Chronic obstructive pulmonary disease: comparative safety and efficacy of long-acting inhaled agents

In a large systematic review comparing long-acting beta agonists (LABA), long-acting antimuscarinic agents (LAMA) and inhaled corticosteroids (ICS) in people with moderate to very severe chronic obstructive pulmonary disease (COPD), indirect comparisons found some differences in safety and efficacy. A separate network meta-analysis in people with stable, moderate to severe COPD suggested that LABA/LAMA combination improved quality of life and symptom scores and reduced the risk of moderate to severe exacerbations compared with monotherapy, and had a similar effect on safety outcomes and severe exacerbations. Both these reviews support current NICE COPD guidance recommendations, where personalisation of therapy is key.

Overview and current advice

The NICE guideline on the management of COPD advises that people with forced expired volume in 1 second (FEV1) 50% predicted or more, who experience exacerbations or persistent breathlessness despite use of a short-acting bronchodilator, should be offered a long-acting inhaled agent (either a LAMA or a LABA). People with an FEV1 less than 50% predicted should be offered either a LABA with an ICS in a combination inhaler or a LAMA. NICE does not give preference to either of these options. People with COPD who remain breathless or have persistent exacerbations despite taking LABA and ICS, irrespective of their FEV1, should also be offered a LAMA.

The choice of medicines(s) should take into account the person's symptomatic response and preference, and the medicine's potential to reduce exacerbations, its side effects and cost. The guidance advises practitioners to be aware of the potential risk of side effects (including non-fatal pneumonia) in people with COPD treated with ICS, especially in high dose, and to be prepared to discuss this risk with patients. This individualised approach to COPD management, where risks and benefits of treatment are considered, is also recommended in the updated Global initiative for Chronic Obstructive Lung Disease guidance (GOLD, published December 2015).

See the previous medicines evidence commentaries on COPD: combination LABAs and inhaled corticosteroids compared with LABAs alone and indacaterol/glycopyrronium combination inhaler compared with tiotropium and formoterol in a randomised, non-inferiority study, for more information on the comparative benefits of long-acting inhaled agents.
The NICE Pathway: COPD brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The NICE clinical knowledge summary on COPD provides a useful overview of the condition and its management.

New evidence

A systematic review and network meta-analysis compared the safety and effectiveness of LABAs, LAMAs and ICS in people with COPD. The review included 208 randomised controlled trials (RCTs, 134,692 participants, publication date ranging from 1989 to 2014) conducted in adults with COPD, most commonly moderate to severe (28.9%) or moderate to very severe (32.2%). Participants were administered long-acting inhaled agents in any combination and compared with each other or placebo (duration of treatment ranging from 9 hours to almost 4 years). Concomitant COPD medications were included if both groups received the same interventions, such as rescue medication with a short-acting beta agonist. The primary outcome was the proportion of participants with moderate to severe exacerbations (defined as those requiring hospitalisations, emergency department visits, treatment with either or both oral steroids and antibiotics, use of rescue medication, or unscheduled visits to a walk-in clinic or to a healthcare provider). Secondary outcomes included the number of people experiencing pneumonia, serious arrhythmia as well as cardiovascular-related and total mortality. Treatment effects were presented using odds ratio (OR) and a treatment hierarchy was obtained using surface under the cumulative ranking (SUCRA) curve analysis. This approach allows the ranking of interventions according to the probability of being the most effective for each outcome (such as reducing the risk of exacerbations or most harmful at increasing the risk of cardiovascular mortality).

Many of the studies had a high or unclear risk of bias (using Cochrane criteria) due to reasons such as unclear allocation concealment (84%), unclear random sequence generation (63%), selective outcome reporting and other reasons such as being funded by a pharmaceutical company or study authors who were employed by the drug manufacturer. However, there was no evidence for small-study effects and publication bias. Due to significant heterogeneity the reviewers were unable to accurately produce a robust network meta-analysis for the outcome of moderate to severe exacerbations so this process was repeated including only those trials with participants who had experienced an exacerbation in the past year (20 RCTs, n=26,141).

Eight treatments were more effective than placebo in reducing the risk of moderate to severe exacerbations: tiotropium, salmeterol, indacaterol, budesonide/formoterol, fluticasone/salmeterol, indacaterol/glycopyrronium, tiotropium/fluticasone/salmeterol and tiotropium/budesonide/formoterol. The most effective were tiotropium/budesonide/formoterol (99% probability of being the most effective in reducing exacerbations according to the SUCRA curve analysis, OR 0.36 [95% CI 0.19 to 0.69] compared with budesonide/formoterol, OR 0.36 [95% CI 0.22 to 0.59] compared with tiotropium and OR 0.35 [95% CI 0.21 to 0.58] compared with fluticasone/salmeterol) and indacaterol/glycopyrronium (86%, OR 0.63 [95% CI 0.51 to 0.78] compared with glycopyrronium, OR 0.62 [95% CI 0.48 to 0.79] compared with indacaterol and OR 0.61 [95% CI 0.48 to 0.78] compared with salmeterol).

Further sensitivity analysis undertaken on studies with a low risk of bias identified that fluticasone, indacaterol/tiotropium and indacaterol/glycopyrronium were the most effective therapies for reducing the risk of moderate to severe exacerbations. Fluticasone/salmeterol combination therapy reduced the risk of mortality compared with placebo and compared with both formoterol and fluticasone monotherapy (secondary outcome, 88 RCTs, 28 treatments, n=97,526). For pneumonia, fluticasone and fluticasone/salmeterol had an increased risk of pneumonia compared with placebo (54 RCTs, 21 treatments, n=61,551). Six treatments statistically significantly decreased risk of cardiovascular-related mortality: salmeterol compared with placebo, salmeterol compared with tiotropium (both Handihaler and Respimat devices), salmeterol/fluticasone compared with tiotropium...
(both devices) and fluticasone compared with tiotropium (Respimat device, 37 RCTs, 20 treatments, n=55,156). However, in sensitivity analysis undertaken only on studies with low risk of bias no statistically significant results were observed for cardiovascular mortality. None of the 66 treatment comparisons undertaken for the secondary outcome of serious arrhythmia identified a statistically significant difference between treatments (26 RCTs, 12 treatments, n=27,407).

Another network meta-analysis\(^3\) considered the efficacy and safety of LABA/LAMA combination therapy for people with stable (without an acute or recent exacerbation) but moderate to severe COPD (n=27,172). The review included 23 RCTs (publication date from 2007 to May 2015), of at least 12 weeks duration (range 12 to 64 weeks), which compared LABA/LAMA combination with placebo, or LABA or LAMA monotherapy. The concomitant use of a fixed dose of ICS was allowed in most studies. The outcomes of interest included change from baseline in lung function (trough FEV\(_1\)), breathlessness score (measured using the Transitional Dyspnoea Index), quality of life (assessed using the St George’s Respiratory Questionnaire), COPD exacerbations and serious adverse events. The reviewers assessed the included studies as generally having a moderate to low risk of bias with no studies of poor quality or having differences in baseline characteristics. However heterogeneity was observed in pairwise and network meta-analysis.

LABA/LAMA combinations were associated with a statistically significant improvement in lung function, breathlessness score and quality of life assessment than monotherapies, with the exception of the change in quality of life compared with LABA at 6 months which was not statistically significant. LABA/LAMA combinations were associated with statistically significantly fewer moderate to severe exacerbations compared with LABAs (hazard ratio [HR] 0.82, 95% credible interval [CrI] 0.73 to 0.93) but not when compared with LAMAs (HR 0.92, 95% CrI 0.84 to 1.00). There were no statistically significant differences associated with LABA/LAMA combinations compared with monotherapies in safety outcomes as well as in severe exacerbations.

Both these network meta-analyses\(^1,3\) included a number of studies with moderate to low risk of bias, involving a large number of people with COPD and considered patient orientated outcomes which may be of clinical importance. The authors of both these reviews\(^1,3\) identified some limitations with the observed results. Heterogeneity of the included RCTs was an identified issue in both papers. As with all meta-analyses despite sensitivity analyses adjustment, the risk of residual confounding bias cannot be excluded because of the differences between trials in study population characteristics and unknown or unmeasured modifying effects. Tricco et al. also note that their literature search, conducted in December 2013, would not include newer trials of which there has been a significant number, particularly for the LABA/LAMA combination. The criteria used by the investigators to define moderate to severe exacerbations was not in line with European Medicines Agency guidelines. Many of the included RCTs according to Tricco et al. were at high risk of bias. Inconsistencies in data limited some of their analysis such as that for moderate to severe exacerbations. In Oba et al. the authors reported that the assessment of severe exacerbations was significantly underpowered except for the combination comparison with LAMA monotherapy. Oba et al. suggested that future studies enrolling people with COPD and a higher risk for exacerbations may provide a more robust efficacy assessment of LABA/LAMA therapy for this outcome. The majority of RCTs included in both network meta-analyses\(^1,3\) involved relatively short treatment durations. For example, in Tricco et al., 47% of the studies had treatment duration of less than 12 weeks and 26% of the studies had treatment duration between 12 and 24 weeks, as too did 65% of the studies in Oba et al. This may be a limitation of the observed results as the long-term relative benefits of these agents for people with COPD are unclear. Neither of the studies\(^1,3\) included a comparison of cost-effectiveness.
Commentary
Commentary provided by NICE medicines and prescribing programme

The NICE guideline on COPD makes several recommendations about long-acting inhaled therapies for managing stable COPD (see overview and current advice section above). An individualised approach to COPD management, where risks and benefits of treatment are considered, is recommended in both NICE guidance and GOLD guidance. For example, based on evidence from published studies highlighting a significantly increased risk of pneumonia with ICS (either alone or in combination with a LABA), the MHRA recommends that ICS should not be used alone in COPD and should be introduced only when COPD progresses to severe disease, in line with NICE guidance. This advice is supported by a more recent Cochrane review on the issue which has previously been discussed in detail in a NICE medicines evidence commentary.

The reviews by Tricco et al. and Oba et al. considered the efficacy and safety of different long-acting inhaled agents in people with COPD. However, as the reviews considered different study populations and evaluated different outcomes there is no overlap in results per se. Definitive assessment of the relative efficacy of different treatments can only be performed through direct comparison in head-to-head RCTs. In the absence of such data, indirect comparisons using network meta-analysis methodology and with the caveat of associated limitations, may be of value in clinical and health economic decision-making. Patient orientated outcomes such as the frequency of exacerbations and the presence of symptoms are important determinants of which therapies to prescribe on an individual basis. In those with moderate disease and infrequent exacerbations there is more emphasis on initially using bronchodilator therapy whereas people at the severe end of the disease spectrum may benefit from both long-acting inhaled therapies and ICS.

In the review by Tricco et al. the included studies were conducted in populations with moderate to very severe COPD and with more frequent exacerbations. In this population triple inhaled therapy with tiotropium/budesonide/formoterol reduced the risk of moderate to severe exacerbations. The observed results also suggested fluticasone/salmeterol reduced mortality but may increase the risk of pneumonia. In Oba et al. the included studies were conducted in people with moderate to severe disease but who had not had an acute or recent COPD exacerbation and a number of whom may also have been using inhaled ICS (data not reported). In this population LABA/LAMA combination were generally better than monotherapy at improving patient orientated outcomes such as quality of life and symptom scores and reducing moderate to severe exacerbation rates.

Neither of these network meta-analyses provided a cost-effectiveness assessment of the different inhaled long-acting therapies but the observed results do support an individualised approach to COPD management as recommended by NICE.

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References
Cochrane Database of Systematic Reviews 3: CD010115

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