NICE National Institute for Health and Care Excellence

Surveillance report 2016 – Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2010) NICE guideline CG101

Surveillance report

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Contents

Surveillance decision

We will plan an update of the guideline.

Reason for the decision

We found 498 new studies through surveillance of this guideline. New evidence that could affect recommendations was identified. Topic experts, including those who helped to develop the guideline, advised us about whether the following sections of the guideline should be updated:

Diagnosing COPD

- Is routine assessment using multidimensional severity assessment indices (e.g. BODE) more predictive of outcomes compared with FEV_1 alone?
- What are the most appropriate tests in a patient with suspected COPD to confirm the diagnosis?

Managing stable COPD

- What is the clinical and cost effectiveness of long-acting muscarinic antagonists (LAMAs) plus long-acting beta2 agonists (LABAs) compared to long-acting muscarinic antagonists in the management of people with stable COPD?
- What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists compared to long-acting muscarinic antagonists in the management of people with stable COPD?
- What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists compared to long-acting beta2 agonists plus inhaled corticosteroids (ICSs) in the management of people with stable COPD?
- Which patients with stable COPD should be treated with long-acting anticholinergics? How should the effects of this treatment be assessed?
- What is the role of antibiotic therapy in patients with stable COPD?

- In patients with stable COPD what therapies can be used to manage pulmonary hypertension?
- Do self-management plans and patient education affect concordance with treatment and improve outcomes in patients with stable COPD?
- What is the role of oxygen therapy in patients with stable COPD?
- In patients with stable COPD, what are the referral criteria for lung surgery?

Management of exacerbations of COPD

- What are the factors known to cause exacerbations of COPD?

New evidence was identified for all the above questions which may impact on recommendations. Please see appendix A for further details.

Decision: These review questions should be updated.

Managing stable COPD

- What is the clinical and cost effectiveness of long-acting muscarinic antagonists compared with long-acting beta2 agonists in the management of people with stable COPD?
- What is the clinical and cost effectiveness of long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting beta2 agonists in the management of people with stable COPD?
- What is the clinical and cost effectiveness of long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists in the management of people with stable COPD?
- What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus inhaled corticosteroids compared to long-acting beta2 agonists in the management of people with stable COPD?
- What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists in the management of people with stable COPD?

- What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting beta2 agonists plus inhaled corticosteroids in the management of people with stable COPD?
- What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting muscarinic antagonists alone in the management of people with stable COPD?
- What is the clinical and cost effectiveness of long-acting muscarinic antagonists compared to short-acting muscarinic antagonists in the management of people with stable COPD?
- What is the clinical and cost effectiveness of long-acting muscarinic antagonists plus long-acting beta2 agonists plus inhaled corticosteroids compared to long-acting beta2 agonists plus long-acting muscarinic antagonists in the management of people with stable COPD?

No new evidence was identified which indicated a need to update the above-mentioned clinical questions; however, they should be updated because they are directly related to other clinical questions in the pathway for inhaled bronchodilator therapy that have been identified for update. The pathway for inhaled therapy is considered as a whole therefore if an individual component of the pathway is amended it is likely that this will impact on other related components.

Decision: These review questions should be updated.

Managing stable COPD

- Which patients with stable COPD should be treated with inhaled steroids? How should the effects of this treatment be assessed?
- What are the most appropriate delivery systems for giving inhaled therapy to patients with stable COPD?

Decision: These review questions should not be updated; however, footnotes highlighting safety considerations will be added to the guideline. This is due to:

- A Drug Safety Update, published in 2010, outlining psychological and behavioural side effects associated with inhaled steroids.

- A Drug Safety Update, published in February 2015, outlining a number of safety considerations when prescribing tiotropium delivered via Respimat or Handihaler to patients with certain cardiac conditions.

Other clinical areas

We also found new evidence that was not thought to have an effect on current recommendations. This evidence related to symptoms; spirometry; further investigations; reversibility testing; identification of early disease; referral for specialist advice; smoking cessation; delivery systems used to treat patients with stable COPD; oral therapy; pulmonary rehabilitation; vaccination and anti-viral therapy; alpha-1 antitrypsin replacement therapy; multi-disciplinary assessment; assessment of need for hospital treatment; hospital-at-home and assisted-discharge schemes; non-invasive ventilation and discharge planning.

Overall decision

After considering all the new evidence and views of topic experts, we decided that an update is necessary for this guideline.

See how we made the decision for further information.

Commentary on selected new evidence

With advice from topic experts we selected 3 studies for further commentary.

Managing stable COPD – Inhaled combination therapy

We selected a network meta-analysis by Oba et al. (2016) for a full commentary because it compared dual bronchodilator therapy (LAMA plus LABA) with LAMA or LABA monotherapy. It was considered that these comparisons may affect guideline recommendations.

What the guideline recommends

Section 1.2.2.6 of CG101 states:

"In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, offer the following as maintenance therapy:

- if $FEV_1 \geq 50\%$ predicted: either LABA or LAMA
- if $FEV_1 < 50\%$ predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA."

Methods

The network meta-analysis by Oba et al. (2016) pooled data from 23 randomised controlled trials, including 27,172 patients, comparing any LAMA plus LABA combination with LAMAs alone, LABAs alone or placebo.

Published and unpublished studies that enrolled patients with moderate to severe COPD, without an acute or recent exacerbation, were included. Additionally, included studies had to be at least 12 weeks in duration. The LAMA group comprised aclidinium, glycopyrronium, umeclidinium and tiotropium while the LABA group comprised formoterol, indacaterol, olodaterol, salmeterol and vilanterol. The LAMA plus LABA group included of any combination of the aforementioned LAMAs and LABAs. Outcome measures included

change from baseline in FEV_1 (in litres), St Georges Respiratory Questionnaire (SGRQ) scores and Transitional Dyspnoea Index (TDI) scores, as well as COPD exacerbation, mortality, serious adverse event, and cardiac serious adverse event rates.

Authors performed a network meta-analysis, using Bayesian Markov chain Monte Carlo approach, as well as a pairwise comparison meta-analysis.

Results

Change from baseline in trough FEV_1 data were available for 4 trials (n=4836 patients) with 12 month follow-up periods. LAMA plus LABA combinations were ranked as the most effective class in improving FEV_1 measurements followed by LAMAs then LABAs. When dual therapy was compared against placebo, the mean difference in FEV_1 measurements was 243 ml (95% Credible Interval [CrI]; 139 to 351) in favour of dual therapy. The mean difference in trough FEV_1 between the LAMA plus LABA group and the LAMA monotherapy group was 73 ml (95% CrI 43 to 149), in favour of the dual therapy. The mean difference in trough FEV_1 between the LAMA plus LABA group and the LABA monotherapy group was 104 ml (95% CrI 84 to 126), in favour of the dual therapy. Authors state that no significant differences in changes in trough FEV_1 were observed between drug classes.

Change from baseline data in SGRQ scores was available from 9 trials (n=12,716) at 6 month follow-up. SGRQ scores range from 0 to 100 with lower scores indicating better quality of life. Dual therapy was ranked highest followed by LABAs and LAMAs in all SGRQ outcomes. LAMA plus LABA combinations reduced SGRQ scores by a mean of 4.1 points (95% CrI 2.3 to 5.9) compared with placebo. When compared with LAMA monotherapy, LAMA plus LABA combinations reduced SGRQ scores by a mean of 1.6 (95% CrI 0.5 to 2.8) points. Finally, dual therapy reduced SGRQ scores by a mean of 1.1 (95% CrI 0.4 to 2.5) compared with LABA monotherapy. Data on SGRQ responders (patients who had at least a 4 point improvement in scores – the minimal clinically important improvement) were available from 12 trials at 6 month follow-up. A significantly greater proportion of SGRQ responders was reported in the LAMA plus LABA group compared with the LAMA monotherapy group (Odds ratio [OR] 1.23; 95% CrI 1.06 to 1.39) and LABA monotherapy group (OR 1.24; 95% CrI 1.11 to 1.36).

Change from baseline data in TDI scores was available from 8 trials (n=14,568) at 6 month follow-up. TDI scores range from −9 to 9 with lower scores indicating a more severe dyspnoea. Dual bronchodilation was ranked highest followed by LABAs and LAMAs. At 3 month follow-up, dual bronchodilation yielded a significant improvement in TDI scores

compared with placebo (mean difference 1.17; 95% CrI 0.96 to 1.38), LAMAs (mean difference 0.40; 95% CrI 0.26 to 0.53), and LABAs (mean difference 0.35; 95% CrI 0.24 to 0.47). All observations were statistically significant. Data on TDI responders (patients who had at least a 1 point improvement in scores – the minimal clinically important improvement) were available from 7 trials at 6 month follow-up. A significantly greater proportion of TDI responders was reported in the LAMA plus LABA group compared with the LAMA monotherapy group (OR 1.34; 95% CrI 1.16 to 1.56) and LABA monotherapy group (OR 1.30; 95% CrI 1.13 to 1.48).

COPD exacerbation data were available from 16 trials (n=18,224) for moderate-to-severe exacerbations and 19 trials (n=25,401) for severe exacerbations (follow-up period was not specified). Dual bronchodilation was associated with significantly fewer moderate-to-severe exacerbations compared with placebo (Hazard ratio [HR] 0.66; 95% CrI 0.57 to 0.77) and LABA alone (HR 0.82; 95% CrI 0.73 to 0.93), but not when compared with LAMA alone (HR 0.92; 95% CrI 0.84 to 1.00). No significant differences in the occurrence of severe exacerbations were observed when LAMA plus LABA combinations were compared with placebo, LABAs or LAMAs.

Due to a considerable degree of overlap in CrIs and rankings, authors stated that there were no significant differences in mortality, serious adverse event, and cardiac serious adverse event rates between groups.

Strengths and limitations

Strengths

The network meta-analysis included a number of strengths:

- The study was robust in terms of study identification, selection, data extraction and data synthesis.
- Included studies were consistent in their key inclusion and exclusion criteria. Generally, patients who were over 35 years, with a diagnosis of COPD in accordance with the American Thoracic Society-European Respiratory society or GOLD guidelines, a smoking history of at least 10 pack-years, and moderate to severe COPD (FEV_1 ranging from 30 to 70% predicted) were included.

- Validated outcome measure which have previously been used to assess COPD (SGRQ and TDI scores) were assessed.

Limitations

The following limitations were identified:

- Authors pooled data on different medications within each drug class to make comparisons.
- The number of included trials varied according to each outcome measure and follow-up period: for example, trough FEV_1 data were available for less than 20% of patients at 12 month follow-up.
- The concomitant use of a fixed dose inhaled corticosteroids (ICS) was permitted in most studies. Authors do not provide any details as to what corticosteroids were used.
- Authors state that there was no evidence of inconsistency within the network but highlight that there may not have been sufficient power to detect inconsistency.

Impact on guideline

The study provides evidence of benefits of dual bronchodilation over LABA or LAMA monotherapy in patients with moderate to severe COPD. Topic experts felt that the new evidence highlights advantages of using dual bronchodilation over monotherapy, in patients with moderate to severe COPD, and suggested that there is a need to review the algorithm for inhaled therapy

Managing stable COPD – Inhaled combination therapy

We selected a network meta-analysis by Tricco et al. (2015) for a full commentary because it provides comparative evidence of different long-acting inhaled therapies (LAMA or LABA monotherapy versus dual bronchodilator therapy with or without ICS) that may impact on guideline recommendations.

What the guideline recommends

Section 1.2.2.6 of CG101 states:

"In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, offer the following as maintenance therapy:

- if $FEV_1 \geq 50\%$ predicted: either LABA or LAMA
- if $FEV_1 < 50\%$ predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA."

Section 1.2.2.7 recommends:

"In people with stable COPD and an $FEV_1 \geq 50\%$ who remain breathless or have exacerbations despite maintenance therapy with a LABA:

- consider LABA+ICS in a combination inhaler
- consider LAMA in addition to LABA where ICS is declined or not tolerated."

Methods

Tricco et al (2015) performed a network meta-analysis of 208 randomised controlled trials, including 134,692 patients, which aimed to compare the safety and effectiveness of various combinations of LAMAs, LABAs and ICSs for managing COPD.

Randomised controlled trials including adults with COPD who received long-acting inhaled agents in any combination compared against each other or placebo, were eligible for inclusion. The majority of patients (61%) had moderate-to-severe COPD. Published studies were included regardless of duration of follow-up, date of dissemination or publication status. Unpublished studies conducted after 2004 were included.

A random-effects network meta-analysis was performed because authors assumed that treatment effects were heterogeneous across included studies. A design-by-treatment interaction model was used because included studies had varying numbers of study arms. The primary outcome of interest was the proportion of patients with moderate-to-severe COPD exacerbations. Secondary outcomes included mortality and the occurrence of pneumonia.

Results

A network meta-analysis of 20 of the 208 identified randomised controlled trials, including 26,141 patients, showed that the following medications were more effective than placebo in reducing the risk of moderate-to-severe COPD exacerbations: tiotropium, salmeterol, indacaterol, formoterol plus budesonide, salmeterol plus fluticasone, glycopyrronium plus indacaterol, tiotropium plus salmeterol plus fluticasone and tiotropium plus formoterol plus budesonide. Of all interventions, tiotropium plus formoterol plus budesonide (OR 0.23; 95% CrI 0.14 to 0.40) and glycopyrronium plus indacaterol (OR 0.48; 95% CrI 0.36 to 0.64) were found to be the most effective agents in reducing the risk of exacerbations when compared with placebo. These results were statistically significant.

A network meta-analysis of 88 randomised controlled trials, including 97,526 patients, indicated that the ultra LABA, AZD3199 (OR 0.46; 95% CrI 0.02 to 10.32), and the combination of tiotropium and formoterol (OR 0.66; 95% CrI 0.08 to 5.18) were the most effective agents in reducing the risk of mortality compared to placebo. However, these results were not statistically significant. Only fluticasone plus salmeterol significantly decreased the risk of mortality when compared with placebo (OR 0.78; 95% CrI 0.63 to 0.96). Analysis also revealed that formoterol increased the risk of mortality when compared with fluticasone plus salmeterol (OR 1.64; 95% CrI 1.01 to 2.67). Furthermore, fluticasone plus salmeterol resulted in a reduced risk of mortality compared fluticasone alone (OR 0.75; 95% CrI 0.60 to 0.94).

To assess the risk of pneumonia, authors pooled data from 54 randomised controlled trials including 61,551 patients. A treatment hierarchy was obtained using the Surface Under the Cumulative Ranking (SUCRA) curve analysis. This approach allowed for ranking of interventions according to the probability of being the least effective in reducing the risk of pneumonia. The most harmful agents were salmeterol plus fluticasone (89% probability), vilanterol plus fluticasone (88%) and fluticasone alone (82%). Unfortunately, authors did not report OR data from the network meta-analysis in the manuscript.

Strengths and limitations

Strengths

The network meta-analysis included a number of strengths:

- The study was robust in terms of study identification, selection, data extraction and data synthesis.
- Since the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria have changed over time, a clinician reviewed all of the included studies to ascertain the average COPD severity of patients included in each randomised controlled trial.
- Before performing the analysis, authors assessed whether any systematic differences were prevalent in the distribution of potential treatment effect modifiers across treatment comparisons in the network.
- Consistency of the data was extensively assessed. If inconsistency was identified, the loop-specific model was used to identify local inconsistency within the networks.

Limitations

The following limitations were identified:

- Only some trials contributed to each meta-analysis.
- Many of the included trials were at a high risk of bias for many of the Cochrane risk-of-bias criteria.
- Investigators did not adjust for differences in treatment doses and durations as they were inconsistently reported across included studies. The assumption was made that these factors had an equal impact on the treatment effect.

Impact on guideline

The study provides strong evidence that dual bronchodilator therapy (specifically, glycopyrronium plus indacaterol) is more effective than LAMA or LABA monotherapy and LABA plus ICS therapy in reducing the risk of moderate-to-severe COPD exacerbations. Topic experts agreed with the evidence and suggested that dual bronchodilation produces greater improvements in FEV_1 and dyspnoea than LABA plus ICS combinations in patients with severe COPD. However, new intelligence suggested that some LABA plus ICS combinations are becoming cheaper due to expiring patents. A review of the clinical and cost effectiveness of inhaled therapies may be needed to identify whether recommendations in the guideline should remain.

Managing stable COPD – Oral prophylactic antibiotic therapy

We selected a systematic review by Ni et al. (2015) for a full commentary because it provides evidence on antibiotic prophylaxis that may impact on guideline recommendations.

What the guideline recommends

Recommendation 1.2.3.12 in CG101 states that 'there is insufficient evidence to recommend prophylactic antibiotic therapy in the management of stable COPD'.

Methods

Ni et al (2015) performed a systematic review of 9 randomised controlled trials, including 1,666 patients, which aimed to evaluate whether prophylactic macrolide therapy prevented acute exacerbations of COPD.

Investigators included randomised controlled trials comparing patients with COPD (severity not specified) who received macrolide prophylaxis and those who did not receive macrolides (controls). Studies were included if they enrolled adults older than 18 years with stable COPD, confirmed by lung function testing ($FEV_1/FV<70\%$, $FEV_1<80\%$ predicted, and an increase in $FEV_1<12\%$ or <200 millilitres). Prophylactic use of macrolides must have been administered orally, in appropriate daily doses, for a minimum of 3 months.

Primary outcome measures included the number of patients with 1 or more exacerbations and the rate of exacerbations per patient per year. Secondary outcome measures included hospitalisation rates, all-cause mortality rates, quality of life scores and adverse event rates.

Results

Meta-analysis of 7 studies, including 1,614 patients, revealed that the proportion of patients with 1 or more exacerbations was significantly lower in the macrolide prophylaxis group than the control group (Risk ratio 0.7; 95% Confidence Interval [CI] 0.56 to 0.87; $p<0.01$; $I^2=66.43\%$).

Meta-analysis of 8 studies, including 1,582 patients, revealed that the rate of exacerbations per patient per year was significantly lower in the macrolide prophylaxis group than the control group (Rate ratio 0.58; 95% CI 0.43 to 0.78; p<0.01; I^2=67.8%). Subgroup analysis, according to type of macrolide, failed to show that azithromycin reduced the rate of exacerbations when administered for 3 months (Rate ratio 0.46; 95% CI 0. 18 to 1.18; p=0.11; I^2 not reported) but significantly reduced the rate of exacerbations when administered for 6 to 12 months (Rate ratio 0.82; 95% CI 0.76 to 0.90; p<0.01; I^2 not reported).

No significant differences in the hospitalisation rates and all-cause mortality rates were observed between groups (p values>0.05).

Meta-analysis of 4 studies, including 1,323 patients, assessed the impact azithromycin on SGRQ scores (scores range from by 0 to 100 with lower scores indicating better quality of life). Results indicated that SGRQ decreased by a mean of 2.12 points in patients who received azithromycin prophylaxis when compared to controls (95%CI 0.79 to 3.44; p=0.002; I^2=0%). Authors state that the result was statistically significant but did not reach the threshold for clinical significance (a 4 or more point difference in SGRQ scores).

Meta-analysis of adverse event rates revealed that the occurrence of adverse events (not specified) was marginally higher in the macrolide prophylaxis group (OR 1.55; 95% CI 1.003 to 2.39; p=0.049; I^2=15.04%).

Strengths and limitations

Strengths

The systematic review included a number of strengths:

- Multiple databases were searched and additional approaches were used to identify as many relevant studies as possible.
- Selection criteria were clear and specific, indicating that appropriate studies would have been included. Consistent diagnostic criteria were used in all included studies.
- Investigators excluded studies which included patients with bronchiectasis, asthma, cystic fibrosis and other genetic diseases.

Limitations

The following limitations were identified:

- I^2 values for the exacerbation rate meta-analyses were above 60%; indicating substantial heterogeneity.
- Authors do not provide any definition of a COPD exacerbation and state that exacerbation definitions were not consistent between included studies. As a result, it is unclear if exacerbation rates were overestimated or underestimated.
- The Jadad scale was used to assess the quality of RCTs included in the meta-analysis. This tool is used to assess the quality of RCTs and does not explicitly assess risk of bias.
- There is no indication that funnel plots were used to assess potential biases. Instead, authors state that Egger regression and subgroup analyses were performed.

Impact on guideline

Current recommendations state that there is insufficient evidence to recommend prophylactic antibiotic therapy in the management of stable COPD. The systematic review indicates some benefits of antibiotic prophylaxis delivered for 6 to 12 months. Topic experts highlighted that guidance on the long-term use of antibiotics may be useful as macrolides are being used extensively in people with COPD, particularly for those with chronic bronchitis and exacerbations.

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 6 years after the publication of chronic obstructive pulmonary disease in over 16s: diagnosis and management (2010) NICE guideline CG101.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

Previous surveillance update decisions for the guideline are on our website.

New evidence

We found 112 new studies in a search for systematic reviews published between 1 January 2014 and 5 November 2015. We also considered 20 additional studies identified by members of the Guideline Committee who originally worked on this guideline.

Evidence identified in previous surveillance 4 years after publication of the guideline was also considered. This included 366 studies identified by search. No studies were identified in comments received during consultation on the 4-year surveillance decision.

From all sources, 498 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: decision matrix for summaries and references for all new evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline and other correspondence we have received since the publication of the guideline.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 6-year surveillance review, and the decision was to update, we did not consult on the decision.

See ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual' for more details on our consultation processes.

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