there was no mention of publication bias.

Within the possible limitations of the evidence, this study indicates the potentially high risk of dying around the time of an acute exacerbation, and that the critical period appears to extend beyond the duration of the hospitalisation. The evidence is unlikely to affect NICE CG101, but emphasises the risks associated with severe exacerbations (in particular the continued elevated risk after discharge), which should be managed according to current guidance.

An observational cohort study of 2138 patients by Hurst et al. (2010) provides further context, noting that exacerbations increased with the severity of COPD. Frequent exacerbations were observed in 22% of patients with GOLD stage 2 disease (exacerbation rate = 0.85 per person during first year of follow-up), 33% with stage 3 (rate = 1.34), and 47% with stage 4 (rate = 2.00). It was also found that a history of exacerbations appeared to be the best predictor of exacerbations at all stages of disease.

Taken together, the two studies show that those with a history of exacerbations and more severe disease may potentially be more likely to experience exacerbations with increased frequency, and that exacerbations may be associated with a high risk of death, even after discharge.

Key reference
Hoogendoorn M, Hoogenveen RT, Rutten-van Molken MP et al. (2011) Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. European Respiratory Journal 37: 508–15
Abstract: www.erj.ersjournals.com/content/37/3/508.abstract

Supporting reference
Hurst JR, Vestbo J, Anzueto A et al. (2010) Susceptibility to exacerbation in chronic obstructive pulmonary disease. New England Journal of Medicine 16: 1128–38
Full text: www.nejm.org/doi/pdf/10.1056/NEJMoa0909883

Pulmonary rehabilitation following an exacerbation

In a Cochrane review of nine trials (432 patients), **Puhan et al. (2011)** found that pulmonary rehabilitation significantly reduced hospital admissions (OR = 0.22; 95% CI 0.08 to 0.58) and mortality (OR = 0.28; 95% CI 0.10 to 0.84) in patients who had recently experienced an exacerbation. This evidence reinforces the value of post-exacerbation rehabilitation and may be a consideration in future reviews of NICE CG101, although the included trials were small.

Key reference
Puhan MA, Gimeno-Santos E, Scharplatz M et al. (2011) Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews issue 10: CD005305
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD005305.pub3/full

Areas not currently covered by NICE guidance

Risk factors

In a meta-analysis of 23 studies, **Fisk et al. (2010)** found that the presence of residential dampness and mould may be linked with both bronchitis (summary estimate OR = 1.45; 95% CI 1.34 to 1.56) and respiratory tract infections (summary estimate OR = 1.45; 95% CI 1.34 to 1.56). These values remained largely unchanged when the analyses were restricted to studies controlling for major confounding variables (age, gender, smoking and socioeconomic status). Some potential issues with the quality of the review should be considered when interpreting the results (only one database was searched, the included studies were largely cross-sectional along with some birth-cohort and case-control studies, and there was no indication that studies were quality assessed). There was some evidence of publication bias in the respiratory infection studies, however a further analysis to take this into account indicated publication bias had little effect on the original summary estimates.

Bearing in mind the potential limitations of the study, this evidence suggests that dampness and mould in the home may be associated with lung health problems, and these data may be relevant to the aetiology of COPD, particularly in the context of the potential links between COPD and poverty. Some patients with COPD may feel that their ill health is linked to domestic mould or dampness, and in light of this evidence further research may be warranted. This area is not currently addressed by NICE CG101.

Key reference
Fisk WJ, Eliseeva EA, Mendell MJ (2010) Association of residential dampness and mold with respiratory tract infections and bronchitis: A meta-analysis. Environmental Health 9: 72
Full text: www.ehjournal.net/content/pdf/1476-069X-9-72.pdf

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs).

Managing stable COPD

Smoking cessation

- Smoking cessation and nicotine replacement therapy in COPD patients
  www.library.nhs.uk/duets/ViewResource.aspx?resID=411746

Inhaled therapy

- Tiotropium plus formoterol vs tiotropium alone in patients with stable COPD
  www.library.nhs.uk/duets/ViewResource.aspx?resID=411748
- Effects of long acting inhaled anticholinergics on cardiovascular events and mortality among vulnerable subgroups at the highest risk of systemic anticholinergic effects
  www.library.nhs.uk/duets/ViewResource.aspx?resID=411747

Pulmonary rehabilitation

- Optimal duration of pulmonary rehabilitation in COPD patients for quality of life and exercise capacity
  www.library.nhs.uk/duets/ViewResource.aspx?resID=411749
- Inspiratory muscle strength training vs endurance training in patients with COPD to improve maximal inspiratory pressure and functional exercise capacity
  www.library.nhs.uk/duets/ViewResource.aspx?resID=411750
- Home-based physiotherapy interventions to reduce breathlessness during activities of daily living in severe COPD
  www.library.nhs.uk/duets/ViewResource.aspx?resID=411751

Vaccination and anti-viral therapy

- Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease
  www.library.nhs.uk/duets/ViewResource.aspx?resID=411737

Multidisciplinary management

- Home care by outreach nursing for chronic obstructive pulmonary disease
  www.library.nhs.uk/duets/ViewResource.aspx?resID=411071
- Action plans with limited patient education only for exacerbations of chronic obstructive pulmonary disease
  www.library.nhs.uk/duets/ViewResource.aspx?resID=411739

Further evidence uncertainties for COPD can be found at www.library.nhs.uk/duets/ and in the NICE research recommendations database at www.nice.org.uk/research/index.jsp?action=rr.

DUETs has been established in the UK to publish uncertainties about the effects of treatment which cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Chronic obstructive pulmonary disease. NICE clinical guideline 101 (2010). Available from www.nice.org.uk/guidance/CG101

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 20 August 2009 (the end of the search period of the most recent annual Evidence Update) to 15 June 2011:

- CINAHL
- Cochrane Database of Systematic Reviews – Cochrane Library
- Embase
- MEDLINE

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews (www.sign.ac.uk/methodology/filters.html).

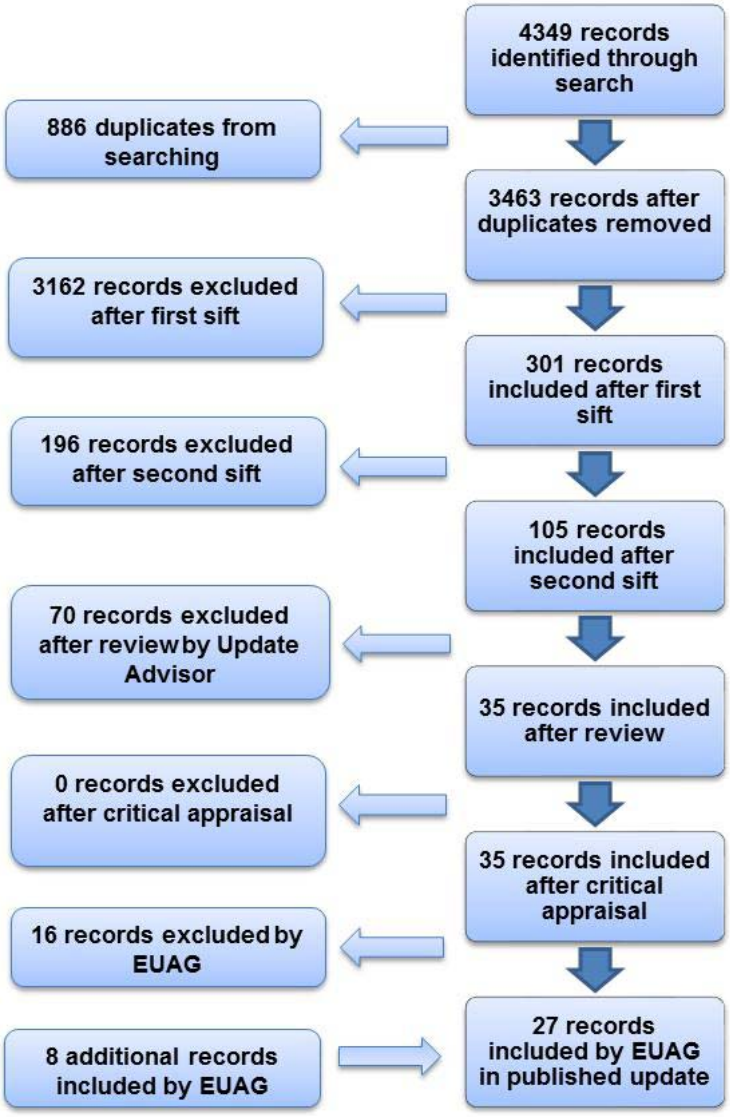
An additional 8 papers were also identified as key new evidence by the EUAG (Buhl 2011, Chapman 2011, Dahl 2010, Donohue 2010, Korn 2011, Kornmann 2011, Puhan 2011, Vogelmeier 2011). Commentaries on these papers are included in this Evidence Update.

Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Update Adviser (the chair of the EUAG), and the full search strategies, are available on request from contactus@evidence.nhs.uk.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp Pulmonary Disease, Chronic Obstructive/
2	copd.ti,ab.
3	coad.ti,ab.
4	Bronchitis/
5	Chronic bronchitis/
6	(chronic adj5 (obstruct$ or limit#$)).ti.
7	(obstruct$ adj3 (airflow$ or airway$ or respirat$ or lung or pulmonary) adj2 (disease$ or disorder$)).ti,ab.
8	Pulmonary emphysema/
9	emphysema.ti,ab.
10	"chronic bronchitis".ti,ab.
11	or/1-10
12	bronchial neoplasms/ or exp bronchiectasis/ or exp bronchiolitis/ or cystic fibrosis/ or lung diseases, interstitial/ or lung neoplasms/
13	exp Sleep Apnea Syndromes/
14	Bronchopulmonary Dysplasia/
15	(cancer or neoplas$).ti.
16	"acute bronchitis".ti.
17	sleep apnea.ti.
18	(bronchiolitis or bronchiectasis).ti.
19	interstitial.ti.
20	(interstitial adj2 (lung or pulmonary or airway$ or airflow$)).ti.
21	exp Asthma/
22	asthma.ti.
23	or/12-22
24	11 not 23
25	letter/
26	editorial/
27	exp historical article/
28	Anecdotes as Topic/
29	comment/
30	case report/
31	animal/ not (animal/ and human/)
32	Animals, Laboratory/
33	exp animal experiment/
34	exp animal model/
35	exp Rodentia/
36	or/25-35
37	24 not 36
38	limit 37 to english language
39	(exp child/ or exp infant/) not exp adult/
40	38 not 39

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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