Should we avoid β-agonists for moderate and severe chronic obstructive pulmonary disease?

YES

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There is concern about the safety of β-agonist use for obstructive pulmonary diseases. β-Agonists can improve symptoms and airflow in asthma and chronic obstructive pulmonary disease (COPD), but substantial tolerance develops with regular use. In trials of COPD, regular β-agonist use was found to increase respiratory deaths twofold compared with placebo, while anticholinergic agents reduced respiratory deaths by 70%. Clinical guidelines should be revised to recommend that anticholinergics be the bronchodilators of choice for patients with COPD and that β-agonist use be avoided.

β-Agonists for obstructive lung diseases

Controversy has surrounded β-agonists since their introduction more than 50 years ago.[1] Short-acting β-agonists became widely used for management of asthma and COPD in the 1960s without good scientific data on long-term efficacy and safety. In the 1990s, the long-acting β-agonist salmeterol was introduced, despite evidence that it might be associated with greater risk of respiratory death than short-acting agents were.[2] After the US Food and Drug Administration received postmarketing reports of several asthma-related deaths associated with salmeterol, the Salmeterol Multicenter Asthma Research Trial was conducted; the trial found a twofold increase in life-threatening asthma exacerbations and a fourfold increase in asthma deaths compared with placebo.[3] Recently, some have asked whether long-acting β-agonists should be taken off the market.[4]

β-Agonists worsen control of obstructive lung diseases through a negative feedback mechanism that is an adaptive response of the β-adrenergic system.[5] Stimulation results in uncoupling and internalization of receptors, known as desensitization, followed by a decrease in receptor density and receptor gene expression, known as down-regulation.[5] This tolerance to β-agonists could explain the counterintuitive results of trials that demonstrate adverse respiratory effects.

Cardiovascular outcomes

β-Blockers reduce morbidity and mortality among patients with cardiovascular disease or other risk factors. β-Agonists exert physiologic effects opposite to those of β-blockers and might be expected to have deleterious cardiovascular effects. Case-control studies demonstrate

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Patients with moderate or severe chronic obstructive pulmonary disease (COPD) experience chronic progressive airflow obstruction and chronic progressive dyspnea that can be disabling. β-Agonist bronchodilators work by binding to and relaxing the airway smooth muscle. This relaxation results in dilation of the airway and allows more trapped air to escape with each exhalation. Reducing air trapping with β-agonists plays an important physiologic role in relieving dyspnea for patients with COPD.[1] Because of the impressive clinical and physiologic effects, all published COPD guidelines advocate using short- or long-acting β-agonist bronchodilators to reduce dyspnea, improve exercise tolerance, and improve quality of life for patients with symptomatic COPD.[2,3]

There would be only 2 reasons to abandon β-agonist bronchodilators for therapy of COPD: if they were shown to be ineffective or if the risk of adverse events caused by the drugs eclipsed their benefits. In the following paragraphs I will summarize clinical trial evidence that proves β-agonist bronchodilators are effective and safe for treating COPD.

Effectiveness

Evidence supporting the effectiveness of short- and long-acting β-agonists for treatment of COPD is overwhelming. A Cochrane Collaboration systematic review of 13 clinical trials evaluated the clinical effectiveness of short-acting β-agonists. The meta-analysis of these 13 trials showed that regular use of short-acting β-agonists for patients with stable COPD was associated with improvements in lung function and a significant decrease in breathlessness compared with placebo. Trial patients were almost 10 times more likely to prefer treatment with β-agonists over placebo. The authors of the Cochrane review thus concluded that treatment with short-acting β-agonists is beneficial for patients with COPD.[4]

The newer long-acting β-agonists have a prolonged duration of action. These drugs have been shown in clinical trials to induce substantial lung deflation in COPD patients and to decrease dyspnea associated with exercise. Patients taking salmeterol (a long-acting β-agonist) improved their peak exercise endurance by 58% compared with placebo.[5]

A 2006 Cochrane Collaboration systematic review evaluated the clinical effectiveness of long-acting

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an association between β-agonist use and increased risk of myocardial infarction, congestive heart failure, cardiac arrest, and acute cardiac death, with odds ratios ranging from 1.3 to 3.4.[6]

A meta-analysis pooled results from 33 randomized placebo-controlled trials of patients with obstructive lung disease and found that a single dose of β-agonist increased heart rate by 9 beats/min and reduced potassium concentration by 0.4 mmol/L compared with placebo.[7] For trials that lasted from 3 days to 1 year, β-agonist treatment increased the risk of cardiovascular events more than twofold compared with placebo. Adverse events included sinus and ventricular tachycardia, syncope, atrial fibrillation, congestive heart failure, myocardial infarction, cardiac arrest, and sudden death.

Respiratory outcomes

β-Agonists and anticholinergics are generally considered to be equivalent choices for treatment of COPD. Many trials of these agents have concentrated on short-term end points, such as airflow or symptoms. Anticholinergics have been shown to have equal or superior efficacy to β-agonists in improving lung-function parameters.[8] Surveys show, however, that prescriptions for β-agonists are 2 to 10 times more common than prescriptions for anticholinergics.[9] Anticholinergics have been shown to reduce severe COPD exacerbations by 40% ($P<.001$), hospitalizations by 30% ($P=.001$), and respiratory deaths by 70% ($P=.02$) compared with placebo, without tolerance to their effects over time[10]; significant tolerance develops to the effects of β-agonists in COPD.[11]

Two meta-analyses[9,10] pooled the results of randomized placebo-controlled trials of β-agonists or anticholinergics for COPD published through December 2005 and showed that β-agonist use increased respiratory deaths more than twofold compared with placebo, without significantly affecting hospitalization or total mortality. Approximately 50% of participants were also taking inhaled corticosteroids. When directly compared with other treatments, β-agonists caused a twofold increase in COPD hospitalizations and a fivefold increase in total mortality compared with anticholinergics, and a twofold increase in total mortality compared with inhaled corticosteroids.[9,10] Adding of β-agonists to anticholinergics or inhaled corticosteroids had no beneficial effect on any long-term clinical outcomes.[9]

Conflicts of interest

Why has it not been clearer to clinicians that β-agonists have such adverse effects on people with obstructive lung diseases? Conflicts of interest can arise from pharmaceutical company sponsorship of trials, as has been found with other medications. A systematic review of

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β-agonists.[6] Twenty-three clinical trials that randomized 6061 patients were assessed. The meta-analysis of these 23 trials showed that there was a significant improvement in lung function in favour of salmeterol (50 µg twice daily) compared with placebo. There were also significant differences in health-related quality of life in favour of salmeterol (50 µg twice daily) compared with placebo. Regular use of salmeterol reduced the incidence of COPD exacerbations compared with placebo (number needed to treat=21). Long-acting β-agonists clearly have been shown to be effective for treating COPD.

Safety

A recent meta-analysis by Salpeter et al questioned whether β-agonists might be associated with increased risk of respiratory death compared with placebo.[7] A closer look at the data used in the Salpeter meta-analysis reveals several important flaws. Only 4 published trials were included. No attempts were made by the authors to obtain mortality data from large randomized trials of β-agonist therapy for COPD that might have contributed important information (such as the 2003 Calverley study,[8] which randomized 1465 patients with COPD). Sixty percent of the weight of the Salpeter meta-analysis came from the results of only 1 study. Most importantly, the Salpeter meta-analysis contains data from duplicate publications. Data from the Donohue trial were duplicated in the Brusasco study. Duplicate publication of results from exactly the same patients inappropriately influenced the results of the Salpeter meta-analysis. In short, because of flawed methodology and inclusion of dubious studies, the results of the Salpeter meta-analysis are unreliable.

A more reliable assessment of the safety of long-term β-agonists for COPD can come from the largest clinical trial of COPD therapy performed to date, which assessed mortality as its primary outcome.[9] The TORCH (Towards a Revolution in COPD Health) study randomized 6112 patients with moderate or severe COPD to 3 years of double-blinded therapy with salmeterol (n=1521), fluticasone (n=1534), fluticasone and salmeterol (n=1533), or placebo (n=1524). The primary outcome was all-cause mortality.[9] Importantly, the risk of death in the group treated with salmeterol monotherapy was slightly lower than the risk in the group that received placebo (hazard ratio of death with salmeterol versus placebo=0.88, 95% confidence interval 0.73-1.06). Clearly, in this very large, 3-year clinical trial there was no signal to suggest that therapy with salmeterol led to excess respiratory deaths compared with placebo; in fact, the odds ratio of 0.88 suggests that salmeterol might have had a small (but not statistically significant) protective effect on mortality. The TORCH trial contained more patients in its salmeterol and placebo arms than all the studies in the Salpeter

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β-agonist trials found that 75% of industry-sponsored trials but only 10% of trials without industry support reported that β-agonists were beneficial.[12] The *P* value for interaction was <.00001, indicating a very strong association between pharmaceutical company funding and reporting beneficial results. Most of the trials longer than 3 months were industry sponsored. It is essential to evaluate hard clinical outcomes, such as hospitalizations or deaths.

Conclusion

In patients with COPD, β-agonists are associated with a twofold increase in respiratory deaths compared with placebo, a fivefold increase in total mortality compared with anticholinergic bronchodilators, and a more than twofold increase in adverse cardiovascular events compared with placebo. With the accumulated evidence on the serious adverse effects of β-agonists in asthma and COPD (**Table 1**[3,7,9,10]), I do not use any β-agonists in my clinical practice. β-Agonists should be avoided for patients with COPD. Anticholinergic agents should be the bronchodilators of choice.

Table 1. Clinical outcomes associated with β-agonist use for patients with obstructive lung disease

CLINICAL OUTCOME	COMPARISON	RELATIVE RISK (95% CONFIDENCE INTERVAL)
Cardiovascular events in patients with obstructive lung disease[7]	β-agonist vs placebo	2.5 (1.6-4.0)
Respiratory deaths in patients with asthma[3]	β-agonist vs placebo	4.4 (1.3-15.3)
Respiratory deaths in patients with COPD[10]	β-agonist vs placebo	2.5 (1.1-5.5)
Total mortality in patients with COPD[9]	β-agonist vs anticholinergic	5.0 (1.1-22.5)

COPD—chronic obstructive pulmonary disease.

CLOSING ARGUMENTS

- Anticholinergics have equal or superior efficacy to β-agonists in improving lung-function parameters without creating tolerance over time; substantial tolerance develops to regular use of β-agonists.
- Regular β-agonist use increases respiratory deaths twofold compared with placebo, while anticholinergic agents reduce respiratory deaths by 70%.
- Anticholinergics should be the bronchodilators of choice in patients with chronic obstructive pulmonary disease. β-Agonist use should be avoided.

NO

meta-analysis taken together. Thus results of this trial would overwhelm the results of the Salpeter meta-analysis. The TORCH study has clearly established that long-term β-agonist therapy is safe and is not associated with excess mortality in patients with COPD.[9]

In summary, long-term therapy with β-agonist bronchodilators is effective and safe for treatment of dyspnea associated with COPD. There is no justification for avoiding β-agonists for patients with symptomatic COPD.

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Competing interests

None declared

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References

1. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* 2001;164:770-7.
2. O'Donnell DE, Aaron SD, Bourbeau J, Hernandez P, Marciniuk DD, Balter M, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease—2003. *Can Respir J* 2003;10(Suppl A):11A-33A.
3. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Crit Care Med* 2001;163:1256-76.
4. Sestini P, Renzoni E, Robinson S, Poole P, Ram FSF. Short-acting beta 2 agonists for stable COPD. *Cochrane Database Syst Rev* 2002;3:CD001495.
5. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J* 2004;24:86-94.
6. Appleton S, Poole P, Smith B, Veale A, Lasserson T, Chan M. Long-acting beta 2-agonists for poorly reversible chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;3:CD001104.
7. Salpeter SR, Buckley NS, Salpeter EE. Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. *J Gen Intern Med* 2006;21:1011-9.
8. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:449-56.
9. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.

CLOSING ARGUMENTS

- Physiologic studies show that β-agonists dilate the airways and reduce air trapping in chronic obstructive pulmonary disease, and this leads to improved lung function and improved exercise tolerance for patients.
- Clinical trials clearly show that short- and long-acting β-agonists improve dyspnea and quality of life and reduce respiratory exacerbations in patients with chronic obstructive pulmonary disease.
- A very large new clinical trial has unequivocally demonstrated that long-term use of long-acting β-agonists over a period of 3 years is safe and is associated with a slightly lower risk of mortality compared with placebo.

YES

Dr Salpeter *is a Clinical Professor of Medicine in the Department of Medicine at Stanford University School of Medicine and Director of Medicine Consultation Services for Santa Clara Valley Medical Center in San Jose, Calif.*

Competing interests

Dr Salpeter *has been consulted on legal cases involving ß-agonist use and was paid on an hourly basis.*

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References

1. Taylor DR, Sears M, Cockcroft DW. The beta-agonist controversy. *Med Clin North Am* 1996;80:719-48.
2. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306:1034-7.
3. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15-26.
4. United States Food and Drug Administration Advisory Committee. *Serevent, Advair, Foradil withdrawals to be considered by Advisory Committee.* Rockville, Md: US Food and Drug Administration; 2005.
5. Johnson M. The beta-adrenoceptor. *Am J Respir Crit Care Med* 1998;158(5 Pt 3):S146-53.
6. Salpeter SR. Cardiovascular safety of beta(2)-adrenoceptor agonist use in patients with obstructive airway disease: a systematic review. *Drugs Aging* 2004;21(6):405-14.
7. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004;125:2309-21.
8. Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease: scientific review. *JAMA* 2003;290:2301-12.
9. Salpeter SR, Buckley NS. Systematic review of clinical outcomes in chronic obstructive pulmonary disease: beta-agonist use compared with anticholinergics and inhaled corticosteroids. *Clin Rev Allergy Immunol* 2006;31:219-30.
10. Salpeter SR, Buckley NS, Salpeter EE. Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. *J Gen Intern Med* 2006;21:1011-9.
11. Donohue JF, Menjoge S, Kesten S. Tolerance to bronchodilating effects of salmeterol in COPD. *Respir Med* 2003;97:1014-20.
12. Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. *Ann Intern Med* 2004;140(10):802-13.