



Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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COPD: withdrawal of inhaled corticosteroids and effect on exacerbations

A study has evaluated stepwise withdrawal of inhaled corticosteroids (ICS) in people with COPD receiving triple therapy with tiotropium, salmeterol and fluticasone propionate. ICS withdrawal was non-inferior to continuing ICS for the time to first moderate or severe exacerbation over 12 months. Despite some limitations, this study gives reassurance to clinicians considering withdrawing ICS treatment in people with COPD. It does not exclude the possibility that there may be subgroups of patients who respond better to ICS and it seems prudent to exercise caution, particularly where the possibility of asthma remains. The potential benefit of ICS in people with COPD needs to be balanced against the risk of side-effects (including non-fatal pneumonia), the NICE guideline on COPD advises that clinicians should be prepared to discuss these risks with patients.

Overview and current advice

The [NICE guideline on COPD](#) recommends that people who experience exacerbations or persistent breathlessness despite use of a short-acting bronchodilator, who have a forced expired volume in 1 second (FEV₁) less than 50% of predicted, should be offered a long-acting beta-2 agonist (LABA) with an ICS in a combination inhaler or a long-acting muscarinic antagonist (LAMA). A LABA with an ICS in a combination inhaler can be considered for people with an FEV₁ of 50% or more of predicted and who remain breathless or have exacerbations despite maintenance therapy with a LABA. NICE also recommends that a LABA with an ICS in a combination inhaler in addition to a LAMA can be considered for people who remain breathless or have exacerbations despite maintenance therapy with a LAMA.

The NICE COPD guideline advises practitioners to be aware of the potential risk of side effects (including non-fatal pneumonia) in people with COPD treated with ICS, and to be prepared to discuss this risk with patients. The potential benefit of ICS in people with COPD needs to be balanced against the risk of side effects; particularly when they are used at a high dose for long-term treatment. Prolonged use of high doses of ICS [carries a risk of systemic side effects](#), including adrenal suppression, decrease in bone mineral density, cataracts and glaucoma. ICS have also been associated with a dose-related increased risk of [diabetes onset and diabetes progression](#), and with an increased risk of [fracture](#). The MHRA has [reminded](#) health professionals to remain vigilant for the

development of pneumonia and other infections of the lower respiratory tract when using ICS to treat people with COPD, because the clinical features of such infections and exacerbations frequently overlap.

See the [NICE Evidence topic page on COPD](#) and the [Clinical Knowledge Summary](#) for a general overview of the condition. The [NICE Pathway: COPD](#) brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A double-blind randomised controlled non-inferiority study has evaluated whether stepwise withdrawal of ICS in people with severe or very severe COPD receiving triple therapy with a LAMA, a LABA and an ICS would have an effect on the exacerbation rate over a 12-month period compared with continuing the ICS¹.

The study included 2485 people (mean age 64 years, 82.5% male) with a diagnosis of severe or very severe COPD (FEV₁ less than 50% of predicted normal [mean 34%] and less than 70% of forced vital capacity post-bronchodilator, and at least 1 exacerbation in the previous 12 months). At baseline, approximately 70% were taking ICS and approximately 39% were taking triple therapy with a LAMA, LABA and ICS.

During a 6-week run-in period, all participants received tiotropium 18 micrograms once daily, salmeterol 50 micrograms twice daily and fluticasone propionate 500 micrograms twice daily. After the run-in period, participants were randomised to continue fluticasone or have it withdrawn in 3 steps over 12 weeks (500 micrograms daily for 6 weeks, 200 micrograms daily for 6 weeks, then stop). All participants continued tiotropium and salmeterol and were followed-up for a further 40 weeks. The use of salbutamol, xanthines and mucolytic agents was allowed throughout the study.

The primary end point was the time to the first moderate or severe exacerbation during the 12-month study period. Secondary outcomes included the time to first severe exacerbation, change from baseline in lung function, dyspnoea and health status. A moderate exacerbation was defined as an increase in respiratory symptoms lasting at least 3 days that required systemic corticosteroids or antibiotics. A severe exacerbation was defined as an exacerbation that required hospitalisation.

In the modified [intention to treat](#) (ITT) population, the [hazard ratio](#) (HR) for a first moderate or severe COPD exacerbation was 1.06 (95% [confidence interval](#) [CI] 0.94 to 1.19) with ICS withdrawal compared with ICS continuation. The upper limit of the 95% CI was within the pre-specified non-inferiority margin of 1.20, suggesting withdrawal of ICS is non-inferior to continuing ICS. However, to establish non-inferiority, this should be shown in both the ITT and per protocol populations². In this study, the per-protocol population was not described or reported. For the secondary endpoint of time to first severe exacerbation, there was no statistically significant difference between the ICS-withdrawal group and the ICS-continuation group (HR 1.20, 95% CI 0.98 to 1.48).

At weeks 18 (when ICS withdrawal was complete) and 52, the decline in trough FEV₁ was statistically significantly greater in the ICS-withdrawal group than the ICS-continuation group (38 ml, $p < 0.001$ and 43 ml, $p = 0.001$ respectively); however, the [clinical importance](#) of this is unclear. No clinically important differences were found between the groups in dyspnoea, health status or dropout rates.

Adverse events were reported in about 71% of people in both groups. Pneumonia occurred in 5.5% (68/1242) of participants in the ICS-withdrawal group and 5.8% (72/1243) of participants in the ICS-continuation group. No statistical analysis was presented for these outcomes.

Commentary

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Evidence suggests that the combination of a LABA and an ICS is superior to a LABA alone; particularly for people with severe airflow obstruction (FEV₁ less than 50% of predicted)³. There is also some evidence to suggest that LABA plus ICS reduces exacerbation rates in people with COPD compared to a LABA alone. However, there is growing concern about the safety of ICS with evidence of increased risk of infection (pneumonia and other infections of the lower respiratory tract), osteoporosis and cataracts. The potential benefit of ICS when used in people with COPD thus needs to be balanced against the risk of side effects, particularly when they are used at a higher dose in the longer term. Previous studies looking at the effects of ICS that have involved the abrupt withdrawal of ICS treatment appeared to show that this was associated with an increased risk of exacerbations and clinical deterioration⁴⁻⁶. Physicians have therefore been wary about withdrawing ICS therapy.

This randomised controlled study suggests that it is possible to withdraw ICS gradually in some patients without an increase in symptoms or exacerbation risk. The study had a pre-specified non-inferiority margin of 1.20 which is in keeping with what the [full NICE guideline on COPD](#) considers the minimum clinically important difference to be for the relative risk reduction for exacerbations (20%). One potential limitation of the study is that participants had to have had at least one exacerbation in the preceding year which may have excluded those with the best response to ICS. This study gives reassurance to clinicians who are considering withdrawing ICS treatment in people with COPD, but does not exclude the possibility that there may be subgroups of patients who respond better to ICS. It seems prudent to exercise caution, particularly with those in whom the possibility of asthma remains.

Study sponsorship

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