Relationship between FEV1 change and patient-reported outcomes in randomised trials of inhaled bronchodilators for stable COPD: a systematic review

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CRD summary
This review concluded that improvements in mean trough forced expiratory volume in one second could be associated with proportional improvements in health status. This was a well-conducted review and the authors’ cautious conclusion appears to reflect the data and is likely to be reliable.

Authors' objectives
To investigate the effect of bronchodilator therapy on the relationship between changes in the forced expiratory volume in one second (FEV1) and health status for patients with chronic obstructive pulmonary disease.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), DARE, and HTA database were searched to October 2009, without language restriction; search terms were reported in an online supplement. ClinicalTrials.gov, websites of licensing agencies, and the Guidelines International Network were searched for additional completed or ongoing trials. Reference lists of retrieved articles and systematic reviews were checked.

Study selection
Parallel, randomised controlled trials (RCTs) of long-acting inhaled bronchodilator therapy (monotherapy) in adult patients (35 years or older) with stable chronic obstructive pulmonary disease, chronic bronchitis or emphysema were eligible for inclusion if they reported FEV1 and health status, dyspnoea or exacerbations. Comparators could include placebo, long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), LABA plus LAMA, and methylxanthines. Trials were required to last at least 12 weeks. The primary outcome was the St George’s Respiratory Questionnaire (SGRQ) total score. Trials that had mixed populations were excluded unless separate data were reported for patients with chronic obstructive pulmonary disease.

All included trials were of LAMA (tiotropium), LABA (salmeterol, formoterol, or arformoterol), or both, with or without placebo. Mean age ranged from 60 to 74 years, with the percentage of male patients ranging from 48 to 88. Where reported, smoking history ranged from 31.5 to 68.4 pack years and FEV1 percentage predicted ranged from 33.3 to 73.4.

Two reviewers independently selected trials; any disagreements were resolved through discussion and checked by a third reviewer.

Assessment of study quality
One reviewer assessed the quality of the included trials, using the Cochrane Collaboration's quality assessment checklist. This assessment was checked by a second reviewer and any disagreements were resolved by consensus.

Data extraction
The data were extracted by one reviewer and checked by a second reviewer, using a standardised form; disagreements were resolved by consensus.

Means and standard deviations were extracted. Baseline and endpoint data were extracted, where available, otherwise, change from baseline data were used. If numerical data were not reported values were estimated from graphs and standard deviations were imputed from other trials. The trough FEV1 was extracted as reported in the trials.

Methods of synthesis
Pearson correlation coefficients were calculated and a regression line added to each scatter plot to estimate the mean change in FEV1 corresponding to a three or four unit change in SGRQ and the mean change in SGRQ associated with a
100mL increase in FEV\textsubscript{1}. Random-effects regression modelling was used to explore the effects of changes in FEV\textsubscript{1} on the change in total SGRQ score, incorporating the length of follow-up.

**Results of the review**

Thirty-six trials were included in the review; 22 trials, with 49 treatment arms and 23,654 participants, provided data on the relationship between changes in FEV\textsubscript{1} and SGRQ scores; 29 trials provided data on exacerbations; and eight trials provided data on dyspnoea.

Random-effects regression modelling found that a 100mL increase in FEV\textsubscript{1} was associated with a statistically significant reduction in SGRQ (2.5, 95% CI 1.9 to 3.1), and clinically relevant SGRQ change was associated with an increase in FEV\textsubscript{1} of 160.6mL (95% CI 129.0 to 211.6). When the placebo arms were excluded this association was no longer statistically significant.

Using all treatment arms and all time points, the mean change in trough FEV\textsubscript{1} and change in SGRQ total score were negatively correlated (r=-0.46; p<0.001). This correlation was found to strengthen with increasing study duration from three to 12 months.

Correlations between the change in FEV\textsubscript{1} and other patient-reported outcomes were presented; associations were generally weak.

**Authors' conclusions**

The results indicated that improvements in mean trough FEV\textsubscript{1} could be associated with proportional improvements in health status.

**CRD commentary**

The review question was supported by clearly defined inclusion criteria. Several sources were searched without restrictions on language or publication type. Steps were taken in the selection of trials, data extraction and validity assessment to minimise the likelihood of error and bias. The quality of the included trials was assessed using appropriate criteria. The authors acknowledged that their review included only RCTs, but the analyses treated the data as observational cohorts and the strengths of the trial designs were lost.

The authors’ cautious conclusion appears to reflect the data and is likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that FEV\textsubscript{1} might offer the perspective of an intermediate endpoint to assess treatment effectiveness at a study level. Longer trials were needed to fully assess the negative correlation of exacerbations with change in FEV\textsubscript{1}, and whether changes in FEV\textsubscript{1} at three months were correlated with long-term changes in outcome.

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