Contemporary management of chronic obstructive pulmonary disease: a scientific review
Sin D D, McAlister F A, Man S F, Anthonisen N R

CRD summary
This review concluded that long-acting bronchodilators and inhaled corticosteroids reduce exacerbations in patients with moderate-to-severe chronic obstructive pulmonary disease. Supplementary oxygen therapy was associated with prolonged survival in patients with resting hypoxia. The exclusion of non-English language publications and limitations in the reporting of the review process weaken the evidence presented.

Authors' objectives
To determine the impact of long-acting bronchodilators, inhaled corticosteroids, nocturnal noninvasive mechanical ventilation (NIMV), pulmonary rehabilitation, domiciliary oxygen therapy, and disease management programmes on clinical outcomes in patients with chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE (from 1980 to 2002) and the Cochrane Database of Systematic Reviews were searched for English language articles; the search terms were given. Additional articles were sought in the reference lists of published articles and through contact with experts.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials (RCTs) of at least 3 months' duration (6 weeks for studies of pulmonary rehabilitation programmes) that had blinded ascertainment of end points and complete or near complete follow-up data, and in which the groups were comparable at baseline, were eligible for inclusion.

Specific interventions included in the review
Studies of long-acting beta-2-agonists, long-acting inhaled anticholinergics (tiotropium), combination therapy with short-acting beta-2-agonists and short-acting anticholinergics, inhaled corticosteroids, combination therapy with inhaled corticosteroids and long-acting beta-2-agonists, pulmonary rehabilitation, long-term administration of nocturnal NIMV, domiciliary oxygen therapy, and disease management programmes (including any combination of patient education, enhanced follow-up, and/or self-management sessions) were eligible for inclusion.

Participants included in the review
Studies of adults (aged 19 years and over) with COPD were eligible for inclusion. Where reported, the mean age of the participants ranged from 52 to 73 years. The severity of COPD varied in the included studies. Details on the forced expiratory volume in one second (FEV1) were given.

Outcomes assessed in the review
Studies that evaluated health-related quality of life using the St. George's Respiratory Questionnaire (SGRQ) or Chronic Respiratory Questionnaire (CRQ), exacerbations associated with COPD, or death were eligible for inclusion. Studies reporting only physiological variables were excluded from the review.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors stated that they did not use a quality assessment tool. However, eligible studies were restricted to those that met predefined criteria relating to study quality: blinded ascertainment of the end points, complete or near complete follow-up data, and the comparability of the groups at baseline. The authors stated that they did not assess the validity of the included studies.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the numbers of exacerbations and deaths were extracted from each study and used to derive a relative risk (RR). Data on the mean SGRQ and CRQ scores and standard deviations were extracted from each individual study to derive a weighted mean difference (WMD).

**Methods of synthesis**

How were the studies combined?
The results from the individual studies were combined using fixed-effect (studies statistically homogeneous) or random-effects (studies not statistically homogeneous) models using the method of DerSimonian and Laird. A pooled RR or WMD with 95% confidence intervals (CIs) was calculated separately for each outcome. Additional data and tables are available on the iCAPTURE Centre website (accessed 23/02/2005). See Web Address at end of abstract.

How were differences between studies investigated?
Heterogeneity was assessed statistically using the Cochran Q test (significance threshold P<0.05). Post hoc subgroup analyses were performed on the baseline FEV1 level and presence of hypoxia for two comparisons.

Sensitivity analyses were performed on those studies that were statistically homogeneous, so as to determine the effect of the model used to pool the studies and the summary statistic used for continuous variables.

**Results of the review**
The authors did not state how many studies or participants were included in the review. However, more than 80 RCTs were detailed in the report.

**Bronchodilators.**

The risk of exacerbation of COPD was 32% lower in patients treated with a combination of short-acting beta-2-agonists and anticholinergics than in patients treated with monotherapy with a short-acting beta-2-agonist (RR 0.68, 95% CI: 0.51, 0.91), based on 3 RCTs (1,399 patients). No statistically significant difference in mortality was found (RR 1.18, 95% CI: 0.34, 4.08). There was no significant difference in the risk of exacerbation (RR 1.04, 95% CI: 0.65, 1.68) or mortality (RR 3.56, 95% CI: 0.59, 21.53) in patients treated with combination therapy, compared with ipratropium monotherapy, based on 2 RCTs (1,186 patients).

Long-acting beta-2-agonists were associated with 21% fewer exacerbations in comparison with placebo (RR 0.79, 95%: 0.69, 0.90), based on 9 RCTs (4,198 patients). Long-acting beta-2-agonists were associated with significant improvements in SGRQ scores (WMD 2.8, 95% CI: 1.6, 4.1) and CRQ scores (WMD 4.3, 95% CI: 1.6, 7.0), based on 5 RCTs (2,551 patients) and 2 RCTs (816 patients), respectively. No statistically significant difference in mortality was found between long-acting beta-2-agonists and placebo (RR 0.76, 95% CI: 0.39, 1.48).

Tiotropium was associated with significantly fewer (22%) exacerbations than ipratropium (RR 0.78, 95% CI: 0.63, 0.95) and 26% fewer exacerbations compared with placebo (RR 0.74, 95% CI: 0.62, 0.89), based on 2 RCTs (823 patients) and 3 RCTs (2,751 patients), respectively. No significant difference was shown between tiotropium and long-acting beta-2-agonists (RR 0.93, 95% CI: 0.80, 1.08), based on 2 RCTs (1,830 patients). Tiotropium was associated with significant improvements in SGRQ scores compared with placebo (WMD 2.9, 95% CI: 1.5, 4.3), based on 3 RCTs (2,751 patients).

Inhaled corticosteroids with and without long-acting beta-2-agonists.

Inhaled corticosteroids were associated with 24% fewer exacerbations in comparison with placebo (RR 0.76, 95% CI: 0.72, 0.80), based on 6 RCTs (1,741 patients). Analysis of the relationship between FEV1 values and treatment effect found that inhaled corticosteroids were only effective in patients with a baseline mean FEV1 of 2.0 L or less. No statistically significant difference in mortality (RR 0.78, 95% CI: 0.58, 1.05), bone fracture (RR 0.70, 95% CI: 0.36, 1.38), or femoral neck bone mineral density (RR -1.57, 95% CI: -2.40, -0.74) was shown between inhaled corticosteroids and placebo; these results were based on 5 RCTs (3,678 patients), 2 RCTs (2,028 patients), and 2 RCTs (2,393 patients), respectively. No statistically significant difference was found in SGRQ score between inhaled corticosteroids and placebo (WMD 1.4, 95% CI: 0.6, 2.1), based on 2 RCTs (995 patients).
Combination therapy with inhaled corticosteroids and long-acting beta-2-agonists was associated with 20% fewer exacerbations than monotherapy with long-acting beta-2-agonists (RR 0.80, 95% CI: 0.71, 0.90) and 30% fewer exacerbations compared with placebo (RR 0.70, 95% CI: 0.62, 0.78), based on 2 RCTs (2,277 patients). No significant difference in exacerbations was shown between combination therapy and inhaled corticosteroids (RR 0.90, 95% CI: 0.80, 1.02). No significant difference in mortality was shown between combination therapy and placebo (RR 0.52, 95% CI: 0.20, 1.34), based on 2 RCTs (1,486 patients).

Adverse events associated with inhaled corticosteroids were inconsistently reported across the included studies. Six studies found that inhaled corticosteroids were associated with a significant increase in the risk of oral thrush (RR 2.98, 95% CI: 2.09, 4.26), 4 studies found an increase in the risk of dysphonia (RR 2.02, 95% CI: 1.43, 2.83), and 3 studies found an increase in the risk of bruising (RR 1.62, 95% CI: 1.18, 2.22).

Non-pharmacological therapies.

Nocturnal NIMV was not associated with fewer cases of hospitalisation or exacerbation compared with usual care (RR 0.87, 95% CI: 0.67, 1.12), based on 2 RCTs (142 patients).

Pulmonary rehabilitation was associated with significant improvements in SGRQ scores (WMD -4.4, 95% CI: -0.3, -8.4) and CRQ scores (WMD 4.1, 95% CI: 2.2, 6.0), based on 6 RCTs (491 patients) and 14 RCTs (1,135 patients), respectively.

Pulmonary rehabilitation did not have a significant effect on mortality (RR 0.90, 95% CI: 0.65, 1.24) or rates of hospitalisation (RR 0.99, 95% CI: 0.56, 1.75), based on 8 RCTs (798 patients) and 1 RCT (200 patients), respectively.

Supplementary oxygen therapy did not have a significant effect on mortality (RR 0.82, 95% CI: 0.55, 1.20), based on 4 RCTs (501 patients). The subgroup analysis found that supplementary oxygen therapy was associated with significantly lower mortality in patients with hypoxia at rest (RR 0.61, 95% CI: 0.46, 0.82), based on 2 RCTs (290 patients). However, no significant effect was found in those without hypoxia at rest (RR 1.16, 95% CI: 0.85, 1.58), based on 2 RCTs (211 patients).

Disease management and/or follow-up programmes did not have a significant effect on the rates of hospitalisation in comparison with usual care (RR 0.86, 95% CI: 0.68, 1.08), based on 5 RCTs (1,049 patients). However, there was evidence of heterogeneity (P=0.34). No significant effect on mortality (RR 0.63, 95% CI: 0.38, 1.04) or improvement in SGRQ score (WMD -2.5, 95% CI: -4.8, -0.1) was found between disease management and usual care, based on 4 RCTs (613 patients) and 3 RCTs (437 patients), respectively.

Authors' conclusions
Long-acting bronchodilators and inhaled corticosteroids reduce exacerbations in patients with moderate to severe COPD. Domiciliary oxygen was associated with prolonged survival in patients with resting hypoxia.

CRD commentary
The review addressed a clear question and the inclusion criteria appear appropriate. The authors searched two relevant electronic databases and the reference lists of published articles. Experts were contacted in an attempt to identify unpublished studies. Foreign language publications were excluded from the review, which may have introduced language bias. The methods used to select studies for inclusion in the review and to extract data from the included studies were not described; therefore, the potential for reviewer bias and error cannot be assessed. Furthermore, the authors stated placebo-controlled RCTs as an inclusion criterion, but included trials with other control groups (such as usual care and other treatments).

Adequate details of the individual studies were provided in the report and on the iCAPTURE Centre website. The methods used to statistically combine the studies appear appropriate. The authors did not report the findings of the tests for statistical heterogeneity, although potential causes of heterogeneity appear to have been explored in the subgroup analyses. The authors' conclusions appear to follow from the evidence presented. However, limitations in the reporting of the review process and the potential for language bias mean that the conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that inhaled bronchodilator therapy given on an as-needed basis should be considered for those who experience occasional exacerbations. Regular bronchodilator therapy using combination therapy (beta-2-agonists and an anticholinergic), or the use of long-acting agents, should be considered in patients with persistent symptoms. The addition of inhaled corticosteroids with or without long-acting beta-2-agonists and pulmonary rehabilitation should be considered in patients who are symptomatic with moderate-to-severe COPD. Supplementary oxygen therapy should be given to patients with hypoxia at rest.

The authors stated that smoking cessation is the cornerstone of the management of chronic COPD. In addition, influenza and pneumococcal vaccination may lead to reductions in hospitalisation and deaths in the elderly and should be considered for most patients with symptomatic COPD. However, these recommendations cannot be verified by this review.

Research: The authors stated that well-conducted comparative studies are required to determine the effectiveness of disease management programmes in patients with COPD.

Bibliographic details

PubMedID
14600189

DOI
10.1001/jama.290.17.2301

Original Paper URL
http://jama.ama-assn.org/

Additional Data URL
https://www.hli.ubc.ca/research/PIs/Sin.html

Other publications of related interest
These additional published commentaries may also be of interest.


Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenergic beta-Agonists /therapeutic use; Bronchodilator Agents /therapeutic use; Cholinergic Antagonists /therapeutic use; Glucocorticoids /therapeutic use; Humans; Influenza Vaccines; Oxygen Inhalation Therapy; Pneumococcal Vaccines; Pulmonary Disease, Chronic Obstructive /therapy; Randomized Controlled Trials as Topic; Respiration, Artificial; Smoking Cessation; Theophylline /therapeutic use; Treatment Outcome

AccessionNumber
12003008699
Date bibliographic record published
31/08/2005

Date abstract record published
31/08/2005

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.