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 dypsnea 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 β₂-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. In developed countries, COPD is already a leading cause of death (ranked fourth in the US) and its prevalence is predicted to increase. In addition, the number of smokers is rising in many countries (notably among women), leading to an escalating prevalence of COPD.

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, 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
is frequently, but not exclusively, due to dyspnea; 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.

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. In a systematic review on the effects of bronchodilators on exercise capacity, Liesker et al 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 β₂-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 (FEV₁) is important for the diagnosis and monitoring of COPD, but clinically relevant improvements in symptoms can occur in the absence of significant changes in FEV₁, and vice versa.

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 changes in dyspnea and exercise tolerance than changes in FEV₁. Hence, air trapping resulting from EFL, rather than EFL per se, may be the significant contributor to dyspnea and exercise limitation in COPD.

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.

Further support for this hypothesis is provided by the fact that improvements in dynamic air trapping correlate highly with reductions in dyspnea.

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.\textsuperscript{16,19} Dyspnea dictates the level of activity undertaken and may discourage some patients from participating in physical activities.\textsuperscript{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.\textsuperscript{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 limitation\textsuperscript{23}; 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.\textsuperscript{24} A limitation is that local muscle fatigue is more predominant with cycle ergometry compared with walking on a treadmill.\textsuperscript{7,12,25} A meta-analysis of clinical trials of respiratory rehabilitation in patients with COPD determined a minimum clinical important difference (MCID) of 8.3 W (95% CI, 2.8–16.5) maximum exercise capacity using incremental or progressive cycle ergometry (PCE).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{29} and an improvement of ≥54 m has been proposed as being clinically important in patients with stable COPD.\textsuperscript{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.\textsuperscript{31} 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.\textsuperscript{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.\textsuperscript{32} Even though the
incremental SWT is not an endurance test and is arguably
less relevant to paced activities of daily living, results do cor-
relate 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{34–38} These tests evaluate
daily-living activities such as climbing stairs, lifting and car-
ying, 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.

\textbf{Impact of bronchodilators on exercise tolerance}

Inhaled $\beta_2$-agonists and anticholinergics currently form the
main classes of bronchodilators used in the treatment of
COPD. Although oral theophyllines are still used, the find-
ings of clinical studies suggest that they have little or no
effect on exercise capacity.\textsuperscript{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.

\textbf{Short-acting bronchodilators (Table 1)}

\textbf{Short-acting $\beta_2$-agonists}

Several salbutamol studies were performed before 2000 and
are reviewed in detail by Liesker, 2002.\textsuperscript{11} In brief, seven
studies assessing the effect of salbutamol on exercise endurance
(using the 6MWD or 12MWD) were reviewed\textsuperscript{46–48} 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,\textsuperscript{41} but
this would achieve MCID according to the $\geq35$ m criteria
proposed by Puhan and colleagues,\textsuperscript{28} but not according to the
$\geq54$ m criteria of Redelmeier and colleagues.\textsuperscript{30}

Since 1999, the impact of the short-acting $\beta_2$-agonist,
salbutamol, has been determined in three studies: two using
cardiopulmonary exercise tests and one using upper limb
exercises (Table 1).\textsuperscript{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.\textsuperscript{49}

In the two studies using cardiopulmonary tests,\textsuperscript{46,47}
enhance was assessed by CWR cycle exercise. A significant
increase in endurance time was observed by Oga et al,\textsuperscript{5}
though this was short of being clinically significant accord-
ing to the criteria of Puente-Maestu and colleagues. Aliverti
et al\textsuperscript{17} 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,\textsuperscript{28}
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\textsuperscript{30,31} have evaluated the impact
of procaterol on exercise performance. Shioya et al\textsuperscript{30} dem-
onstrated clinically significant improvements in walking
distance using the 6MWD ($42$ m, $P < 0.05$) together with
significant improvements in dyspnea and FEV\textsubscript{1}. In the
study by Sukisaki and colleagues,\textsuperscript{31} statistically significant
improvements in the incremental SWT ($37$ m, $P < 0.001$)
were reported, despite no significant improvements in FEV\textsubscript{1},
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<sub>1</sub> (% pred.) | Change in resting lung volume | Change in exercise dyspnea (Borg score) | Changes in exercise performance |
|---------------|---------------------|---------------------------|-----|-----------------------------------|-------------------------------|----------------------------------------|---------------------------------|
|               |                     |                           |     |                                   |                              |                                        | Walking                         |
|               |                     |                           |     |                                   |                              |                                        | CWR cycling                     |
|               |                     |                           |     |                                   |                              |                                        | Progressive cycling             |
|               |                     |                           |     |                                   |                              |                                        | Other                           |
| **Short-acting β<sub>2</sub>-agonists** |                     |                           |     |                                   |                              |                                        |                                 |
| **Salmeterol** |                     |                           |     |                                   |                              |                                        |                                 |
| Porto et al<sup>16</sup>  | 400 µg               | Single-dose, randomized   | 16  | 41%                               | Δ IC P = 0.001<sup>1</sup>    | –                                 | –                               |
| Aliverti et al<sup>27</sup> | 5 mg nebulized      | Single-dose, crossover    | 18  | 40.6%                             | Δ FEV<sub>1</sub> P < 0.001<sup>1</sup> | NS<sup>1</sup>                  | NS<sup>1</sup>                  |
| Oga et al<sup>36</sup>  | 400 µg               | Single-dose, crossover    | 67  | 44.2%                             | Δ FEV<sub>1</sub> P < 0.001<sup>1</sup> | P < 0.001<sup>1</sup>            | –                               |
| **Procateryl**    |                     |                           |     |                                   |                              |                                        |                                 |
| Shioya et al<sup>35</sup> | 20 µg qid           | 52-week, randomized      | 20  | 48.1%                             | Δ FEV<sub>1</sub> P < 0.05<sup>b</sup> | 6MWD: Δ 42 m (+10%) P < 0.05<sup>b</sup> | –                               |
| Sukisaki et al<sup>31</sup> | 20 µg               | Single-dose, crossover    | 19  | 38.5%                             | Δ FEV<sub>1</sub> NS<sup>1</sup> | SWT: Δ 37 m (P = 0.01<sup>`</sup>) | –                               |
| **Short-acting anticholinergics** |                     |                           |     |                                   |                              |                                        |                                 |
| **Ipratropium**  |                     |                           |     |                                   |                              |                                        |                                 |
| O’Donnell et al<sup>37</sup> | 500 µg nebulized    | Single-dose, crossover    | 16  | 90%                               | Δ FEV<sub>1</sub> P < 0.05<sup>`</sup> | NS<sup>1</sup>                  | –                               |
| Pepin et al<sup>36</sup> | 500 µg nebulized    | Single-dose, crossover    | 14  | 50%                               | Δ FEV<sub>1</sub> P < 0.001<sup>`</sup> | –                               | SWT: Δ 144 m (P = 0.03) 6MWD: NS |
| Pepin et al<sup>7</sup>  | 500 µg nebulized    | Single-dose, crossover    | 17  | 56%                               | Walk and Cycle: Δ FEV<sub>1</sub> P < 0.001<sup>`</sup> | NS                              | SWT: Δ endurance time 2 mins 44 s (P < 0.01<sup>`</sup>) | NS<sup>`</sup> |
| Akkoca et al<sup>35</sup> | 40 µg qid           | 2 week, crossover         | 10  | 69%                               | Δ FEV<sub>1</sub> NS<sup>`</sup> | –                               | –                               |

(Continued)
| Study          | Dose of study drug | Study design   | N  | Baseline FEV\textsubscript{1} (% pred.) | Change in resting lung volume | Change in exercise dyspnea (Borg score) | Changes in exercise performance |
|---------------|-------------------|---------------|----|---------------------------------------|-------------------------------|----------------------------------------|----------------------------------|
|               |                   |               |    |                                       |                               |                                        | Walking                          |
| Saey et al\textsuperscript{12}  | 500 µg nebulized  | Single-dose   | 18 | 38%                                   | ∆ FEV\textsubscript{1}, P < 0.05\textsuperscript{a} | -                                      | ∆ endurance time                  |
|               |                   |               |    |                                       | ∆ IC, P < 0.001\textsuperscript{a} | ∆ FRC, P < 0.01\textsuperscript{a} | 1 min 58 s (+37%)                   |
|               |                   |               |    |                                       | ∆ RV, P < 0.001 \textsuperscript{a} | ∆ FEV\textsubscript{1}, P < 0.01\textsuperscript{a} | 62 s (+37%)                      |
| Oga et al\textsuperscript{16}   | 80 µg             | Single-dose, crossover | 67 | 44.2%                                | ∆ FEV\textsubscript{1}, P < 0.001\textsuperscript{a} | P < 0.001\textsuperscript{a} | -                                 |
|               |                   |               |    |                                       | ∆ FVC, P < 0.001\textsuperscript{a} | ∆ FEV\textsubscript{1}, P < 0.001\textsuperscript{a} | ∆ endurance time                  |
| Liesker et al\textsuperscript{12} | 80 µg tid        | 1 week, crossover | 34 | 55.6%                                | ∆ FEV\textsubscript{1}, P < 0.0001\textsuperscript{a} | -                                      | ∆ endurance time                  |
|               |                   |               |    |                                       | ∆ IC, P < 0.0001\textsuperscript{a} | ∆ FRC, P < 0.01\textsuperscript{a} | 46 s (+14%)                       |
|               |                   |               |    |                                       | ∆ FVC, P < 0.01\textsuperscript{a} | ∆ RV, P < 0.001\textsuperscript{a} | P < 0.0001\textsuperscript{a}     |
| Wadbo et al\textsuperscript{54}  | 80 µg tid         | 12 weeks, parallel | 183 | 33.6%                                | ∆ FEV\textsubscript{1}, P < 0.05\textsuperscript{a} | -                                      | SWT: NS\textsuperscript{a}       |
|               |                   |               |    |                                       | ∆ FVC, P < 0.05\textsuperscript{a} | ∆ FEV\textsubscript{1}, P < 0.05\textsuperscript{a} | -                                 |
| Rennard et al\textsuperscript{52} | 36 µg qid        | 12 weeks, parallel | 405 | -                                    | ∆ FEV\textsubscript{1}, P < 0.05\textsuperscript{a} | -                                      | 6MWD: NS\textsuperscript{a}      |
|               |                   |               |    |                                       | ∆ FVC, P < 0.05\textsuperscript{a} | ∆ FEV\textsubscript{1}, P < 0.05\textsuperscript{a} | -                                 |
| Oxitropium    |                   |               |    |                                       | ∆ FEV\textsubscript{1}, P < 0.0001\textsuperscript{b} | -                                      | -                                 |
| Shioya et al\textsuperscript{50} | 200 µg qid       | 52-week, randomized | 20 | 49.4%                                | ∆ FEV\textsubscript{1}, NS\textsuperscript{b} | -                                      | 6MWD: NS\textsuperscript{b}      |
|               |                   |               |    |                                       | ∆ FVC, NS\textsuperscript{b} | ∆ FEV\textsubscript{1}, NS\textsuperscript{b} | -                                 |
| Oga et al\textsuperscript{58}  | 400 µg            | Single-dose, crossover | 38 | 40.8%                                | ∆ FEV\textsubscript{1}, P < 0.001\textsuperscript{b} | -                                      | ∆ endurance time                  |
|               |                   |               |    |                                       | ∆ FVC, P < 0.01\textsuperscript{b} | ∆ FEV\textsubscript{1}, P < 0.001\textsuperscript{b} | 34 s (+18%)                       |
|               |                   |               |    |                                       | (PCE test only) | ∆ FEV\textsubscript{1}, P < 0.001\textsuperscript{b} | P < 0.01\textsuperscript{b}     |

\textsuperscript{a}Active drug versus placebo; \textsuperscript{b}Active drug versus baseline.

Abbreviations: FEV\textsubscript{1}, forced expiratory volume in 1 second; FRC, forced residual capacity; IC, inspiratory 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.
| 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 | Progressive cycling |
| **Long-acting \(\beta_2\)-agonists** |              |                           |    |                              |                             |                            |                               |
| Salmeterol            | 50 µg        | Single dose, 5-visit      | 20 | 52%                          | \(\Delta FEV_1, P < 0.001\) | \(\Delta Borg score 5.6, P = 0.006\) | SWT: \(\Delta 160\) m P = 0.02 \(\Delta\) endurance time 1 min 57 s P = 0.02 |              |              |              |
| Brouillard et al \(^{17}\) | 50 µg bid    | 12-month, parallel       | 426| 46.1%                       | \(\Delta FEV_1, P < 0.001\) | \(\Delta Borg score 5.6, P = 0.006\) | SWT: \(\Delta 30\) m P = 0.04 |              |              |              |
| Stockley et al \(^{76}\) | 50 µg bid    | 8-week, parallel         | 123| 39.5%                       | \(\Delta FEV_1, P < 0.05\) | \(\Delta Borg score 0.84, P = 0.02\) | NS \(^b\) |              |              |              |
| O’Donnell et al \(^{75}\) | 50 µg bid    | 2-week, crossover       | 16 | 31.1%                       | \(\Delta FEV_1, NS\) | \(\Delta Borg score 0.84, P = 0.02\) | Treadmill endurance test: NS \(^b\) |              |              |              |
| Man et al \(^{74}\)   | 50 µg bid    | 2-week, crossover       | 42 | 42%                         | \(\Delta FEV_1, P < 0.05\) | \(\Delta Borg score 0.84, P = 0.02\) | NS \(^b\) |              |              |              |
| O’Donnell et al \(^{72}\) | 50 µg bid    | 12-week, parallel       | 405| 33%                         | \(\Delta FEV_1, P < 0.05\) | \(\Delta Borg score 0.84, P = 0.02\) | 6MWD: NS \(^b\) |              |              |              |
| Gupta et al \(^{72}\) | 42 µg bid    | 8-week, parallel         | 405| 33%                         | \(\Delta FEV_1, P < 0.05\) | \(\Delta Borg score 0.84, P = 0.02\) | 6MWD: NS \(^b\) |              |              |              |
| Weiner et al \(^{71}\) | 50 µg bid    | 18-week, parallel       | 23 | 33%                         | \(\Delta FEV_1, NS\) | \(\Delta Borg score 0.84, P = 0.02\) | 6MWD: NS \(^b\) |              |              |              |
|                       | 50 µg bid    | 18-week, parallel       | 17 | 35%                         | \(\Delta FEV_1, NS\) | \(\Delta Borg score 0.84, P = 0.02\) | 6MWD: NS \(^b\) |              |              |              |
Table 2 (Continued)

| Study          | Dose of drug | Study design      | N  | Baseline FEV<sub>1</sub> (% pred.) | Change in resting lung volume | Change in exercise dyspnea | Changes in exercise performance |
|----------------|--------------|-------------------|----|-----------------------------------|-----------------------------|----------------------------|--------------------------------|
|                |              |                   |    |                                   |                             | Borg score                 | Walking | CWR | Progressive cycling |
|                |              |                   |    |                                   |                             | CRQ or TDI/BDI score       |                      |     |                 |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
| **Formoterol** |              |                   |    |                                   |                             |                            |                      |     |                 |
| Cazzola et al<sup>20</sup> | 12 µg bid | 5-day crossover | 22 | 14%–56%                          | Δ FEV<sub>1</sub>, P < 0.05<sup>a</sup> | Δ IC, P < 0.05<sup>a</sup> | Δ Borg score: P < 0.01<sup>b</sup> | 6MWD: Δ 50 m (±20%), P < 0.05<sup>b</sup> |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
| Neder et al<sup>26</sup> | 12 µg bid | 2-week, crossover | 21 | 38.8%                            | Δ IC, P < 0.05<sup>a</sup> | Δ EELV, P < 0.05<sup>a</sup> | Δ RV, P < 0.05<sup>a</sup> | NS<sup>a</sup> | 6MWD: Δ 53.6 m, P = 0.006<sup>b</sup> 12MWD: Δ 59.9 m, P = 0.018<sup>b</sup> |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
| Akkoca et al<sup>35</sup> | 12 µg bid | 2 week, crossover | 10 | 69%                              | Δ FEV, NS                  | Δ FVC, NS                  | Δ FEV/FVC, P < 0.05<sup>a</sup> | NS<sup>a</sup> | 6MWD: Δ 53.6 m, P = 0.006<sup>b</sup> 12MWD: Δ 59.9 m, P = 0.018<sup>b</sup> |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
| Wadbo et al<sup>44</sup> | 18 µg bid | 12-week, parallel | 183 | 33.3%                            | Δ FEV<sub>1</sub>, P < 0.05<sup>a</sup> | Δ FVC, P < 0.05<sup>a</sup> | NS                    | 6MWD: Δ TET 45 s, P < 0.05<sup>b</sup> |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
| Aalbers et al<sup>48</sup> | 4.5 µg bid | 12-week, parallel | Total 692 | 54%                             | Δ FEV<sub>1</sub>, P < 0.01<sup>a</sup> | Δ FRC, P < 0.05<sup>a</sup> | Δ FVC, P < 0.05<sup>a</sup> | NS<sup>a</sup> | SWT: NS |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
| Liesker et al<sup>34</sup> | 4.5 µg bid | 1-week, crossover | 34 | –                                 | Δ FEV<sub>1</sub>, P < 0.05<sup>a</sup> | Δ FRC, P < 0.05<sup>a</sup> | Δ FVC, P < 0.05<sup>a</sup> | NS<sup>a</sup> | SWT: NS |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |
|                |              |                   |    |                                   |                             |                            |                      |     |                 |

Notes:
- Δ: Change
- NS: Not Significant
- SWT: Six-Minute Walk Test
- 6MWD: Six-Minute Walk Distance
- 12MWD: Twelve-Minute Walk Distance
- Borg score: Borg Dyspnea Score
- CRQ or TDI/BDI score: Chronic Respiratory Questionnaire or Tampa dyspnea inventory/Bellevue dyspnea inventory
- FEV<sub>1</sub>: Forced Expiratory Volume in One Second
- IC: Inspiratory Capacity
- EELV: End Expiratory Lung Volume
- RV: Residual Volume
- FVC: Forced Vital Capacity
- TLC: Total Lung Capacity
- FRC: Functional Residual Capacity
- RV: Residual Volume
- IC: Inspiratory Capacity
- FEV<sub>1</sub>/FVC: Ratio of Forced Expiratory Volume in One Second to Forced Vital Capacity
- FEV<sub>1</sub>/RVC: Ratio of Forced Expiratory Volume in One Second to Residual Volume
- IC/VC: Ratio of Inspiratory Capacity to Vital Capacity
- FEV<sub>1</sub>/FEV<sub>1</sub>: Ratio of Forced Expiratory Volume in One Second to Forced Expiratory Volume in One Second
- Δ: Change
- P: Probability

*Significant at P < 0.05

**Significant at P < 0.01
18 µg bid 34 – \( \Delta \text{FEV}, P < 0.05^a \) \( \Delta \text{FRC} P < 0.05^a \) \( \Delta \text{FVC} NS^a \) \( \Delta \text{IC} P < 0.05^a \) \( \Delta \text{RV} P < 0.05^a \) NS – – – \( \Delta \text{s} P < 0.05^a \)

### Long-acting Anticholinergics

**Tiotropium**

| Study Authors | Dose | Duration | N | FEV\(_1\) % | \( \Delta \text{FEV}, P \leq 0.05 \) | \( \Delta \text{FVC} P \leq 0.05 \) | \( \Delta \text{IC} P \leq 0.05 \) | \( \Delta \text{RV} P \leq 0.05 \) | Time to exhaustion (for PCE) | NS | PR |
|--------------|------|----------|---|-------------|----------------------|----------------------|----------------------|----------------------|----------------------|-----|-----|
| Ambrosino et al\(^{36}\) | 18 µg qd | 4-week, parallel | 117 | 42.5% | – | – | – | – | – | – | – |
| | 18 µg qd + rehabilitation | 25-week (including 8 weeks’ rehabilitation), parallel | 117 | 42.5% | \( \Delta \text{FEV}, P \leq 0.05 \) | \( \Delta \text{FVC} P \leq 0.05 \) | \( \Delta \text{IC} P \leq 0.05 \) | \( \Delta \text{RV} P \leq 0.05 \) | – | – | – |
| Travers et al\(^{37}\) | 18 µg qd | 7–10 day, crossover | 18 | 40% | \( \Delta \text{FEV}, P < 0.01^a \) | \( \Delta \text{FRC} P < 0.01^a \) | \( \Delta \text{RV} P < 0.01^a \) | – | – | – |
| Okudan et al\(^{38}\) | 18 µg qd | Single-dose, crossover | 44 | – | – | – | – | – | 6MWD: \( \Delta 14.6 \) m (+4%) \( P < 0.05^a \) | – | – |
| Verkindre et al\(^{39}\) | 18 µg qd | 12-week, parallel | 46 | 34.7% | \( \Delta \text{FVC} P < 0.05^a \) | \( \Delta \text{IC} P < 0.05^a \) | \( \Delta \text{RV} P < 0.01^a \) | – | TDI: NS\(^a\) | SWT: \( \Delta 36 \) m \( P < 0.05^a \) | – | – |
| Casaburi et al\(^{40}\) | 18 µg qd | 4-week, parallel | 55 | 34% | \( \Delta \text{FEV}, P < 0.01^a \) | \( \Delta \text{FVC} P < 0.001^a \) | – | – | TDI: NS\(^a\) | Treadmill endurance test: NS\(^a\) | – | – |
| | 18 µg qd + rehabilitation | 25-week (8 weeks’ rehabilitation) parallel | 55 | 34% | \( \Delta \text{FEV}, P < 0.01^a \) | \( \Delta \text{FVC} P < 0.001^a \) | – | – | 1.67 units \( P < 0.01^a \) | \( \Delta 6 \) min 36 s \( P < 0.05^a \) | – | – |
| Maltais et al\(^{41}\) | 18 µg qd | 6-week, parallel | 131 | 43.1% | \( \Delta \text{FEV}, P < 0.001^a \) | \( \Delta \text{FVC} P < 0.001^a \) | \( \Delta \text{IC} P < 0.001^a \) | \( \Delta \text{RV} P < 0.001^a \) | \( \Delta \text{TLC} P < 0.01^a \) | – | – | \( \Delta 3 \) min 54 s (+41%) \( P < 0.001^a \) |
| | 18 µg qd | 6-week, parallel | 96 | 42% | \( \Delta \text{FEV}, P < 0.001^a \) | \( \Delta \text{FVC} P < 0.0001^a \) | \( \Delta \text{IC} P < 0.05^a \) | \( \Delta \text{RV} P < 0.001^a \) | \( \Delta \text{TLC} P < 0.01^a \) | – | – | \( \Delta 1 \) min 45 s (+21%) \( P < 0.01^a \) |

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\( ^a \) Active drug versus placebo; \( ^b \) Active drug versus baseline.

**Abbreviations**: EELV, end-expiratory lung volume; FEV\(_1\), 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). In general, they are recommended for the management of mild COPD and as required in symptomatic patients. 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. In many of the studies using 6MWD, including those reviewed by Liesker et al, the significant results did not reach the MCID proposed by Puhan and colleagues. MCID responses have been reported with the SWT and CWR cycling, 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, only Liesker et al and Akkoca et al found a significant improvement in exercise performance. Ipratropium significantly increased time to exhaustion in the incremental cycle exercise used by Liesker et al and Akkoca et al, though the latter small study was not statistically significant with respect to change in work rate.

Two studies examining the effect of oxtitropium on exercise performance have been published since 1999. Oga et al 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 \( \mu \)g oxtitropium. However, in the study by Shioya et al, 6MWD in patients receiving 600 \( \mu \)g oxtitropium was not shown to differ significantly from baseline after 12, 24 or 52 weeks of treatment. A total of six oxtitropium studies were included in the review of Liesker et al, and in five of these studies a statistically significant improvement in exercise performance was observed, though these did not achieve a definite MCID.

In two single-dose studies 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 al who reported an improvement in 6MWD of 21 m (+6%, \( P < 0.05 \)) compared with placebo. In comparison, Peters et al 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 \( \beta_2 \)-agonists

The effects of two long-acting \( \beta_2 \)-agonists on exercise capacity have been evaluated: formoterol and salmeterol (Table 2).

In a study by Cazzola et al, 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, formoterol treatment resulted in no significant improvement in the performance of the incremental SWT compared with placebo.

Using PCE to symptom limitation, Liesker et al 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 al 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 al).

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. 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. One study 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. 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
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 Verkendre et al.\(^8^0\) 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, \( P < 0.01 \))\(^9^8\) and by 3 min 54 s (41% increase, \( P < 0.001 \))\(^8^7\) 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 colleagues\(^7^7\) 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.\(^5^2\)

Casaburi et al demonstrated that tiotropium amplified the effects of pulmonary rehabilitation on CWR treadmill endurance,\(^7^9\) which has also been associated with an increase in self-reported participation in physical activity.\(^6^5\) 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 al\(^6^3\) 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.

**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).\(^1^8,7^8–8^3\) As with other types of bronchodilators,\(^1^3,7^3\) tiotropium has shown reductions in parameters of hyperinflation, and improvements in exercise endurance time correlated with IC.\(^1^8,7^8,8^4\)

As observed with other bronchodilators, use of the 6MWD to investigate changes in exercise endurance with tiotropium has had limited success.\(^8^1,8^5\) A significant increase in the 6MWD (\( P < 0.05 \)) was observed by Okudan et al\(^4^1\) 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.\(^2^8\) 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 Verkendre et al.\(^8^0\) 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, \( P < 0.01 \))\(^9^8\) and by 3 min 54 s (41% increase, \( P < 0.001 \))\(^8^7\) 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 colleagues\(^7^7\) 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.\(^5^2\)

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**Comparative studies (Table 3)**

Five studies\(^5^6,5^2–5^5\) directly evaluated the effects of different classes of bronchodilators (Table 3). Oga et al\(^5^6\) compared the effects of the short-acting \( \beta_2 \)-agonist salbutamol with the short-acting anticholinergic ipratropium on exercise capacity using a CWR cycle ergometry test. Improvement in FEV\(_1\) 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\(^5^2–5^5\) compared the short-acting anticholinergic ipratropium with the long-acting \( \beta_2 \)-agonists salmeterol\(^5^2\) or formoterol.\(^5^3–5^5\) 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 FEV₁ (% pred.) | Change in resting lung volumes | Change in exercise dyspnea (Borg score) | Changes in exercise performance |
|----------------------|----------------------------------------|--------------|----|-------------------------|--------------------------------|----------------------------------------|----------------------------------|
| Oga et al⁵⁶          | 80 µg ipratropium vs 400 µg salbutamol | Single-dose, crossover | 67 | 44.2%                   | FEV₁, P < 0.003 in favor of salbutamol | NS (P = 0.23)                        | CWR: NS (P = 0.71)               |
|                      |                                        |              |    |                         | FVC P < 0.001 in favor of salbutamol |                                |                                    |
|                      | Comparision of short- and long-acting bronchodilators |          |    |                         |                                |                                |                                    |
| Akkoca et al⁵⁵       | 40 µg qid ipratropium vs formoterol 12 µg bid | 2 weeks, crossover | 10 | 69%                     | NS                            | –                                      | –                                 |
| Liesker et al¹³      | 80 µg ipratropium tid vs formoterol 4.5 µg bid, 9 µg bid, 18 µg bid | 1 week, crossover | –  | 55.6%                   | NS                            | NS                                    | –                                 |
| Wadbo et al⁵⁴        | 80 µg tid ipratropium vs 18 µg bid formoterol | 12 weeks, parallel | 183 | 33.6%                   | FEV₁, P < 0.05 at Wk 4 in favor of formoterol vs ipratropium (treatment differences NS at study end) | NS                                    | SWT: NS                          |
|                      |                                        |              |    |                         | FVC NS                        |                                        | 6MWD: NS                         |
| Rennard et al⁵²       | 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 al.58 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 al; 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., 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 β2-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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