

Long-acting inhaled bronchodilators for cystic fibrosis

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Study design (if review, criteria of inclusion for studies)

Randomised controlled trials (RCTs). We will assess quasi-RCTs on their merit using the Cochrane risk of bias tool and if both reviewers are satisfied that the groups were similar at baseline, we will include them.

Participants

Children and adults with CF diagnosed by sweat test or genetic testing, with all stages and severity of lung disease and with or without concomitant asthma.

Interventions

Long-acting inhaled bronchodilators delivered via any device and at any dose, frequency or duration. For this review the term inhaled includes the use of pressurised metered dose inhalers (MDIs) with or without a large volume spacer, dry powder devices and nebulisers. Both types of long-acting bronchodilators which have a duration of action of at least 12 hours: beta-2 agonists, e.g. salmeterol, formoterol; anticholinergics, e.g. tiotropium, aclidinium. Not considered: combined inhalers (with inhaled steroids or another bronchodilator) or short-acting bronchodilators (e.g. salbutamol, ipratropium bromide). The comparator will be an inhaled placebo, another long-acting bronchodilator (or the same drug at a different dose) or usual treatment.

Outcome measures

Primary outcomes Change in forced expiratory volume in one second (FEV1) from baseline (litres and per cent (%) predicted). Participant-reported outcomes including quality of life (QoL) using standardised and validated QoL scores (e.g. CFQ-R (Quittner 2009)) and symptom scores (e.g. Respiratory and Systemic Symptoms Questionnaire (RSSQ), Respiratory Symptom Score (RSS) (Goss 2007)) 1 Adverse effects (especially those associated with long-acting inhaled bronchodilators i.e. for beta-2 agonists tremor, nervous tension, headache, peripheral dilatation and palpitation, increased heart rate, dry mouth, increased wheeze and shortness of breath; for anticholinergics dry mouth, gastrointestinal motility disorder (constipation and diarrhoea), nausea, gastro-oesophageal reflux disease, dysphagia, tachycardia); 2 frequency of adverse effects; 3 severity of adverse effects, e.g. mild or moderate or severe (where it has been reported).

Main results

The searches identified 195 unique references, of which 155 were excluded on title and abstract. We assessed the full texts of the remaining references, excluded 16 trials (28 references) and included four trials (12 references) in the review with 1082 participants. One trial (n = 16) measuring the effect of beta-2 agonists reported an improvement in forced expiratory volume at one second (FEV1) after treatment (at one month), but the trial was small with an unclear risk of bias so we judged the evidence to be very low quality. The trial did not report on participant-reported outcomes, quality of life or adverse events. Three trials (n = 1066) looked at the effects of the muscarinic antagonist tiotropium at doses of 2.5 µg and 5.0 µg in both the short term (up to 28 days) and the longer term (up to three months). Only one of the trials reported the change in FEV1 (L) after 28 days treatment and showed no significant difference between groups; with 2.5 µg tiotropium, mean difference (MD) -0.02 (95% confidence interval (CI) -0.13 to 0.09), or 5.0 µg tiotropium, MD 0.00 (95% CI -0.10 to 0.10) (moderate-quality evidence). All three trials of muscarinic antagonists provided data on adverse events which were found to differ little from placebo at doses of 2.5 µg, risk ratio (RR) 1.01 (95% CI 0.92 to 1.11) or 5.0 µg, RR 0.98 (95% CI 0.90 to 1.06). Very little participant-reported outcome data or quality of life data were available for analysis. Two of the trials were at low risk of bias overall whilst the remaining trial was at an unclear risk overall.

Authors' conclusions

Neither long-acting beta-2 agonists nor long-acting muscarinic antagonist bronchodilators demonstrate improvement in our primary outcome of FEV1. No difference was observed between intervention and placebo in terms of quality of life or adverse events. The quality of evidence for the use of beta-2 agonists was very low. The use of a long-acting inhaled bronchodilator may help to reduce the burden of treatment for people with cystic fibrosis as it is taken less often than a short-acting inhaled bronchodilator, but future trials would benefit from looking at the effects on our primary outcomes (spirometric changes from baseline, quality of life and adverse effects) in the longer term.

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See also

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Keywords

Adrenergic beta-Agonists; Adult; Albuterol; Bronchodilator Agents; Child; Inhalation OR nebulised; Ipratropium; pharmacological_intervention; Respiratory System Agents; Anticholinergic Agents; Respiratory Tract Diseases;