

Impact of bronchodilator therapy on exercise tolerance in COPD

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Abstract: Exercise tolerance is an important parameter in patients with COPD and a primary goal of treatment is to reduce dyspnea to facilitate physical activities and improve health-related quality of life. This review examines the link between expiratory flow limitation and dyspnea to explain the rationale for the use of bronchodilators and review the characteristics of different types of exercise tests, with specific focus on which tests are likely to show a response to bronchodilators. An earlier literature search of studies published up to 1999 assessed the effects of bronchodilator therapy on dyspnea and exercise tolerance among patients with COPD. This current review examines the clinical evidence published since 1999. Thirty-one randomized studies of exercise tolerance associated with short- and long-acting β_2 -agonists and anticholinergics were identified. Evidence for the efficacy of bronchodilators in enhancing exercise capacity is often contradictory and possibly depends on the exercise test and study methodology. However, further studies should confirm the benefit of long-acting bronchodilators in improving spontaneous everyday physical activities.

Keywords: COPD, exercise, bronchodilator, walk test, exercise test

Introduction

Chronic obstructive pulmonary disease (COPD) is a substantial healthcare burden worldwide.¹ In developed countries, COPD is already a leading cause of death (ranked fourth in the US) and its prevalence is predicted to increase.² In addition, the number of smokers is rising in many countries (notably among women), leading to an escalating prevalence of COPD.^{3,4}

COPD is characterized by dyspnea-induced impairment that can significantly impair performance of everyday tasks. Hence, a primary goal in the management of COPD is to improve dyspnea to facilitate physical activities and, ideally, should be obtained whatever the severity of the disease to improve the patient's health-related quality of life (HRQoL).

Exercise testing is an increasingly used outcome measure in assessing COPD treatments in lieu of the ability to measure improvement in physical activity itself. Indeed, physical activity in COPD or aging patients is correlated with maximal exercise capacity determined by an incremental cycle exercise test. Moreover, poor exercise capacity in COPD patients is a predictor of mortality,^{5,6} and hence would be a useful measure during clinical practice, though most methods for measuring exercise capacity are appropriate for the laboratory. Another important finding from laboratory exercise testing is determining the locus of limiting symptom in poor exercise capacity, which

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is frequently, but not exclusively, due to dyspnea^{7,8}; however, many patients also show a degree of muscle fatigue that highlights the importance of conditioning through exercise for patients with COPD.

Bronchodilation is a key therapy in COPD, aimed at alleviating bronchial obstruction and airflow limitation. Guidelines recommend bronchodilators as first-line maintenance therapy for patients with all severities of disease.^{9,10} Yet, despite the efficacy of bronchodilators in improving both bronchial obstruction and pulmonary distension at rest, evidence for their beneficial effect on exercise capacity is inconsistent.^{11,12} In a systematic review on the effects of bronchodilators on exercise capacity, Liesker et al¹¹ reported that a significant improvement in exercise tolerance was observed in only half of the studies. Since 1999, numerous additional studies have investigated the effects of bronchodilators on exercise capacity, including studies with once-daily bronchodilators, such as the anticholinergic tiotropium and the β_2 -agonist indacaterol, which had not previously been reviewed. In addition, there have been some advances in our understanding of the mechanisms by which bronchodilators can improve exercise capacity and tolerance, and which exercise tests are likely to show a response to bronchodilators.

This review aims to examine the clinical evidence published since 1999 on the effect of bronchodilators on exercise tolerance among patients with COPD, and to review the characteristics and clinical significance of exercise tests. First, the link between expiratory flow limitation and dyspnea is examined to explain the rationale for using bronchodilators and the advantages of improved airflow in relation to exercise tolerance.

Selection of studies for review

Literature on the impact of short- and long-acting bronchodilators on exercise tolerance in patients with COPD was reviewed by performing a PubMed database search, using the search terms “exercise”, “COPD”, “pulmonary disease” and the drug scientific name. The search was limited to articles published in English between 1999 and 2009, reporting on studies of adult (≥ 19 years) patients. Studies in asthma were excluded. A total of 14 studies of short-acting bronchodilators (salbutamol, procaterol, ipratropium and oxitropium) and 22 studies of long-acting bronchodilators (salmeterol, formoterol and tiotropium) were identified. At the time of writing, no published studies with indacaterol were found to include exercise testing.

Air trapping and exercise pulmonary hyperinflation – the link from expiratory flow limitation to daily-living dyspnea

Expiratory flow limitation (EFL) is the primary physiological hallmark of COPD, and the most prominent and distressing symptom is dyspnea. The relationship between EFL and the ability to perform day-to-day activities is complex; for example, forced expiratory volume in 1 second (FEV_1) is important for the diagnosis and monitoring of COPD,⁶ but clinically relevant improvements in symptoms can occur in the absence of significant changes in FEV_1 , and vice versa.^{13,14}

A physiological link between EFL and patient-centered outcomes may be air trapping and resultant hyperinflation. Spirometric indices of hyperinflation, such as inspiratory capacity (IC), correlate more closely with improvements in dyspnea and exercise tolerance than changes in FEV_1 .^{13–15} Hence, air trapping resulting from EFL, rather than EFL per se, may be the significant contributor to dyspnea and exercise limitation in COPD.^{16,17}

Air trapping can occur due to both static and dynamic hyperinflation processes. Static air trapping can occur due to the emphysema and other structural changes in the lung that causes the lung to be capable of expelling less air. Dynamic air trapping additionally occurs when there is insufficient expiratory time for adequate lung emptying. As a result, the volume of air left in the lung at the end of expiration is increased and the IC is decreased. It is dynamic hyperinflation that is susceptible to manipulation with bronchodilator treatment. This process of dynamic air trapping is exacerbated during more rapid rates of ventilation, such as that which occurs during exercise. In COPD patients with a severe EFL, dynamic air trapping may even occur at a resting respiratory rate. Air trapping may occur gradually or abruptly, depending on the severity of EFL and the intensity of the exercise, which can affect exercise endurance. For example, if air trapping progresses gradually relative to the ventilation rate, patients will endure the ensuing dyspnea and exercise for longer than if it occurs abruptly. This suggests that air trapping is the primary functional limitation on exercise tolerance.¹⁶ Further support for this hypothesis is provided by the fact that improvements in dynamic air trapping correlate highly with reductions in dyspnea.¹⁸

Activity limitation is accelerated through a vicious circle that develops as the gradual decline of lung function causes

dynamic air trapping, which triggers a reduction in exercise tolerance due to dyspnea and muscle fatigue.^{16,19} Dyspnea dictates the level of activity undertaken and may discourage some patients from participating in physical activities.^{20,21} Chronic inactivity results in more rapid muscle fatigue due to deconditioning, leading to worsening of disease and further deterioration of the patient's HRQoL.²² Thus, the alleviation of exercise dyspnea by the reduction of dynamic air trapping and hyperinflation remains the principal goal of treatment.

Clinical exercise testing

Since dyspnea is the primary cause of impaired daily-living activities in patients with COPD, it is important to evaluate exercise tolerance using clinical testing to determine the patient's level of incapacity and response to treatment. There are several types of structured clinical exercise tests ranging from the simple and inexpensive self-paced 6-minute or 12-minute walk distance (6MWD/12MWD) test and externally-paced shuttle walk test (SWT), to the sophisticated and expensive cardiopulmonary exercise test.

The protocols used for exercise tests can be classified as constant work rate (CWR) or incremental. In the former, the work rate is virtually constant throughout the test; hence, the duration of the test can be relatively long compared with incremental workload tests, in which the workload is increased to volitional exhaustion and maximal or near maximal aerobic capacity.

Cardiopulmonary exercise testing (CPET) provides the most complete physiological evaluation, including insights into the mechanisms of exercise limitation²³; however, the equipment is expensive and requires regular maintenance and calibration. Furthermore, qualified personnel are needed to supervise the tests to ensure patient safety.

CPET can be used with both incremental and CWR protocols and permits the evaluation of submaximal and peak exercise responses. Modes of exercise most commonly used are the treadmill and cycle ergometer. In respiratory clinical tests, the cycle ergometer is often preferred as it offers direct quantification of the work rate, the static upper body allows easier collection of blood samples and fewer artifacts on the electrocardiogram, and it is often cheaper and safer.²⁴ A limitation is that local muscle fatigue is more predominant with cycle ergometry compared with walking on a treadmill.^{7,12,25} A meta-analysis of clinical trials of respiratory rehabilitation in patients with COPD determined a minimum clinically important difference (MCID) of 8.3 W (95% CI, 2.8–16.5) maximum exercise capacity using incremental or progressive cycle ergometry (PCE).²⁶ Recently, the MCID

for CWR on a cycle ergometer has been suggested to be an increase in exercise time of approximately 33% of baseline, though further validation is required.²⁷ A literature search revealed no studies that have determined the MCIDs for treadmill CPET.

Flat-course walk-tests are the easiest and most economical procedures for evaluating exercise capacity, as no specialist equipment is required; however, results are dependent on the motivation of the patient and the degree of encouragement offered. In addition, there exists some uncertainty about the interpretation of results, particularly with respect to the MCID.²⁸

The 6MWD test differs from the other tests in that it is self-paced and dependent on patient characteristics and methodology. The American Thoracic Society has developed guidelines to standardize the use of the 6MWD test in clinical settings, in particular for the measurement of outcomes before and after treatment,²⁹ and an improvement of ≥ 54 m has been proposed as being clinically important in patients with stable COPD.³⁰ A more recent analysis estimated that the 6MWD should change by approximately 35 m (or 10% from baseline) for patients with moderate-to-severe COPD in order to represent a clinically important effect.²⁸ These discrepancies in MCID may reflect the variable nature of the walk tests but also highlight the need to consider disease severity when interpreting treatment changes.

Recent reviews of published studies suggest that the 6MWD test is less sensitive in discerning an effect of bronchodilators than cycle ergometry, though there are correlations in results between the two tests in general. A number of factors have been suggested to account for this difference, including the short duration of the self-paced, non-maximal exercise and the variability between patients. The 6MWD test also has a lower correlation to lung function than cycle ergometry CPET. Nevertheless, changes in exercise endurance with non-pharmacological interventions have been discernable using the 6MWD.

The SWT was designed to overcome the criticism that patients are unlikely to extend themselves during self-paced timed-walk tests.³¹ The technique allows objective measurement of subjective performance and reduces the effects that frailty and comorbidity may have in elderly patients. The test comprises a 10 m course, externally paced by an audiotape, which increases at set intervals until volitional exhaustion. The SWT is standardized and both incremental and CWR exercise tests can be performed.

The outcome parameter for the incremental SWT is the distance covered before the patient stops because of dyspnea

or muscle fatigue and the MCID for the incremental SWT has recently been defined as 47.5 m.³² Even though the incremental SWT is not an endurance test and is arguably less relevant to paced activities of daily living, results do correlate with the 6MWD. As with the 6MWD, the correlation between the incremental SWT and lung function is low, but changes in dyspnea have greater similarity to incremental CPET than to the 6MWD.

The endurance SWT is of considerable interest following recent work demonstrating that this CWR test is sufficiently sensitive to detect changes with inhaled bronchodilators.⁷ Indeed, exercise endurance time with the SWT may be more sensitive to change from bronchodilators than cycle ergometry, though the reasons for this are unclear. The constant walking speed for the endurance SWT is calculated as 85% of the maximum sustainable walking speed from the incremental SWT. Endurance SWT correlates with treadmill testing, though the actual endurance times are shorter with SWT and there is no MCID established for the endurance SWT.

The performance-based tests described above, although providing reliable estimates of exercise capacity, may not be suited for primary care due to cost and time constraints. In addition, it remains uncertain whether such tests accurately reflect performance of daily activities such as stair-climbing.³³ Other tests used to evaluate functional ability and exertion-induced dyspnea include unsupported arm exercise tests, such as the sit-to-stand test, step testing and Glittre activity daily living [ADL] test.^{34–38} These tests evaluate daily-living activities such as climbing stairs, lifting and carrying, bending down and rising from a seated position, and are beneficial in that they are less time-consuming, easy to implement in the primary care environment, and complement conventional exercise tests such as the 6MWD. However, additional studies are required to evaluate their validity and reproducibility.

Impact of bronchodilators on exercise tolerance

Inhaled β_2 -agonists and anticholinergics currently form the main classes of bronchodilators used in the treatment of COPD. Although oral theophyllines are still used, the findings of clinical studies suggest that they have little or no effect on exercise capacity.¹¹ Moreover, there have been no new exercise studies with theophylline since 1999.

The database search identified 31 double-blind, typically placebo-controlled studies published since 1999 that included monotherapy with a bronchodilator (Tables 1

and 2). These studies are discussed below. When interpreting the data, it is important to remember the limitations of comparison between the different methodologies and patient populations.

Short-acting bronchodilators (Table 1)

Short-acting β_2 -agonists

Several salbutamol studies were performed before 2000 and are reviewed in detail by Liesker, 2002.¹¹ In brief, seven studies assessing the effect of salbutamol on exercise endurance (using the 6MWD or 12MWD) were reviewed^{39–45} and a significant improvement in endurance, compared with placebo, was observed in all but one of the studies. Only one of the two 6MWD trials could be assessed for MCID,⁴³ but this would achieve MCID according to the ≥ 35 m criteria proposed by Puhan and colleagues,²⁸ but not according to the ≥ 54 m criteria of Redelmeier and colleagues.³⁰

Since 1999, the impact of the short-acting β_2 -agonist, salbutamol, has been determined in three studies: two using cardiopulmonary exercise tests and one using upper limb exercises (Table 1).^{46–48} In each of these studies, salbutamol was administered as a single dose, reflecting the fact that its most appropriate use is as rescue medication.⁴⁹

In the two studies using cardiopulmonary tests,^{46,47} endurance was assessed by CWR cycle exercise. A significant increase in endurance time was observed by Oga et al,⁵ though this was short of being clinically significant according to the criteria of Puente-Maestu and colleagues. Aliverti et al⁴⁷ observed no change in CWR cycling exercise endurance time with salbutamol despite a significant decrease in IC, suggesting that salbutamol was efficacious in avoiding dynamic hyperinflation during the exercise, but this did not affect endurance time. In the study by Porto et al,⁴⁸ a significant decrease in IC was observed after performing an incremental arm exercise test following inhalation with placebo; however, no change was observed following inhalation with salbutamol, suggesting again that the bronchodilator prevented hyperinflation development.

More recently, two studies^{50,51} have evaluated the impact of procaterol on exercise performance. Shioya et al⁵⁰ demonstrated clinically significant improvements in walking distance using the 6MWD (42 m, $P < 0.05$) together with significant improvements in dyspnea and FEV₁. In the study by Sukisaki and colleagues,⁵¹ statistically significant improvements in the incremental SWT (37 m, $P < 0.001$) were reported, despite no significant improvements in FEV₁, though this distance is below the MCID.

Table 1 Impact of short-acting bronchodilators on exercise capacity

Study	Dose of study drug	Study design	N	Baseline FEV ₁ (% pred.)	Change in resting lung volume	Change in exercise dyspnea (Borg score)	Changes in exercise performance			
							Walking	CWR cycling	Progressive cycling	Other
Short-acting β₂-agonists										
<i>Salbutamol</i>										
Porto et al ⁴⁸	400 µg	Single-dose, randomized	16	41%	Δ IC, P = 0.001 ^a	–	–	–	–	Incremental Arm Exercise: Δ IC, NS ^b
Aliverti et al ⁴⁷	5 mg nebulized	Single-dose, crossover	18	40.6%	Δ FEV ₁ P < 0.001 ^a Δ FRC P < 0.01 ^a Δ IC P < 0.001 ^a	NS ^a	NS ^a	–	–	–
Oga et al ⁴⁶	400 µg	Single-dose, crossover	67	44.2%	Δ FEV ₁ P < 0.001 ^a Δ FVC P < 0.001 ^a	P < 0.001 ^a	–	–	Δ endurance time 29 s (+15%) P < 0.001 ^a	–
<i>Procaterol</i>										
Shioya et al ⁵⁰	20 µg qid	52-week, randomized	20	48.1%	Δ FEV ₁ P < 0.05 ^b Δ FVC P < 0.05 ^b	P < 0.05 ^b	–	–	6MWD: Δ 42 m (+10%) P < 0.05 ^b	–
Sukisaki et al ⁵¹	20 µg	Single-dose, crossover	19	38.5%	Δ FEV ₁ NS ^a	NS ^b	–	–	SWT: Δ 37 m (P = 0.001 ^b)	–
Short-acting anticholinergics										
<i>Ipratropium</i>										
O'Donnell et al ⁵⁷	500 µg nebulized	Single-dose, crossover	16	90%	Δ FEV ₁ P < 0.05 ^a Δ FVC P < 0.05 ^a Δ TLC NS ^a Δ FRC P < 0.05 ^a Δ IC NS ^a	NS ^a	–	–	NS ^a	–
Pepin et al ⁵⁶	500 µg nebulized	Single-dose, crossover	14	50%	Δ FEV ₁ P < 0.001 ^a	–	–	–	SWT: Δ 144 m (P = 0.03) 6MWD: NS	–
Pepin et al ⁷	500 µg nebulized	Single-dose, crossover	17	56%	Walk and Cycle: Δ FEV ₁ P < 0.001 ^a	NS	–	–	SWT: Δ endurance time 2 mins 44 s (P < 0.01 ^a)	–
Akkoca et al ⁵⁵	40 µg qid	2 week, crossover	10	69%	Δ FEV ₁ NS ^b Δ FVC NS ^b Δ TLC NS ^b Δ FRC NS ^b Δ IC NS ^b	–	–	–	–	Δ W max = NS ^b Δ endurance time 1 min 18 s P < 0.05 ^b

(Continued)

Table 1 (Continued)

Study	Dose of study drug	Study design	N	Baseline FEV ₁ (% pred.)	Change in resting lung volume	Change in exercise dyspnea (Borg score)	Changes in exercise performance			
							Walking	CWR cycling	Progressive cycling	Other
Saey et al ¹²	500 µg nebulized	Single-dose	18	38%	Δ FEV ₁ P < 0.05 ^b Δ IVC P < 0.0001 ^a Δ FRC P < 0.01 ^a Δ RV P < 0.001 ^a	–	Δ endurance time 1 min 58 s (+37%) P = 0.06 ^a	–	–	–
Oga et al ¹⁶	80 µg	Single-dose, crossover	67	44.2%	Δ FEV ₁ P < 0.001 ^a Δ FVC P < 0.001 ^a	P < 0.001 ^a	Δ endurance time 27 s (+14%) P < 0.001 ^a	–	–	–
Liesker et al ⁵³	80 µg tid	1 week, cross-over	34	55.6%	Δ FEV ₁ P < 0.0001 ^a Δ IVC P < 0.0001 ^a Δ FVC NS ^a Δ FRC P < 0.01 ^a Δ RV P < 0.001 ^a	NS ^a	–	–	Δ endurance time 46 s P < 0.0001 ^a	–
Wadbo et al ⁵⁴	80 µg tid	12 weeks, parallel	183	33.6%	Δ FEV ₁ P < 0.05 ^a Δ FVC P < 0.05 ^a	NS ^a	SWT: NS ^a	–	–	–
Rennard et al ⁵²	36 µg qid	12 weeks, parallel	405	–	Δ FEV ₁ P < 0.05 ^a Δ FVC P < 0.05 ^a	NS ^a	6MWD: NS ^a	–	–	–
<i>Oxitropium</i>										
Shioya et al ⁵⁰	200 µg qid	52-week, randomized	20	49.4%	Δ FEV ₁ NS ^b Δ FVC NS ^b	NS ^b	6MWD: NS ^b	–	–	–
Oga et al ⁵⁸	400 µg	Single-dose, crossover	38	40.8%	Δ FEV ₁ P < 0.001 ^a Δ FVC P < 0.01 ^a	Δ 0.2 P < 0.05 ^a (PCE test only)	6MWD: Δ 6 m (+1%) P < 0.05 ^a	Δ endurance time 34 s (+18%) P < 0.001 ^a	Δ Wmax 3 W P < 0.01 ^a	–

^aActive drug versus placebo; ^bActive drug versus baseline.**Abbreviations:** FEV₁, forced expiratory volume in 1 second; FRC, forced residual capacity; FVC, forced vital capacity; CWR, constant work rate; PCE, progressive cycle ergometry; CWR, constant work rate; 6MWD, 6 minute walk distance; SWT, shuttle walk test; NS, not significant.

Table 2 Impact of long-acting bronchodilators on exercise capacity

Study	Dose of drug	Study design	N	Baseline FEV ₁ (% pred.)	Change in resting lung volume	Change in exercise dyspnea		Changes in exercise performance		
						Borg score	CRQ or TDI/BDI score	Walking	CWR cycling	Progressive cycling
Long-acting β_2-agonists										
<i>Salmeterol</i>										
Brouillard et al ⁷⁷	50 μ g	Single dose, 5-visit (≥ 48 h, ≤ 4 days apart), crossover	20	52%	Δ FEV ₁ P < 0.0001 ^a Δ FVC P < 0.0001 ^a Δ IC NS ^a Δ FRC NS ^a Δ RV P < 0.05 ^a	Δ Borg score 5.6 P = 0.006 ^a (isotime)	–	SWT: Δ 160 m P = 0.02 ^a Δ endurance time 1 min 57 s P = 0.02 ^a	–	–
Stockley et al ⁷⁶	50 μ g bid	12-month, parallel	426	46.1%	Δ FEV ₁ P < 0.0001 ^a Δ FVC P < 0.01 ^a Δ SVC P < 0.05 ^a Δ IC P < 0.05 ^a	NS ^a	–	SWT: Δ 30 m P = 0.04 ^a	–	–
O'Donnell et al ⁷⁵	50 μ g bid	8-week, parallel	123	39.5%	Δ FEV ₁ P < 0.05 ^a Δ FVC P < 0.05 ^a Δ FRC P < 0.05 ^a Δ RV P < 0.05 ^a Δ IC P < 0.05 ^a	NS ^a	–	–	NS ^a	–
Man et al ⁷⁴	50 μ g bid	2-week, crossover	16	31.1%	Δ FEV ₁ NS ^a Δ VC NS ^a Δ IC P < 0.05 ^a Δ RV NS ^a	Δ Borg score 0.84 (P = 0.02 ^a) (isotime)	–	Treadmill endurance test: NS ^a	–	–
O'Donnell et al ⁷³	50 μ g bid	2-week, crossover	23	42%	Δ FEV ₁ P < 0.01 ^a Δ FVC P < 0.01 ^a Δ FRC P < 0.01 ^a Δ RV P < 0.01 ^a Δ IC P < 0.01 ^a	NS ^a	–	–	Δ endurance time 1 min 36 s (+58%) P = 0.018 ^a	–
Gupta et al ⁷²	50 μ g bid	8-week, parallel	33	–	Δ FEV ₁ P < 0.05 ^b Δ FVC P < 0.05 ^b	–	TDI: P < 0.01 ^a	6MWD: NS ^a	–	–
Rennard et al ⁵²	42 μ g bid	12-week, parallel	405	–	Δ FEV ₁ P < 0.05 ^a Δ FVC P < 0.05 ^a	NS ^a	–	6MWD: NS ^a	–	–
Weiner et al ⁷¹	50 μ g bid 50 μ g bid+ exercise	18-week, parallel	23 17	33% 35%	Δ FEV ₁ NS ^a	NS ^a NS ^b	–	6MWD NS ^a 6MWD: Δ 42 m (+17%) P < 0.05 ^b	–	–

(Continued)

Table 2 (Continued)

Study	Dose of drug	Study design	N	Baseline FEV ₁ (% pred.)	Change in resting lung volume	Change in exercise dyspnea		Changes in exercise performance		
						Borg score	CRQ or TDI/BDI score	Walking	CWR cycling	Progressive cycling
	50 µg bid + exercise + inspiratory muscle training		11	35%		P < 0.01 ^b	6MWD: Δ 50 m (+20%) P < 0.05 ^b			
Formoterol										
Cazzola et al ⁷⁰	12 µg bid	5-day crossover	22	14%–56%	Δ FEV ₁ P < 0.05 ^b Δ IC P < 0.05 ^b	Δ Borg score –1.7 P = 0.005 ^b (pre-last dose) –1.8 P = 0.001 ^b (post-last dose)	6MWD: Δ 53.6m P = 0.006 ^b 12MWD: Δ 59.9 m P = 0.018 ^b	–	–	–
Neder et al ⁶⁹	12 µg bid	2-week crossover	21	38.8%	Δ IC P < 0.05 ^a Δ EELV P < 0.05 ^a Δ RV P < 0.05 ^a	NS ^a	–	–	Δ 2 min 10 s P = 0.052	–
Akkoca et al ⁵⁵	12 µg bid	2 week crossover	10	69%	Δ FEV ₁ NS Δ FVC NS Δ FEV ₁ /FVC P < 0.05 ^b Δ TLC NS Δ FRC NS Δ IC NS	–	–	–	–	Δ TTE 45 s P < 0.05 ^b
Wadbo et al ⁵⁴	18 µg bid	12-week, parallel	183	33.3%	Δ FEV ₁ P < 0.05 ^a Δ FVC P < 0.05 ^a	NS	SWT: NS	–	–	–
Aalbers et al ⁶⁸	4.5 µg bid 9 µg bid 18 µg bid	12-week, parallel	Total 692 144 136 150	54% 53.1% 54.4% 54.7%	Δ FEV ₁ P < 0.01 ^a Δ FEV ₁ P < 0.05 ^a Δ FEV ₁ P < 0.001 ^a	–	SWT: NS ^a NS ^a NS ^a	–	–	–
Liesker et al ⁵³	4.5 µg bid	1-week crossover	34	–	Δ FEV ₁ P < 0.05 ^a Δ FRC P < 0.05 ^a Δ FVC NS ^a Δ IVC P < 0.05 ^a Δ RV P < 0.05 ^a	NS	–	–	–	Δ TTE 44 s P < 0.0001 ^a
	9 µg bid		34	–	Δ FEV ₁ P < 0.05 ^a Δ FRC P < 0.05 ^a Δ FVC NS ^a Δ IVC P < 0.05 ^a Δ RV P < 0.05 ^a	NS	–	–	–	34 s P < 0.01 ^a

Author	Dose	Study Design	n	Time to exhaustion (min)	FEV ₁ (L)	FVC (%)	IC (L)	RV (L)	6MWD (m)	SWT (m)	TDI (units)	Statistical significance
Long-acting Anticholinergics												
<i>Tiotropium</i>												
Ambrosino et al ⁸³	18 µg qd	4-week, parallel	117	42.5%	Δ FEV ₁ P < 0.05 ^a	–	–	–	6MWD: NS ^a	–	–	–
	18 µg qd + rehabilitation	25-week (including 8 weeks' rehabilitation), parallel	117	42.5%	Δ FRC P < 0.05 ^a	–	–	–	Week 13: NS ^a	–	–	–
					Δ FVC NS ^a	–	–	–	Week 25: NS ^a	–	–	–
					Δ IVC P < 0.05 ^a	–	–	–	At end of PR (Week 13): 3.60 units	–	–	–
					Δ RV P < 0.05 ^a	–	–	–	P = 0.001 ^a	–	–	–
						–	–	–	At Week 25: NS ^a	–	–	–
Travers et al ⁸²	18 µg qd	7–10 day, crossover	18	40%	Δ FEV ₁ P < 0.01 ^a	–	–	–	–	–	–	NS ^a
					Δ RV P < 0.01 ^a	–	–	–	–	–	–	–
					Δ FRC P < 0.01 ^a	–	–	–	–	–	–	–
Okudan et al ⁸¹	18 µg qd	Single-dose, crossover	44	–	–	–	–	–	–	–	–	–
					Δ FVC P < 0.05 ^a	–	–	–	6MWD: Δ 14.6 m (+4%) P < 0.05 ^a	–	–	–
					Δ IC P < 0.05 ^a	–	–	–	SWT: Δ 36 m	–	–	–
Verkindre et al ⁸⁰	18 µg qd	12-week, parallel	46	34.7%	–	–	–	–	–	–	–	–
					Δ FEV ₁ P < 0.01 ^a	–	–	–	–	–	–	–
					Δ FVC P < 0.001 ^a	–	–	–	–	–	–	–
Casaburi et al ⁷⁹	18 µg qd	4-week, parallel	55	34%	–	–	–	–	–	–	–	–
					Δ FEV ₁ P < 0.01 ^a	–	–	–	–	–	–	–
					Δ FVC P < 0.001 ^a	–	–	–	–	–	–	–
					Δ FEV ₁ P < 0.01 ^a	–	–	–	–	–	–	–
					Δ FVC P < 0.001 ^a	–	–	–	–	–	–	–
					Δ FEV ₁ P < 0.001 ^a	–	–	–	–	–	–	–
					Δ FVC P < 0.001 ^a	–	–	–	–	–	–	–
					Δ SVC P < 0.001 ^a	–	–	–	–	–	–	–
					Δ IC P < 0.001 ^a	–	–	–	–	–	–	–
					Δ FRC P < 0.001 ^a	–	–	–	–	–	–	–
					Δ RV P < 0.001 ^a	–	–	–	–	–	–	–
					Δ TLC P < 0.01 ^a	–	–	–	–	–	–	–
					Δ FEV ₁ P < 0.001 ^a	–	–	–	–	–	–	–
					Δ FVC P < 0.0001 ^a	–	–	–	–	–	–	–
					Δ IC P < 0.05 ^a	–	–	–	–	–	–	–
					Δ RV P < 0.001 ^a	–	–	–	–	–	–	–
					Δ FRC P < 0.001 ^a	–	–	–	–	–	–	–
O'Donnell et al ¹⁸	18 µg qd	6-week, parallel	96	42%	Δ FEV ₁ P < 0.001 ^a	–	–	–	–	–	–	–
					Δ FVC P < 0.0001 ^a	–	–	–	–	–	–	–
					Δ IC P < 0.05 ^a	–	–	–	–	–	–	–
					Δ RV P < 0.001 ^a	–	–	–	–	–	–	–
					Δ FRC P < 0.001 ^a	–	–	–	–	–	–	–

^aActive drug versus placebo; ^bActive drug versus baseline.

Abbreviations: EELV, end-expiratory lung volume; FEV₁, forced expiratory volume in 1 second; CRQ, chronic respiratory disease questionnaire; BDI, baseline dyspnea index; TDI, transition dyspnea index; FRC, forced residual capacity; IC, inspiratory capacity; FVC, forced vital capacity; VC, vital capacity; RV, residual volume; CWR, constant work rate; IVC, inspiratory vital capacity; PCE, progressive cycle ergometry; 6MWD, 6 minute walk distance; SWT, shuttle walk test; TTE, Time to exhaustion (for PCE); NS, not significant; PR, pulmonary rehabilitation.

Short-acting anticholinergics

The effect of short-acting anticholinergics on exercise is inconsistent (Table 1).^{7,12,46,50,52–58} In general, they are recommended for the management of mild COPD and as required in symptomatic patients.^{10,59} Prior to the availability of the once-daily anticholinergic, tiotropium, short-acting anticholinergics had been used for chronic treatment across all severities of the disease.

Single doses of ipratropium have shown some beneficial effect on exercise tolerance.^{7,46,56} In many of the studies using 6MWD, including those reviewed by Liesker et al,¹¹ the significant results did not reach the MCID proposed by Puhan and colleagues.²⁸ MCID responses have been reported with the SWT⁵⁶ and CWR cycling,¹² though the latter did not achieve statistical significance, but did include study patients with more severe COPD than many of the other studies.

In longer-term studies involving treatment periods of up to 12 weeks,^{52–55} only Liesker et al⁵³ and Akkoca et al⁵⁵ found a significant improvement in exercise performance. Ipratropium significantly increased time to exhaustion in the incremental cycle exercise used by Liesker et al⁵³ and Akkoca et al,⁵⁵ though the latter small study was not statistically significant with respect to change in work rate.

Two studies examining the effect of oxitropium on exercise performance have been published since 1999.^{50,58} Oga et al⁵⁸ observed statistically significant (but not MCID) improvements in both the 6MWD (6 m increase, $P < 0.05$) and CWR cycle ergometry (34 s increased endurance, $P < 0.001$) compared with placebo, following a single dose of 400 µg oxitropium. However, in the study by Shioya et al,⁵⁰ 6MWD in patients receiving 600 µg oxitropium was not shown to differ significantly from baseline after 12, 24 or 52 weeks of treatment. A total of six oxitropium studies^{60–65} were included in the review of Liesker et al,¹¹ and in five of these studies^{60,62–65} a statistically significant improvement in exercise performance was observed, though these did not achieve a definite MCID.

In two single-dose studies^{66,67} evaluating the effect of a combination of salbutamol and ipratropium, improvements in endurance were observed, although statistical significance was only observed in that of Cukier et al⁶⁶ who reported an improvement in 6MWD of 21 m (+6%, $P < 0.05$) compared with placebo. In comparison, Peters et al⁶⁷ reported that endurance time, using CWR cycle ergometry improved by 1 min 42 s (+31%) with a salbutamol-ipratropium combination, although this improvement failed to achieve statistical significance versus placebo ($P = 0.067$).

Long-acting bronchodilators (Table 2)

Long-acting β_2 -agonists

The effects of two long-acting β_2 -agonists on exercise capacity have been evaluated: formoterol^{53–55,68–70} and salmeterol^{52,71–77} (Table 2).

In a study by Cazzola et al,⁷⁰ 5-day treatment with formoterol was shown to increase walking distance by 53.6 m at the end of the 6MWD test (achieving MCID) and by 59.9 m at the end of the 12MWD test compared with baseline. The perception of breathlessness measured by the Borg scale was also significantly reduced with formoterol compared with baseline. However, in two larger studies,^{54,68} formoterol treatment resulted in no significant improvement in the performance of the incremental SWT compared with placebo.

Using PCE to symptom limitation, Liesker et al⁵³ showed significant enhancement of time to exhaustion after 1-week treatment with formoterol compared with placebo of between 23 and 44 seconds, as was reported in the previous review. Also using PCE, Akkoca et al⁵⁵ demonstrated a significant improvement in time to exhaustion of 45 seconds compared with baseline after dosing with formoterol and following 14 days' treatment with formoterol. Using CWR cycling in patient with more severe COPD than in the previous two trials, change in endurance time with 2-week treatment with formoterol did not achieve statistical significance compared with placebo (Neder et al⁶⁹).

For salmeterol, Liesker 2002 reviewed three studies performed before 2000, all of which did not find a significant effect of salmeterol on walking distance (6MWD or 12MWD) after treatment for up to 12 weeks.¹¹ Similar results have been found in three further studies using the 6MWD test since 2000 that are reported in Table 2, though the perception of dyspnea during exercise was significantly reduced in one of these studies.^{52,71,72} One study⁷¹ showed significant improvements in 6MWD with a combination of salmeterol and 6 weeks of general exercise training (16% improvement; $P < 0.05$) or 6 weeks' general exercise training plus inspiratory muscle training (20% improvement; $P < 0.05$). This may suggest an additive or synergistic effect of salmeterol and exercise training; however, this cannot be confirmed due to the study design.

Salmeterol has significantly improved exercise capacity measured using the SWT.^{76,77} In a large 1-year trial, patients treated with salmeterol walked a statistically significant 30 m further in an incremental SWT than patients treated with placebo, though the difference was below that considered clinically significant and perception of breathlessness was

not statistically different.⁷⁶ In a smaller, single-dose study, Brouillard et al⁷⁷ demonstrated statistically significant improvements in walking performance with salmeterol compared with placebo measured by both incremental (160 m; $P < 0.05$) and endurance SWT (1 min 57 s; $P < 0.05$), with the difference in incremental SWT exceeding the MCID. Salmeterol also reduced the perception of dyspnea during exercise in this study when compared with placebo at an isotime, but not at the end of exercise.

O'Donnell et al⁷³ demonstrated a clinically significant improvement of exercise endurance with 2-week treatment with salmeterol (1 min 36 s, 58% increase above placebo; $P < 0.05$) using a CWR cycle exercise test. This improvement in endurance time correlated with increases in IC, both at rest and during exercise, supporting the notion that hyperinflation has a major impact on exercise tolerance. However, a statistically significant difference from placebo was not observed in a later, larger CWR cycle exercise test trial following 8-week treatment with salmeterol.⁷⁵ Perception of dyspnea during exercise with salmeterol did not differ from placebo in either of these studies. A significant change in endurance time compared with placebo was also not seen following 2 weeks of treatment with salmeterol in a study using a CWR treadmill exercise test,⁷⁴ though perception of dyspnea during exercise was reduced with salmeterol.

Long-acting anticholinergic: tiotropium

The once-daily anticholinergic, tiotropium, was first introduced for COPD in Europe in 2002 and has become one of the most prescribed maintenance treatments. Seven exercise studies with tiotropium have been published since 1999 and were not included in the previous systematic review (Table 3).^{18,78–83} As with other types of bronchodilators,^{13,73} tiotropium has shown reductions in parameters of hyperinflation, and improvements in exercise endurance time correlated with IC.^{18,78,84}

As observed with other bronchodilators, use of the 6MWD to investigate changes in exercise endurance with tiotropium has had limited success.^{81,83} A significant increase in the 6MWD ($P < 0.05$) was observed by Okudan et al⁸¹ following administration of a single dose of tiotropium compared with placebo, but this was below the MCID proposed by Puhan and colleagues and perception of dyspnea during exercise was not changed.²⁸ However, no significant differences were observed in 6MWD or perception of dyspnea following 4-week treatment with tiotropium compared with placebo in a study that continued to investigate pulmonary rehabilitation. Compared with placebo, tiotropium significantly increased

the mean distance walked during the SWT by 36 m (11.8% increase; $P < 0.05$) after 12 weeks of treatment in the study by Verkindre et al.⁸⁰ However, this too is below the MCID and perception of dyspnea was not different from placebo, despite a significant change in lung volumes.

Tiotropium has been reported to significantly increase CWR cycle endurance time compared with placebo by 1 min 45 s (21% increase, $P < 0.01$)¹⁸ and by 3 min 54 s (41% increase, $P < 0.001$)⁷⁸ following 6 weeks of daily administration in two independent studies. The change in endurance time in the second of these studies exceeds the MCID proposed by Puente-Maestu and colleagues²⁷ and perception of dyspnea during exercise was also significantly reduced by tiotropium in both trials. A statistically significant difference compared with placebo in CWR endurance time improvement and perception of dyspnea was not found in a smaller crossover trial by Travers et al.⁸²

Casaburi et al demonstrated that tiotropium amplified the effects of pulmonary rehabilitation on CWR treadmill endurance,⁷⁹ which has also been associated with an increase in self-reported participation in physical activity.⁸⁵ Although 4-week treatment with tiotropium did not significantly increase endurance time alone compared with placebo (a difference of 1 min 39 s; 15.6% increase), tiotropium significantly improved CWR treadmill endurance times compared with placebo following an 8-week pulmonary rehabilitation programme such that the difference between the groups was 6 min 36 s (41.9% increase). In contrast, Ambrosino et al⁸³ reported no improvement in 6MWD following the addition of tiotropium to pulmonary rehabilitation for 8 weeks, although significant improvements in dyspnea were observed compared with placebo ($P < 0.01$). These seemingly contradictory results may be reflective of the difference in sensitivity of the exercise tests used in these trials.

Comparative studies (Table 3)

Five studies^{46,52–55} directly evaluated the effects of different classes of bronchodilators (Table 3). Oga et al⁴⁶ compared the effects of the short-acting β_2 -agonist salbutamol with the short-acting anticholinergic ipratropium on exercise capacity using a CWR cycle ergometry test. Improvement in FEV₁ was significantly greater with salbutamol compared with ipratropium, but the magnitudes of improvement in the CWR cycle ergometry test were similar with both treatments. Four studies^{52–55} compared the short-acting anticholinergic ipratropium with the long-acting β_2 -agonists salmeterol⁵² or formoterol.^{53–55} No significant treatment differences between ipratropium and formoterol were observed in either the PCE

Table 3 Comparison of different classes of bronchodilators on exercise capacity

Study	Dose of drugs	Study design	N	Baseline FEV ₁ (% pred.)	Change in resting lung volumes	Change in exercise dyspnea (Borg score)	Changes in exercise performance			
							Walking	CWR cycling	Progressive cycling	
Oga et al ¹⁶	80 µg ipratropium vs 400 µg salbutamol	Single-dose, crossover	67	44.2%	FEV ₁ P < 0.003 in favor of salbutamol FVC P < 0.001 in favor of salbutamol	NS (P = 0.23)	–	–	CWR: NS (P = 0.71)	–
Comparison of short- and long-acting bronchodilators										
Akkoca et al ¹⁵	40 µg qid ipratropium vs formoterol	2 weeks, crossover	10	69%	NS	–	–	–	–	PCE: NS
Liesker et al ¹³	80 µg ipratropium tid vs. formoterol 4.5 µg bid, 9 µg bid, 18 µg bid	1 week, crossover	–	55.6%	NS	NS	–	–	–	PCE: Significant increase in TTE (23 s) in favor of ipratropium compared with 18 µg formoterol (but not 4.5 and 9 µg formoterol)
Wadbo et al ¹⁴	80 µg tid ipratropium vs 18 µg bid formoterol	12 weeks, parallel	183	33.6%	FEV ₁ P < 0.05 at Wk 4 in favor of formoterol vs ipratropium (treatment differences NS at study end) FVC NS	NS	–	SWT: NS	–	–
Renard et al ¹²	36 µg qid ipratropium vs 42 µg bid salmeterol	12 weeks, parallel	405	–	NS	NS	–	6MWD: NS	–	–

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PCE, progressive cycle ergometry; CWR, constant work rate; 6MWD, 6 minute walk distance; SWT, shuttle walk test; TTE, Time to exhaustion (for PCE); NS, not significant.

test performed by Akkoca et al⁵⁵ or the SWT performed by Wadbo et al.⁵⁴ A significant difference in favor of ipratropium compared with 18 µg formoterol was found in time to exhaustion in the PCE test performed by Liesker et al⁵³; however, no significant treatment difference was found between ipratropium and 4.5 µg or 9 µg formoterol. In the comparison between ipratropium and salmeterol by Oga et al,⁴⁶ no significant difference between the two treatments was observed in terms of lung function, dyspnea or 6MWD.

As of yet, there are no published studies that have compared the effects on exercise capacity of long-acting β_2 -agonists with the long-acting anticholinergic tiotropium.

Conclusions

Evidence for the efficacy of bronchodilators in enhancing the exercise capacity of patients with COPD is often contradictory. Some of the inconsistency may be explained by differences in the mode and duration of action of bronchodilators; however, considerable variations may be due to inherent differences in study design or patients studied. In particular, the method of assessing exercise tolerance is a matter for considerable discussion and requires further investigation before we can fully appreciate which bronchodilators consistently improve exercise endurance. However, some general points can be made from systematic review of the literature.

Short-acting bronchodilators may be an appropriate choice for additional bronchodilation when required, but are not suitable for use on a day-to-day basis to provide sustained bronchodilation and improve HRQoL. Important factors that contribute to HRQoL are enhanced symptom control and increased exercise capacity. For short-acting bronchodilators, the data suggest that their effects on exercise capacity are limited.

Longer-acting bronchodilators play an important role in the long-term management of patients with COPD, improving airflow limitation, reducing dyspnea linked to moderate exercise intensities, reducing exacerbation frequency, and improving HRQoL. Whether this generally leads to an increase in daily physical activities is currently unclear. Factors other than drug therapy alone are undoubtedly important in obtaining significantly improved exercise tolerance from bronchodilators.

The improvements in exercise tolerance and dyspnea observed under clinical trial conditions with some bronchodilators may impact on the everyday circumstances of COPD patients, reversing the vicious circle of chronic inactivity and muscle deconditioning, and leading to sustained improvements in HRQoL.

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