

# Inhaled mannitol for cystic fibrosis

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

Randomised controlled studies comparing mannitol with placebo, active inhaled comparators (for example, hypertonic saline or dornase alfa) or with no treatment.

## List of included studies (6)

Aitken 2012; Bilton 2011; Jaques 2008; Minasian 2010

## Participants

Adults (16 years old and over) and children (under 16 years old) with CF

## Interventions

Mannitol with placebo, active inhaled comparators (for example, hypertonic saline or dornase alfa) or with no treatment.

## Outcome measures

Primary outcomes: QoL, FEV1, FVC, FEF25-75, number of participants free of pulmonary exacerbations, time to next pulmonary exacerbation

## Main results

Six studies (reported in 36 unique publications) were included with a total of 784 participants. Duration of treatment in the included studies ranged from 12 days to six months, with open-label treatment for an additional six months in two of the studies. Five studies compared mannitol with control (a very low dose of mannitol or non-respirable mannitol) and the final study compared mannitol to dornase alfa alone and to mannitol plus dornase alfa. Two large studies had a similar parallel design and provided data for 600 participants, which could be pooled where data for a particular outcome and time point were available. The remaining studies had much smaller sample sizes (ranging from 22 to 95) and data could not be pooled due to differences in design, interventions and population. Pooled evidence from the two large parallel studies was judged to be of low to moderate quality and from the smaller studies was judged to be of low to very low quality. In all studies, there was an initial test to see if participants tolerated mannitol, with only those who could tolerate the drug being randomised; therefore, the study results are not applicable to the cystic fibrosis population as a whole. While the published papers did not provide all the data required for our analysis, additional unpublished data were provided by the drug's manufacturer and the author of one of the studies. Pooling the large parallel studies comparing mannitol to control, up to and including six months, lung function (forced expiratory volume at one second) measured in both mL and % predicted was significantly improved in the mannitol group compared to the control group (moderate-quality evidence). Beneficial results were observed in these studies in adults and in both concomitant dornase alfa users and non-users in these studies. In the smaller studies, statistically significant improvements in lung function were also observed in the mannitol groups compared to the non-respirable mannitol groups; however, we judged this evidence to be of low to very low quality. For the comparisons of mannitol and control, we found no consistent differences in health-related quality of life in any of the domains except for burden of treatment, which was less for mannitol up to four months in the two pooled studies of a similar design; this difference was not maintained at six months. It should be noted that the tool used to measure health-related quality of life was not designed to assess mucolytics and pooling of the age-appropriate tools (as done in some of the included studies) may not be valid so results were judged to be low to very low quality and should be interpreted with caution. Cough, haemoptysis, bronchospasm, pharyngolaryngeal pain and post-tussive vomiting were the most commonly reported side effects in both treatment groups. Where rates of adverse events could be compared, statistically no significant differences were found between mannitol and control groups; although some of these events may have clinical relevance for people with CF. For the comparisons of mannitol to dornase alfa alone and to mannitol plus dornase alfa, very low-quality evidence from a 12-week cross-over study of 28 participants showed no statistically significant differences in the recorded domains of health-related quality of life or measures of lung function. Cough was the most common side effect in the mannitol alone arm but there was no occurrence of cough in the dornase alfa alone arm and the most commonly reported reason of withdrawal from the mannitol plus dornase alfa arm was pulmonary exacerbations. In terms of secondary outcomes of the review (pulmonary exacerbations, hospitalisations, symptoms, sputum microbiology), evidence provided by the included studies was more limited. For all comparisons, no consistent statistically significant and clinically meaningful differences were observed between mannitol and control treatments (including dornase alfa).

## Authors' conclusions

There is evidence to show that treatment with mannitol over a six-month period is associated with an improvement in some measures of lung function in people with cystic fibrosis compared to control. There is no evidence that quality of life is improved for participants taking mannitol compared to control; a decrease in burden of treatment was observed up to four months on mannitol compared to control but this difference was not maintained to six months. Randomised information regarding the burden of adding mannitol to an existing treatment is limited. There is no randomised evidence of improvement in lung function or quality of life comparing mannitol to dornase alfa alone and to mannitol plus dornase alfa. Mannitol as a single or concomitant treatment to dornase alfa may be of benefit to people with cystic fibrosis, but further research is required in order to establish who may benefit most and whether this benefit is sustained in the longer term. The clinical implications from this review suggest that mannitol could be considered as a treatment in cystic fibrosis; however, studies comparing its efficacy against other (established) mucolytic therapies need to be undertaken before it can be considered for mainstream practice.

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### See also

Nevitt SJ, Thornton J, Murray CS, Dwyer T. Inhaled mannitol for cystic fibrosis. Cochrane Database of Systematic Reviews 2020, Issue 5. Art. No.: CD008649. DOI: 10.1002/14651858.CD008649.pub4.

### Keywords

Expectorants; Inhalation OR nebulised; Mannitol; pharmacological\_intervention; Airway clearance drugs -expectorants- mucolytic-mucociliary-; Respiratory System Agents; Powders;