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FROM THE FAMILY PRACTICE INQUIRIES NETWORK

Are beta-2-agonists or anticholinergics more effective for treating COPD?

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EVIDENCE-BASED ANSWER

Both β_2-agonists and anticholinergics appear to improve symptoms for patients with chronic obstructive pulmonary disease (COPD). Recent research indicates that adding a long-acting anti-cholinergic to a β_2-agonist may improve quality of life for patients with stable COPD more than the use of β_2-agonists alone.

Both drug classes increase exercise capacity and alleviate symptoms of COPD, although neither alters disease progression (strength of recommendation [SOR]: **A**). Combination therapy can lead to greater improvements in forced expiratory volume in 1 second (FEV_1) than either drug alone (SOR: **A**). However, until recently there were no convincing direct head-to-head comparisons of the 2 classes, and it is unclear whether this difference is clinically significant.

EVIDENCE SUMMARY

A review of 33 double-blind randomized placebo-controlled studies showed a significant effect of bronchodilator therapy on exercise capacity in COPD patients in about one half of studies. Anticholinergic agents had significant beneficial effects in the majority, and these effects tended to be somewhat dose-dependent. Short-acting β_2-agonists improved exercise capacity in more than two thirds of the studies, but long-acting agents led to mixed outcomes. The researchers identified no superior agent between the 2 classes, citing a lack of adequate studies making a direct comparison.[1]

A recent Cochrane Review comparing the short-term effects of ipratropium to β_2-agonists in changes in $FEV_1$and arterial oxygen pressure (PaO_2) concluded there was no evidence that the degree of bronchodilation from ipratropium was greater than that from short-acting β_2-agonists.[2]Subjective endpoints such as dyspnea and quality of life were not assessed, and neither of the above reviews included studies focusing on long-term

outcomes.

A 12-week double-blind, double-placebo-controlled parallel group study published in 2000 followed 144 patients (age 64 ± 7 years with a $FEV_1$of 44 ±11% predicted) randomized to receive salmeterol 50 µg twice daily alone, salmeterol 50 µg twice daily plus ipratropium 40 µg 4 times daily, or placebo. Patients were assessed for changes in FEV_1, daytime symptom scores, specific airway conductance, and the need for rescue medication. The study demonstrated a significant benefit from the addition of ipratropium to salmeterol in terms of reduction of airway obstruction, but not in symptom control or need for rescue medication.[3] However, no patients were randomized to receive ipratropium alone, so comparison of the relative contribution of the 2 classes is limited.

A 6-month, randomized double-blind placebo-controlled study evaluating the efficacy of salmeterol 50 µg twice daily vs tiotropium (a new long-acting inhaled anticholinergic) 18 µg once daily was published in 2002. Endpoints in 623 patients were assessed using 12-hour spirometric performance, transition dyspnea index (TDI), and the St. George Respiratory Questionnaire (SGRQ). (SGRQ is a validated disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being. It measures activity limitations, symptoms, and psychosocial impact.) Tiotropium showed superiority over salmeterol in all endpoints assessed (0.14 L increase in morning FEV_1vs 0.09 L, 1.02 U improvement in TDI score vs 0.24, and –5.14 U improvement of SGRQ total score from baseline vs –3.54). However, it should be noted that a difference of 1 on the TDI score was necessary to suggest a clinical benefit. While the overall difference in SGQR between tiotropium and salmeterol did not reach statistical significance, the proportion of patients in the tiotropium group that reached the clinically significant threshold of 4 units improvement in SGRQ score was significantly higher than in the salmeterol group (51% vs 40%; $P<.05$).[4]

In a similar study in 2003, 1207 patients were randomized to receive the above doses of salmeterol, tiotropium, or placebo. Over the course of 6 months, tiotropium was associated with a significant delay in onset of the first exacerbation compared with placebo, and overall it led to the fewest exacerbations per patient-year. Fewer hospital admissions were also demonstrated in the tiotropium group per patient-year, and the number of days that patients were unable to perform usual activities was lowest for the tiotropium group. Again, improvement in TDI and SGRQ scores was significantly greater with tiotropium than placebo. In almost all outcomes, the salmeterol results were intermediate between those of tiotropium and placebo, and were not statistically different from placebo.[5]

RECOMMENDATIONS FROM OTHERS

The GOLD (Global Strategy for the Diagnosis, Management, and Prevention of COPD) Report states that the choice between β_2-agonist, anti-cholinergics, or combination therapy depends on the availability and the response of a given patient in terms of symptom relief and side effects. The 2003 GOLD Workshop Report update further recommends the use of regular treatment with long-acting bronchodilators, including tiotropium, rather than short-acting bronchodilators for moderate-to-severe COPD.[6]

A separate report for the Joint Expert Panel on Chronic Obstructive Pulmonary Disease of the American College of Chest Physicians and the American College of Physicians—American Society of Internal Medicine

states that both are beneficial for management of acute exacerbations, but that anticholinergics should be considered first because they are associated with fewer and more benign side effects.[7]

CLINICAL COMMENTARY:

Patient response and tolerance of side effects determine which drug class to use

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Although recent national guidelines for the management of COPD, such as the GOLD report, give more cohesiveness to treatment strategies for patients with COPD, there is still room for tailoring a treatment approach. I find that when choosing between beta-agonists and anticholinergics, patient response and tolerability of side effects determine what I use.

This Clinical Inquiry supports my clinical impression that neither class of drug is significantly superior to the other in regards to COPD outcome measures. In my experience, when neither drug offers a clear advantage, factors affecting compliance and tolerability tend to determine how effective it is for my patients. Therefore, a trial of either class seems reasonable at first and follow-up determines what is used in the long run.

REFERENCES

1. Liesker JJ, Wijkstra PJ, Ten Hacken NH, Koeter GH, Postma DS, Kerstjens HA. A systematic review of the effects of bronchodilators on exercise capacity in patients with COPD. *Chest* 2002;121:597–608.
2. McCrory DC, Brown CD. Anti-cholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease. In: *The Cochrane Library*, Issue 1,2004. Chichester, UK: John Wiley, Ltd; 2003.
3. van Noord JA, de Munck DR, Bantje TA, Hop WC, Akveld ML, Bommer AM. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. *Eur Respir J* 2000;15:878–885.
4. Donohue JF, van Noord JA, Bateman ED , et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002;122:47–55.
5. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003;58:399–404.
6. Fabbri LM, Hurd SS. GOLD Scientific Committee. Global Strategy for the Diagnosis, Management, and Prevention of COPD: 2003 update. *Eur Respir*

J 2003;22:1–2.

7. Snow V, Lascher S, Mottur-Pilson C. Joint Expert Panel on Chronic Obstructive Pulmonary Disease of the American College of Chest Physicians and the American College of Physicians-American Society of Internal Medicine. Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 2001;134:595–599.