Review: Long-acting inhaled therapies and pulmonary rehabilitation are effective in stable COPD

Wilt TJ, Niewoehner D, Macdonald R, Kane RL. **Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline.** Ann Intern Med. 2007;147:639-53.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Hospitalists ★★★★★★☆ Phys Med & Rehab ★★★★☆☆☆ Pulmonology ★★★★★☆☆

QUESTION

In patients with stable chronic obstructive pulmonary disease (COPD), are inhaled therapies and other interventions effective?

METHODS

Data sources: MEDLINE and Cochrane Library (1966 to March 2007), Cochrane Database of Systematic Reviews of Effectiveness, reference lists, and experts.

Study selection and assessment: English-language, randomized, controlled trials (RCTs); controlled clinical trials; or reviews evaluating inhaled therapies (β-agonists, corticosteroids [CSs], anticholinergics, or combination), pulmonary rehabilitation (PR), disease management, or oxygen therapy (OT) in patients with stable COPD. Studies reporting only spirometry outcomes or comparing different PRs were excluded. Assessment of individual study quality was based on blinding, allocation concealment, follow-up, intention-to-treat analysis, and funding; review quality was based on the Strength of Recommendation Taxonomy. 42 RCTs (mean age range 48 to 77 y) and 8 meta-analyses met the selection criteria.

Outcomes: Included exacerbations, death, and changes in St. George's Respiratory Questionnaire (SGRQ) or Chronic Respiratory Disease Questionnaire (CRDQ) scores.

MAIN RESULTS

Meta-analyses showed that long-acting bronchodilators and CSs, but not ipratropium, were more effective than placebo for reducing the number of patients with ≥ 1 exacerbation (Table); combination therapy and monotherapy did not differ, but short-acting β-agonists plus ipratropium were more effective than such β-agonists alone (Table). Long-acting β-agonists (LABAs) plus CSs led to fewer deaths than did placebo or CSs alone but did not differ from LABAs alone (Table); LABAs, CSs, and anticholinergics did not differ from placebo. In general, monotherapy, combination therapy, or placebo did not differ for SGRQ or CRDQ scores. PR led to better scores on SGRQ (pooled mean difference [PMD] −4.4, 95% CI −0.3 to −8.4, 6 RCTs) and CRDQ (PMD 4.1, CI 2.2 to 6.0, 14 RCTs) than did usual care; disease management and ambulatory OT did not improve outcomes.

CONCLUSION

Long-acting inhaled therapies reduce exacerbations and pulmonary rehabilitation may improve health status in symptomatic patients with stable chronic obstructive pulmonary disease.

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Comparisons of inhaled therapies with placebo (PLAC) or other therapies in chronic obstructive pulmonary disease*

Outcomes at 5 wk to 5 y	Number of trials (*n*)	Comparisons	Weighted event rates	RRR (95% CI)	NNT (CI)
Patients with ≥ 1 exacerbation	4 (4562)	TTP vs PLAC	35% vs 42%	16% (10 to 22)	16 (11 to 25)
	17 (8679)	LABA vs PLAC	28% vs 33%	13% (7 to 18)	24 (18 to 44)
	8 (3557)	CS vs PLAC	30% vs 35%	15% (4 to 25)	19 (12 to 72)
	4 (1988)	LABA + CS vs PLAC	30% vs 38%	23% (–1 to 42)	Not significant
	5 (2967)	LABA + CS vs LABA	34% vs 39%	12% (–4 to 25)	Not significant
	4 (1982)	LABA + CS vs CS	31% vs 32%	4% (–8 to 15)	Not significant
	3 (1006)	SABA + ITP vs SABA†	12% vs 18%	32% (8 to 50)	18 (10 to 77)
Death	5 (4689)	LABA + CS vs PLAC	8.6% vs 11%	18% (2 to 31)	53 (31 to 474)
	5 (4652)	LABA + CS vs LABA	7.9% vs 9.7%	18% (–28 to 48)	Not significant
	5 (4678)	LABA + CS vs CS	8.7% vs 11%	21% (6 to 33)	44 (28 to 152)

*CS = corticosteroid; ITP = ipratropium (short-acting anticholinergic); LABA = long-acting β-agonist; SABA = short-acting β-agonist; TTP = tiotropium (long-acting anticholinergic); other abbreviations defined in Glossary. RRR, NNT, and CI calculated from relative risks in article using a random-effects model. †RRR, NNT, and CI calculated from data in article.

COMMENTARY

In managing stable COPD, physicians aim to reduce symptoms and improve quality of life. Given the significant effect of exacerbations of COPD on quality of life, decline in lung function, and mortality, treatments that lessen their effect are of profound importance. Long-acting anticholinergics, LABAs, and ICSs are effective in reducing exacerbation rates in COPD. Positive effects on health-related quality of life are reported in most studies.

Combination therapy with inhaled LABAs plus CSs is effective in reducing exacerbations, but the reviews by Wilt and colleagues and by Nannini and colleagues differ in their conclusions about the efficacy of combination therapy compared with its monoconstituents. In the review and another recent meta-analysis by Nannini and colleagues, combination therapy was more effective than either monocomponent for reducing exacerbations, whereas Wilt and colleagues found no additional benefit for combination therapy compared with its monocomponents. The differing findings relate to variations in analyses of exacerbation rates and inclusion of different studies in the meta-analyses. Wilt and colleagues reported exacerbation rates as the proportion of patients having an exacerbation, while Nannini and colleagues reported their results as mean exacerbation rates for each group. Both methods appear to be valid, but Aaron and colleagues (1), who reviewed the difficulties surrounding counting, analyzing, and reporting exacerbations in COPD trials, argue that future studies should report results using mean exacerbations per patient-year as the primary outcome. As they contend, methods of defining and analyzing exacerbation rates in COPD differ greatly among trials, and such differences can lead to marked variations in assessments of treatment effects.

(continued on page 49)