Optimizing pulmonary rehabilitation in chronic obstructive pulmonary disease – practical issues: A Canadian Thoracic Society Clinical Practice Guideline

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The Canadian Thoracic Society COPD Committee Expert Working Group

Pulmonary rehabilitation (PR) participation is the standard of care for patients with chronic obstructive pulmonary disease (COPD) who remain symptomatic despite bronchodilator therapies. However, there are questions about specific aspects of PR programming including optimal site of rehabilitation delivery, components of rehabilitation programming, duration of rehabilitation, target populations and timing of rehabilitation. The present document was compiled to specifically address these important clinical issues, using an evidence-based, systematic review process led by a representative interprofessional panel of experts.

The evidence reveals there are no differences in major patient-related outcomes of PR between non-hospital- (community or home) sites or hospital-based sites. There is strong support to recommend that COPD patients initiate PR within one month following an acute exacerbation due to benefits of improved dyspnea, exercise tolerance and health-related quality of life relative to usual care. Moreover, the benefits of PR are evident in both men and women, and in patients with moderate, severe and very severe COPD. The current review also suggests that longer PR programs, beyond six to eight weeks duration, be provided for COPD patients, and that while aerobic training is the foundation of PR, endurance and functional ability may be further improved with both aerobic and resistance training.

Key Words: COPD; Chronic obstructive pulmonary disease; Management; Pulmonary rehabilitation

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder largely caused by smoking, and is characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations (1,2). Effective management of COPD includes both pharmacological and nonpharmacological therapies, which leads to improvement in meaningful patient-centred outcomes. Pulmonary rehabilitation (PR) is now the standard of care for individuals with COPD who remain symptomatic despite bronchodilator therapies (1,3). In addition to the significant benefits realized by the patient, it has recently become clear that PR also reduces health care resource use (4).

Despite recent evidence-based guidelines (3,5), practical clinical questions regarding many specific aspects of PR programming remain, including optimal site of rehabilitation delivery, components of rehabilitation programming, duration...
of rehabilitation, target populations and timing of rehabilitation. The present document was designed to specifically address these important clinical issues using an evidence-based, systematic review process led by a representative interprofessional panel of experts in the field.

TARGET POPULATION
The present clinical practice guideline applies to adult patients diagnosed with COPD.

TARGET USERS
The current document is intended for those involved in the coordination, design, delivery and evaluation of PR programs. They include university- and community-based respirologists, physiotherapists, exercise therapists, nurses, respiratory therapists, exercise physiologists, occupational therapists and health care administrators.

METHODOLOGY
Guideline development process
The Canadian Thoracic Society (CTS) Optimizing Pulmonary Rehabilitation in COPD Clinical Practice Guideline document was developed by an Expert Working Group panel of representative professionals involved in the coordination, design, delivery and evaluation of PR. The guideline was developed in accordance with the convention of the 23-item Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument (6) – the current gold standard in appraising the reporting of clinical practice guidelines. The process was coordinated by the CTS Respiratory Guideline Committee and staff, with the assistance of a consultant librarian and methodology experts. The research questions are based on the Working Group’s recognition of clinical care gaps and solicited needs of the target populations. Questions were constructed in accordance with the ‘PICO’ process, taking into consideration the Problem, Intervention, Comparison and Outcomes within each question, thus ensuring that an appropriate and answerable question was constructed. This process also enabled the development of a search strategy that outlined the types of studies, main topics and terms, inclusion and exclusion criteria considered in the search, as well as suitable databases for the search.

Literature search
Based on the criteria outlined within the search strategy for each of the research questions, various databases (MEDLINE, EMBASE, the Cochrane Library, the Canadian Medical Association InfoBase and the National Guideline Clearinghouse) were searched for pertinent literature published between 1990 and April 2009. In addition, supplementary references from articles and reviews identified by the Expert Working Group members were also scanned for additional citations.

Study selection criteria
Articles were selected for inclusion in the systematic review of the evidence if they reported data on the role of PR among adult individuals with COPD. Studies were required to report data on at least one of the following outcomes of interest: activity, exacerbations, health care use, quality of life or health status, and cost benefit or use.

Evidence synthesis
An initial review of abstracts informed the selection of full-text articles, with a minimum of two Working Group members assigned to each question. Data extraction tables were used to systematically extract evidence from included full-text articles, based on the predetermined inclusion and exclusion criteria supporting the research question. These tables were used to summarize and organize information such as study design, target population, interventions, outcomes, functional and clinical significance of findings, and for formulation of recommendations and supporting narrative text. Rejected full-text articles were also listed with reasons for their exclusion. Data extraction tables are available as online supplemental material (www.respiratoryguidelines.ca or www.pulsus.com). Narrative text of the key evidence and conclusions supporting the recommendations were completed before formulation of the recommendations.

Critical appraisal
The strengths and weaknesses of the evidence, along with the potential harms and benefits related to PR programs, were carefully considered in the generation of the recommendations. Although the majority of the evidence on this topic is comprised of small randomized trials or nonrandomized data, strong recommendations were provided when it was agreed through consensus that the majority of practitioners would choose similar recommendations if they were responsible for the development of similar guidance. This process was further strengthened by the circulation of the draft guideline to external experts who were given an opportunity to comment and help formulate the final recommendations before formal organizational approval and peer-review publication.

Recommendations
Decision regarding the strength of recommendations (Table 1) was achieved by a consensus process whereby Working Group members assigned to each of the research questions considered the strength of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (7). In addition, adverse effects, health benefits to patients, patient burden associated with adherence to the recommendations, cost effectiveness, extent to which the evidence answered the research question, and impact on morbidity, mortality and quality of life were considered (7,8) by the Expert Working Group members. Final consensus on the recommendations by the full committee was achieved via an open voting process. Extensive discussions were used to edit, correct and update the document.

Expert commentary and review
Expert reviewers identified by the Working Group and the Canadian Respiratory Guidelines Committee on the basis of their clinical and methodological expertise were invited to review the document. A draft of the clinical practice guidelines was circulated to the reviewers, feedback was gathered and relevant changes were incorporated into the document. Reviewers also used a short AGREE II (6) appraisal form to document their appraisal and further enhance the usability of the document.

It is anticipated that the present document, including the questions and content, will be regularly reviewed and updated to reflect the changing and growing bodies of evidence in this area.
TABLE 1
Strength of evidence and grading of recommendations

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Grade A</th>
<th>Well-designed randomized controlled trials with consistent and directly applicable results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade B</td>
<td>Randomized trials with limitations including inconsistent results or major methodological weaknesses</td>
<td></td>
</tr>
<tr>
<td>Grade C</td>
<td>Observational studies, and from generalization from randomized trials in one group of patients to a different group of patients</td>
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Strength of recommendation

| Grade 1 | Strong recommendation, with desirable effects clearly outweighing undesirable effects (or vice versa) |
| Grade 2 | Weak recommendation, with desirable effects closely balanced with undesirable effects |

Adapted from references 3 and 7

RESULTS

Literature search results

Table 2 summarizes the overall literature search results comprising the evidence base to inform the role of PR in patients with COPD. Results of the literature search are reported in each of the separate sections related to the questions of interest. Key recommendations and the supporting level of evidence were developed around each section and, where possible, barriers to implementation of recommendations were identified.

SECTION I

Question
Are nonhospital-based PR programs as effective as hospital-based PR programs in COPD?

Background
It is estimated that only 1.2% of the more than 750,000 Canadians suffering from COPD have access to PR programs (9). The capacity for increasing access to these programs may be hampered by various factors including cost, accessibility and patients’ mobility limitations (10). Nonhospital-based programs presently account for only 7% of the total number of programs accessible by patients in Canada, but could be an alternative to hospital-based programs if effectiveness was assured (9,10).

Key evidence
The search strategy identified 453 citations, which were initially retrieved and reviewed for their relevance to the question. Of these citations, 423 were initially excluded, while a further 16 were excluded following more in-depth evaluation, thus, leaving 14 articles that were fully reviewed. Five articles met the criteria and were selected for data extraction and utilization, which included three randomized controlled trials, one noninferiority trial and one meta-analysis.

Strijbos et al (11) compared the effectiveness of nonhospital- and hospital-based programs on outcomes in moderate to severe COPD patients, and found no initial differences in the improvement in exercise tolerance or the reduction in dyspnea between rehabilitation sites. However, the reductions in dyspnea and improved exercise tolerance were maintained over the subsequent 18 months only in the nonhospital rehabilitation group. Elliott et al (12) compared the outcomes of three programs (group 1: three months of hospital followed by nine months of nonhospital rehabilitation; group 2: three months of hospital followed by nine months of community rehabilitation; and group 3: 12 months of community rehabilitation) and found that in patients with moderate to severe COPD, all three programs showed comparable reductions in dyspnea and improvements in health-related quality of life (HRQL). Only subjects in groups 1 and 2 increased 6 min walk test distance (6MWD), with no significant differences in the increase between these two groups. Güell et al (13) demonstrated similar improvements in 6MWD and dyspnea reduction between hospital and nonhospital rehabilitation groups in patients with severe to very severe COPD. The subjects also demonstrated similar increases in respiratory muscle and arm muscle strength. The hospital-based group increased their emotional domain on the Chronic Respiratory Questionnaire (CRQ) slightly more than the nonhospital-based group.

Maltais et al (14) reported the results of a multicentre, randomized, noninferiority trial in which 252 patients with moderate to very severe COPD were randomly assigned to either an outpatient hospital- or home-based eight-week rehabilitation program. In this study, the reductions in dyspnea were significant and not different between groups, and were maintained after 12 months. In addition, 6MWD improved only slightly in the outpatient hospital-based group; however, cycling endurance time increased significantly and similarly in both groups. These benefits were similarly maintained in both rehabilitation interventions at one year.

<table>
<thead>
<tr>
<th>Section</th>
<th>Topic</th>
<th>Publications informing recommendations for practice, n (references)</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Are nonhospital-based pulmonary rehabilitation programs as effective as hospital-based pulmonary rehabilitation programs in patients with COPD?</td>
<td>5 (11–15)</td>
</tr>
<tr>
<td>II</td>
<td>Does adding resistance training to aerobic training in pulmonary rehabilitation improve outcomes in individuals with COPD?</td>
<td>5 (17–21)</td>
</tr>
<tr>
<td>III</td>
<td>Does continuing pulmonary rehabilitation beyond the typical program length (ie, 6–8 weeks) improve outcomes in COPD patients compared with standard duration pulmonary rehabilitation?</td>
<td>6 (22–27)</td>
</tr>
<tr>
<td>IV</td>
<td>Are pulmonary rehabilitation programs as effective in patients with mild/moderate compared with patients with severe/very severe COPD?</td>
<td>5 (29–33)</td>
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<tr>
<td>V</td>
<td>Are pulmonary rehabilitation programs as effective in female compared with male COPD patients?</td>
<td>8 (24,25,36,41–45)</td>
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<tr>
<td>VI</td>
<td>Do patients who start pulmonary rehabilitation within one month of an AECOPD do better than patients who do not undergo pulmonary rehabilitation within one month of an AECOPD?</td>
<td>7 (51–57)</td>
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AE: Acute exacerbation; COPD: Chronic obstructive pulmonary disease

TABLE 2
Literature search results informing recommendations

<table>
<thead>
<tr>
<th>Section</th>
<th>Topic</th>
<th>Publications informing recommendations for practice, n (references)</th>
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Conclusions
The findings from the three randomized trials confirm that functional outcomes were similar between nonhospital- and hospital-based programs. These conclusions were corroborated by Oh and Seo (15) in a 2007 meta-analysis examining the effectiveness of PR programs. The analysis demonstrated that the pooled effect sizes for exercise tolerance from 19 studies were not different, regardless of whether rehabilitation occurred at home or in hospital.

In summary, outcomes including HRQL, exercise tolerance and reductions in dyspnea did not differ according to the site of PR. It is highly recommended that patients with COPD have access to either hospital- or nonhospital- (home or community) based PR programs.

QUESTION #1
Are nonhospital-based PR programs as effective as hospital-based PR programs in patients with COPD?

The following recommendation is based on evidence from four studies, one meta-analysis and consensus of the CTS COPD expert panel.

RECOMMENDATION #1
There are no differences in major patient-related outcomes of PR between nonhospital- (community or home sites) or hospital-based sites. It is strongly recommended that all COPD patients have access to PR programs regardless of program site. (GRADE: 1A)

SECTION II
Question
Does adding resistance training (RT) to aerobic training (AT) in PR improve outcomes in patients with COPD?

Background
More than one decade previously, an American Thoracic Society (ATS) statement noted that peripheral muscle weakness was associated with exercise limitation in patients with COPD (16). The ATS’s guidelines stated that strength training was a rational component of a PR program. More recently, the ATS/European Respiratory Society Statement on Pulmonary Rehabilitation (5) noted that individually tailored endurance training (aerobic exercise such as walking or cycling) was the cornerstone of PR. The authors also added that RT (strength training using progressive resistance techniques with free or machine weights, elastic resistance, or lifting the body against gravity to increase the ability to exert or resist a force) appears to be worthwhile because it has the potential to improve muscle mass and strength, and may cause less dyspnea than AT. The benefit of combining aerobic with resistance training (AT+RT) in healthy individuals remains controversial. This subject has not been systematically reviewed in patients with COPD.

Key evidence
A total of 527 abstracts were initially identified by the search process, of which 26 were selected for complete review. Five studies fully met the criteria and were selected for data extraction and utilization.

All exercise training programs were offered on an outpatient basis, and varied from eight to 13 weeks in duration with sessions two (17,18) or three (19-21) times per week. All AT used 20 min to 40 min of lower extremity exercise. Three studies (17,18,20) used treadmill or cycle ergometer training, while the other studies (19-21) used cycle ergometer training only. AT intensity was prescribed as a percentage of maximum workload from a graded exercise test, peak heart rate on the 6 min walk test (17) or in terms of perceived exertion (18). All RT programs included upper and lower extremity exercise and used variable resistance machines for weight training. These included universal gym apparatus (17,18,21) and equipment that used hydraulic resistance (19,20). Three studies (19-21) used a one repetition maximum, while the others (17,18) used the number of repetitions completed to prescribe and progress exercise intensity.

There were greater improvements in lower and upper extremity strength following AT+RT compared with AT alone. There was a nonsignificant tendency for greater improvements in functional tasks for the upper (reach test or arm raise: P=0.16) and lower extremities (sit to stand: P=0.10). Changes in exercise capacity were comparable for both training groups, although the change in 6MWD tended to be higher for AT+RT, and the maximum work rate for the cycle ergometer test tended to be higher for the AT group. No post-training between group differences were found for HRQL as measured by the CRQ.

This systematic review suggests that AT+RT is more effective than AT alone in improving endurance and functional ability. However, the training volume in four of the five studies was greater in the AT+RT group. The study by Ortega et al (21) demonstrated that using one-half the volume of the aerobic component and one-half the volume of the strengthening component resulted in similar improvements in endurance, dyspnea and quality of life when compared with either AT alone or strength training alone. Therefore, training volume more than or in addition to RT may be the primary stimulus for the improvements noted in the AT+RT groups. AT+RT resulted in better performance on functional tests (17,18). The superiority of AT+RT may also have been influenced by the fact that only one study specified how AT was progressed over the training period (20). Lack of progression would have limited improvements in endurance. In contrast, progression of RT occurred in all studies.

Conclusions
The evidence supports RT performed in conjunction with aerobic exercise. The benefits of exercise are specific to the metabolic and recruitment demands placed on muscle. AT is required to improve cardiovascular and muscular endurance; thus, it should not be excluded from PR programming – but serve as its foundation. Given the specificity of training, exercise must be individually tailored to maximize benefits and to minimize any possible risks to the cardiovascular and musculoskeletal systems.

QUESTION #2
Does adding RT to an AT protocol in PR improve outcomes in individuals with COPD?

The following recommendation is based on evidence from five studies and consensus of the CTS COPD expert panel.
**SECTION III**

**Question**
Does continuing PR beyond the typical program length (ie, six to eight weeks) improve outcomes in COPD patients compared with standard duration PR?

**Background**
The length of PR varies in programs across Canada (9). Studies have examined the effect of program duration as short as four weeks (22) and as long as 18 months (23). The length of the program may have important implications on accessibility and adherence to exercise (24), as well as on the effectiveness and duration of benefits.

**Key evidence**
The search strategy identified 209 citations, of which 178 were excluded after review. Of the remaining 31 articles, six studies with 707 participants met the inclusion criteria.

One large study – The Reconditioning Exercise and COPD Trial (REACT) – examined the effect of a three-month versus an 18-month supervised PR program in individuals with COPD (23,25,26). The 18-month exercise program resulted in greater improvements in self-reported disability and physical function than the three-month program (23), but provided little added benefit for cognitive function (26). Foy et al (25) reported on the above program and noted greater benefit for the longer duration program in men compared with women. However, a longer program may also negatively impact attendance. A retrospective review (24) recently reported that a longer PR program was an independent risk factor for lower attendance.

Although not directly addressing the research question, two studies (22,27) conducted by the same group of researchers compared a four-week PR program to a program of seven weeks duration, both using twice-weekly exercise. One study (27) demonstrated that the longer program resulted in a greater benefit in health status, while the other study (22) found the shorter and longer programs to be equivalent.

Studies specifically examining maintenance protocols after rehabilitation did not directly address the question and were, therefore, not included. A Cochrane review (28) on this topic is registered, but not yet complete.

**Conclusion**
The results of this review provided evidence of greater benefits of a longer program (18 months) compared with a shorter program (three months), although the results may be moderated by a number of factors including sex.

**QUESTION #3**
Does continuing PR beyond the typical program length (ie, six to eight weeks) improve outcomes in COPD patients compared with a standard duration PR?

The following recommendation is based on limited evidence from six studies and consensus of the CTS COPD expert panel.

**RECOMMENDATION #2**
AT + RT is more effective than AT alone in improving endurance and functional ability. While AT is the foundation of PR, it is recommended that both AT and RT be prescribed to COPD patients. (GRADE: 2B)

**RECOMMENDATION #3**
It is recommended that longer PR programs, beyond six to eight weeks duration, be provided for COPD patients. (GRADE: 2B)

**SECTION IV**

**Question**
Are PR programs as effective in patients with mild to moderate COPD compared with patients with severe to very severe COPD?

**Background**
The effectiveness of PR on subgroups of COPD patients (eg, mild versus severe), remains unclear for two primary reasons. First, few studies have implemented identical PR programs among various COPD subgroups and, second, many patients may not recognize early COPD or consider it disabling enough to necessitate or consider PR.

**Key evidence**
The search strategy identified 534 citations, of which 489 were excluded after review. Of the remaining 45 articles, three met the inclusion criteria and two others were identified after review of the full-text article reference lists. A total of five studies with 427 participants satisfied the inclusion criteria.

Four studies were open-label observational studies that prospectively enrolled participants with COPD into inpatient (29) or outpatient PR programs (30-32). Another study (33) randomly assigned participants to endurance training plus strength training and calisthenics (treatment arm) versus strength training and calisthenics alone (control arm), but provided data according to the severity of airflow limitation for the treatment arm only. Program length varied from two to 12 weeks, with sessions two to six times per week. Four programs combined strength training with endurance exercise (29,30,32,33), and one used endurance training alone (31). In one study (29), PR was administered following an acute exacerbation of COPD (AECOPD). The definition of disease severity varied among the studies, and a cut-off for forced expiratory volume in 1 s (FEV1) per cent predicted of either 40% or 50% predicted was used to differentiate mild to moderate from severe to very severe COPD.

All five studies demonstrated improvements in peak work rate (31-33) or 6MWD (29,30,32) independent of COPD severity. There were clinically meaningful improvements in 6MWD (34) for all participants irrespective of disease severity, although these improvements were not statistically significant in all studies. Two studies (29,32) reported improvements in Borg dyspnea and fatigue ratings among all groups studied.

Improved quality of life was reported in three studies with similar improvements in St George's Respiratory Questionnaire scores regardless of disease severity (29,32), and similar improvements in the CRQ-Dyspnea and CRQ-Fatigue scores regardless of disease severity (30). There were improvements in CRQ-Mastery scores in the severe group only, and no change in CRQ-Emotional function scores in any group. None of the studies reported the impact of rehabilitation on activity level, exacerbation rates, health care use, cost effectiveness or patient burden.

These results are similar to those of a meta-analysis (35) of PR that assessed effectiveness according to disease severity
from the patients’ Medical Research Council (MRC) dyspnea grade. Only randomized controlled trials evaluating PR versus no rehabilitation were included. There were similar improvements in 6MWD and CRQ-Dyspnea scores when studies were pooled according to disease severity.

Three studies evaluated the effect of PR according to the MRC dyspnea grade (1) at baseline. Two observational studies (36,37) found that the benefit was similar regardless of baseline MRC grade. However, a randomized controlled trial (38) that was stratified according to MRC dyspnea grade found that participants with severe dyspnea (MRC grade 5) did not benefit in exercise capacity or quality of life, whereas those with less dyspnea (MRC grade 3 or 4) showed improvements in both. Baseline FEV₁ per cent predicted was similar in both groups despite differing MRC dyspnea scores.

Conclusions
PR results in improvements in exercise capacity, dyspnea and quality of life in patients with moderate, severe and very severe COPD. Presently, there are insufficient data to make a recommendation regarding patients with mild COPD. It is uncertain whether prescribing PR to all patients regardless of disease severity is cost effective.

**QUESTION #4**
Are PR programs as effective in patients with mild to moderate COPD compared with patients with severe to very severe COPD?

The following recommendation is based on evidence from five studies and consensus of the CTS COPD expert panel.

**RECOMMENDATION #4**
It is strongly recommended that patients with moderate, severe and very severe COPD participate in PR. (GRADE: 1C)

Currently, there are insufficient data to make a recommendation regarding patients with mild COPD.

**SECTION V**

**Question**
Are PR programs as effective in female compared with male COPD patients?

**Background**
Women now contribute significantly to the prevalence and disease burden of COPD, yet a meta-analysis of PR outcomes completed by Lacasse et al (39) in 1996, found only four studies that investigated an equal number of men and women, with only 22% of the total reported population in the analysis being women. The question of whether rehabilitation programs are as effective in women compared with men has also been recently addressed in the cardiovascular setting (40).

**Key evidence**
The search strategy identified 111 citations, of which 84 were excluded after initial review. Of the remaining 27 articles, a total of eight studies with 1671 participants satisfied the inclusion criteria. One study was a randomized controlled trial, two were case-controlled trials and five were observational trials.

Two other papers were identified after review of the full-text article reference lists: one was a review article exploring women and COPD, and the other was an observational analysis of women entering PR.

Quality of life is uniformly improved with PR for both men and women. The only significant sex difference reported was that men had ongoing quality of life benefits in a maintenance PR program of 18 months compared with no further documented benefit for women beyond a program lasting three months (25). This was not due to nonadherence with the program or the magnitude of exercise training. Another study (41) examining outcomes after intensive inpatient PR showed a trend for more men to display a significant improvement in HRQL than women; however, this difference did not reach significance.

Four of six studies that objectively assessed exercise capacity using the 6MWD or 12 min walk test distance reported similar improvements for both men and women (36,42-44). One study demonstrated that men had a statistically greater improvement in 6MWD than women; however, values were not adjusted as per cent predicted and did not attain a minimal clinically important difference (41). Another study (45) found that women had a greater loss in 12 min walk distance than men following PR, which was not explained by the initial pre-PR assessment.

Symptoms of dyspnea in women were improved as much as men during and after PR. In fact, three studies (25,43,44) showed a significantly greater improvement in dyspnea scores with PR in women than in men. Furthermore, sex did not seem to predict PR attendance (24).

The interesting issue raised from this review relates to potential sex differences in disease manifestations, although this was not a primary objective of this review. One study (42) found no difference in self-reported variables, such as health status or quality of life between men and women, despite women having a higher FEV₁ per cent predicted and 6MWD per cent predicted. Another study (43) revealed that although women were younger and had less smoking exposure and better lung function, the clinical severity of COPD and mortality was similar in men and women. A cohort study comparing men with women entering a pulmonary clinic and matched for FEV₁ (response to PR was not assessed), showed women were younger and had less smoking exposure, but worse quality of life, higher dyspnea scores and more exacerbations of COPD (46).

**Conclusions**
There is limited information available regarding the impact of sex on the response to PR. Clinical studies that have compared the responses of women with that of men, or studies that have provided a subanalysis that considers sex, suggest the benefits of PR are realized by both women and men.

**QUESTION #5**
Are PR programs as effective in female compared with male COPD patients?

The following recommendation is based on evidence from eight studies and consensus of the CTS COPD expert panel.

**RECOMMENDATION #5**
The benefits of PR are realized by both women and men. It is strongly recommended that both women and men be referred for PR. (GRADE: 1C)
SECTION VI

Question
Do patients who undergo PR within one month of an AECOPD do better than patients who do not undergo PR within one month of an AECOPD?

Background
AECOPD represent a significant burden to the patient and the health care system. According to the Canadian Institute for Health Information, COPD accounts for the highest rate of hospital admissions among major chronic illnesses in Canada (47). The average cost for a 10-day admission for COPD in 2008 was $10,000 (48). Eighteen per cent of patients with AECOPD were readmitted to hospital once in the year following their exacerbation, while 14% were readmitted twice during that time frame (47). Moreover, AECOPD contributes to disease progression and are associated with a decline in quality of life and premature death (49). Because an AECOPD can be a distressing event for COPD patients, the time immediately following an AECOPD may represent an ideal opportunity for rehabilitation to facilitate lifestyle change (50); however, the effectiveness of PR immediately after AECOPD has yet to be rigorously evaluated.

Key evidence
The search strategy identified 220 citations that were initially retrieved and reviewed for relevance to the question. Sixteen articles were selected for full-text review, with four articles satisfying the inclusion criteria and their data extracted after review. Data were also extracted from an additional three articles not identified in the initial search. In total, six prospective, randomized controlled trials that enrolled 317 participants and cles not identified in the initial search. In total, six prospective, randomized controlled trials that enrolled 317 participants and satisfied the inclusion criteria and their data extracted after review. Sixteen articles were selected for full-text review, with four articles satisfying the inclusion criteria and their data extracted after review. Data were also extracted from an additional three articles not identified in the initial search. In total, six prospective, randomized controlled trials that enrolled 317 participants and studied PR within one month of an AECOPD, as well as one meta-analysis, were included.

PR consisted of AT with or without strength training. Walking was the most common aerobic exercise. Some programs began at the inpatient stage (51-54) and used daily exercise sessions. In one study (54), the majority of patients were mechanically ventilated at the beginning of PR. Outpatient interventions ranged from daily to twice per week and program duration varied greatly, from eight weeks to 18 months. All studies were single-centre trials with modest sample sizes (n=26 to n=84).

Compared with usual care, PR within one month of an AECOPD was found to improve exercise capacity (51-56), dyspnea (51-53,55) and quality of life (51,52,54-56). Four studies (52,54,55,57) examined health care use, two studies (52,55) reported reduced hospital readmission rates in the PR group when compared with usual care, while one study (56) demonstrated a trend toward reduction (P=0.06). A recent Cochrane review (58) found a significant reduction in the odds of hospital readmission (OR 0.13; 95% CI 0.04 to 0.35) and death between PR and usual care groups (OR 0.29; 95% CI 0.10 to 0.84). Two trials (51,55) explicitly examined adverse events with PR, with none noted. These results were consistent with a recent randomized controlled trial (59), which demonstrated that early mobilization of critically ill patients was well tolerated and resulted in better functional outcome compared with patients who did not exercise. Seymour et al (60) also recently found that postexacerbation PR in COPD patients significantly reduced re-exacerbation events requiring hospital attendance or admission.

Conclusions
PR initiated within one month of an AECOPD is safe and improves exercise capacity, dyspnea and HRQL compared with usual care. It appears to decrease mortality and is associated with decreased health care costs.

PR performed immediately following an AECOPD improves health outcomes compared with usual care. The long-term benefits of early postexacerbation rehabilitation versus later conventional rehabilitation of stable COPD patients have not been studied. There is no evidence that PR performed within one month following an AECOPD increases the risk of adverse events.

QUESTION #6
Do patients who undergo PR within one month of an AECOPD do better than patients who do not undergo PR within one month of an AECOPD?

RECOMMENDATION #6
It is strongly recommended that COPD patients undergo PR within one month following an AECOPD due to evidence supporting improved dyspnea, exercise tolerance and HRQL compared with usual care. (GRADE: 1B)

PR within one month following AECOPD is also recommended due to evidence supporting reduced hospital admissions and mortality compared with usual care. (GRADE: 2C)

DISCUSSION
The present clinical practice guideline addresses a number of clinically meaningful issues using an evidence-based, systematic review process led by a representative interprofessional panel of experts in the field. The evidence from the reviews, and the experience and guidance afforded by the Expert Working Group members, enabled the formulation of practical answers, direction and guidance for the various professionals involved in the coordination, design, delivery and evaluation of PR programs (Table 3).

However, the process also clearly identified many gaps in our understanding that are deserving of further study and attention. These include gaps relating to optimal maintenance programming and maintaining the benefits of rehabilitation, the intensity of exercise training, incremental benefits of various program components, the value of exercise and activity outside the PR setting, the contributions and effects of anxiety and depression or other patient-specific factors in this setting, various adjunct techniques to maximize the training afforded by PR, and barriers to participation and adherence to PR.

Access to PR and adherence to participation remain two of the most significant challenges in this field. Only a very small proportion of patients with COPD have access to PR programs (9). Acknowledging the important benefits of the intervention (3-5,61) and appreciating that PR is now the standard of care for patients who remain symptomatic despite appropriate bronchodilator therapies (1), there is an immediate urgency for these obstacles to be addressed and to be removed. It is not acceptable for health care providers, patients or health care systems to accept the current status quo – the benefits cannot be ignored.
TABLE 3
Summary of evidence-based recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Summary</th>
<th>Strength of recommendation/ quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>There are no differences in major patient-related outcomes of pulmonary rehabilitation between nonhospital- (community or home sites) or hospital-based sites. It is strongly recommended that all COPD patients have access to pulmonary rehabilitation programs regardless of program site</td>
<td>GRADE 1A</td>
</tr>
<tr>
<td>2</td>
<td>Aerobic and resistance training offered together is better than aerobic training alone in improving endurance and functional ability. While aerobic training is the foundation of pulmonary rehabilitation, it is recommended that both aerobic and resistance training be prescribed to COPD patients</td>
<td>GRADE 2B</td>
</tr>
<tr>
<td>3</td>
<td>It is recommended that longer pulmonary rehabilitation programs, beyond six to eight weeks duration, be provided for COPD patients</td>
<td>GRADE 2B</td>
</tr>
<tr>
<td>4</td>
<td>It is strongly recommended that patients with moderate, severe and very severe COPD participate in pulmonary rehabilitation</td>
<td>GRADE 1C</td>
</tr>
<tr>
<td>5</td>
<td>The benefits of pulmonary rehabilitation are realized by both women and men. It is strongly recommended that both women and men be referred for pulmonary rehabilitation</td>
<td>GRADE 1C</td>
</tr>
<tr>
<td>6</td>
<td>It is strongly recommended that COPD patients undergo pulmonary rehabilitation within one month following an AECOPD due to evidence supporting improved dyspnea, exercise tolerance and health-related quality of life compared with usual care</td>
<td>GRADE 1B</td>
</tr>
<tr>
<td></td>
<td>Pulmonary rehabilitation within one month following an AECOPD is also recommended due to evidence supporting reduced hospital admissions and mortality compared with usual care</td>
<td>GRADE 2C</td>
</tr>
</tbody>
</table>

Similarly, we must better understand issues concerning adherence to participation in PR programs. Patients and health care systems can not realize the benefits of PR with infrequent or short-lived participation. Patients must advance their attitudes and behaviours, and accept PR as an integral component of their management. However, changes in more than patient adherence are necessary for this to be successful. Barriers to participation in PR and the burdens of therapy must also be acknowledged and minimized (62). Health care professionals and health care systems involved in the care of patients must support and enable patients to participate in PR. A collective effort by health care professionals is required for patients, families and health care systems to fully realize the many substantive benefits of PR in COPD.

DISCLAIMER: The COPD Committee Pulmonary Rehabilitation Expert Working Group is functionally and editorially independent from any funding sources of the CTS. The Pulmonary Rehabilitation Expert Working Group and the COPD Committee do not receive any direct funding from external sources. The Expert Working Group was formed by the CTS COPD Committee, which is accountable to the CTS Respiratory Guidelines Committee and the CTS Board of Directors.

CONFLICTS OF INTEREST: Members of the COPD Committee Pulmonary Rehabilitation Expert Working Group declared potential conflicts of interest at the time of appointment and were updated throughout the development process. Individual member conflict of interest statements are posted at <www.respiratoryguidelines.ca/copd-committee>.

ACKNOWLEDGEMENTS: Members of the COPD Committee Pulmonary Rehabilitation Expert Working Group thank the CTS Respiratory Guidelines Committee for their expert guidance and support.

REFERENCES
Marciniuk et al


<table>
<thead>
<tr>
<th>1st Author, Year</th>
<th>Study Design 1</th>
<th>Study Design 2</th>
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<th>Ethics Approval</th>
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<th>Health Care Setting</th>
<th>Intervention</th>
<th>Randomization Method</th>
<th>Side Effects</th>
<th>Limits</th>
<th>Reproducibility</th>
<th>Authors</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Strijbos JH, 1996</td>
<td>0=Observ, 1=Case Ctl</td>
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<td>Elliot M, 2004</td>
<td>2 0 1 1 1</td>
<td>Not specified Mod-severe COPD Standard CAD/MSK/SaO2 ≤ 85%, Or cognitive problems, communication difficulties, recent inspiratory infections 2 Hosp/Home 1;Hosp/Community 2; Community/community 3: three groups received education and exercise program (2x 1.5hrs/sem) CRQ Dyspnea dimension: Improved in 1,2 and 3 6MWD improved in 1 and 2 but not 3 Not measured Improved in 1,2 and 3. Not measured No t measured Not measured Not described 43 ~66 yrs 23M/20F Not mentioned Not reported RDM not described; Exercise prescription not adequately describe Community based exercise programs do not improve 6MWD, improve only domains of mastery and Dyspnea on the CRQ, long term participation is poor.</td>
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<tr>
<td>Güell PMR, 2007</td>
<td>2 0 1 1 1 Severe to very severe COPD, 50-75 yrs, stable condition, free of exacerbation in the last 4 weeks Standard CAD/MSK, significant reversibility in obstruction, hypoxemia, diagnosis of asthma 0 Hosp training 1/home training 2 CRQ Dyspnea dimension: Improved in 1 and 2 Pimax and TPImax improved in 1 and 2;arm strength improved in 1 and 2; 6 MWD improved in 1 and 2 Not measured Improved in 1, only Dyspnea in 2 Not measured Not measured Not measured Sealed envelopes; testing blinded 57 ~66 yrs 0 Not mentioned Not reported Exercise regimen different between 1 and 2, walking treated as leg muscle training; small groups; only men. Benefits between 1 and 2 similar for exercise tolerance. HRQOL (emotional domain only) improvement greater in 1.</td>
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<tr>
<td>Maltais, 2008</td>
<td>5 (randomized non-inferiority trial) 0 1 1 1 2 GOLD II - IV Standard CAD/MSK, asthma, terminal disease, psychologic 0 Hosp training 1/home training 2 CRQ Dyspnea dimension: Improved in 1 and 2 (statistically and clinically significant), maintained in 1 and 2 at 12 months (only clinical sig in 2 at 12 months) 6MWD improved in 1 only, not maintained; cycling endurance time improved in 1 and 2 and maintained in both Not measured Improved in 1 and 2, maintained in both except fatigue only maintained in 2 Not measured Not measured Not measured Computer generated permuted block scheme; stratified by sex and trial site 252 66 yrs 140M/112F Not mentioned 665 adverse events (similar between 1 and 2) including: 101 hosp, 52 CV and 2 deaths Primarily cycling exercise which resulted in smaller exercise capacity improvements in walk distance than usual N/A 2 is not inferior to 1 in Dyspnea, health status and exercise capacity</td>
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<tr>
<td>Oh, 2007</td>
<td>5 (meta-analysis) 1 N/A N/A 0 Local university COPD - Not specified Not specified Hosp training 1/home or home and hosp 2 Not reported Pooled effect sizes significant but no difference between them for 1 and 2 Not measured Not measured Not measured Not measured Not measured N/A 19 studies 63.8 yrs pooled N/A N/A N/A N/A N/A Site does not have an impact on changes in exercise capacity</td>
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Excluded Studies

Bibliographic Citation Reason for Exclusion

1st Author, Year

ACCP/AACVPR _1997 Not Relevant

Aizawa, 2007 No information. Rejected for analysis purposes (opinion based on literature review only)

Alexander JL_2008 Not Relevant

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Ries AL_2008 Not Relevant

Ries, 2005 Pre NETT trial - supervised sessions only

Ringbaek T_2008 Not Relevant

Rochester, 2000 No information. Rejected for analysis purposes (opinion based on literature review only)

Schoo AM_1997 Not Relevant

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Societe (French ) 2005 Nov Not Relevant

Societe (French ) 2005 Sep Not Relevant

Spencer J_2007 Not Relevant

Steele BG_2008 Not Relevant

Stulbarg MS_2002 Not Relevant

Ward JA_2002 Not Relevant

Wijkstra PJ_1995 Not Relevant

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<tr>
<th>Participant Characteristics</th>
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<th>Primary Outcomes</th>
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<tr>
<td><strong>Method</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Side Effects</strong></td>
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<td></td>
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<tr>
<td><strong>Limits Reproducibility</strong></td>
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<td></td>
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<tr>
<td><strong>Authors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Conclusion</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Method

**Side Effects**

- None related
- Back pain in one participant

**Limits Reproducibility**

- Fair
- Poor

**Authors**

- Phillips, 2006
- Mador, 2004

**Conclusion**

- Improved activity
- Decreased dyspnea
- Improved quality of life

### Participant Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Open Label</th>
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<td>Not</td>
<td>3=Healthcare</td>
<td>1=Rural</td>
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</table>

### Primary Outcomes

- **6MWD CRQ**
  - Yes both groups but not group
  - No significant differences.

- **6MWT**
  - Decreased in 2 or 3 domains
  - Increased in most domains

- **ISWT**
  - Increased in most domains
  - Decreased in 2 or 3 domains

- **WL**
  - Decreased in 2 or 3 domains
  - Increased in most domains

- **1RM**
  - Increased in both groups but not between groups
  - No significant differences.

<table>
<thead>
<tr>
<th>CRQ</th>
<th>sig</th>
<th>TUG</th>
<th>Arm</th>
<th>6MWT</th>
<th>PT</th>
<th>Quads, Gluts</th>
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<tbody>
<tr>
<td>CRQ</td>
<td>sig</td>
<td>TUG</td>
<td>Arm</td>
<td>6MWT</td>
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<td>Quads, Gluts</td>
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</table>

### Other N Age Gender

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<thead>
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<th>Other</th>
<th>N</th>
<th>Age</th>
<th>Gender</th>
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<tr>
<td>0=C</td>
<td>19</td>
<td>-</td>
<td></td>
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</tbody>
</table>

### Method

- Used 6MWT to assess endurance
- Used GXT cycle to measure VO2
- Used 6MWD CRQ to assess dyspnea
- Used 6MWT (distance) to measure walking capacity
- Used ISWT to measure performance
- Used WL to measure work capacity
- Used 1RM to measure strength

### Improvement

- Improved activity
- Decreased dyspnea
- Improved quality of life

### Conclusion

- Improved activity
- Decreased dyspnea
- Improved quality of life
### Excluded Studies

<table>
<thead>
<tr>
<th>Bibliographic Citation</th>
<th>Reason for Exclusion</th>
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<tr>
<td>Arnardottir RH 2006</td>
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<td>Chavannes N 2002</td>
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<td>Maltais F 1997</td>
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<td>Marrara KT 2008</td>
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<td>Martinez FJ 1993</td>
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<td>McCarren B 2000</td>
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<td>Nakamura Y 2008</td>
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<td>Normandin EA 2002</td>
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<td>O'Donnell DE 1998 May</td>
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<td>Paciocco G 2004</td>
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<td>Rooyackers JM 2003</td>
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<td>Troosters T 2000</td>
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</tbody>
</table>
Included Studies

1 Berry et al., 2001
2 Etnier and Berry, 2001
3 Sabit et al., 2008

Eligibility Criteria

1. Age: 20-80 years, FEV1/FVC <70% and FEV1 >20% predicted; (2) reported difficulty in performing at least one of the following activities as a result of their condition: walking upstairs, walking 200 meters, or doing housework; (3) self-reported smoking status: current, former, or never; (4) presence of major co-morbidities, such as diabetes, coronary artery disease, stroke, or severe cardiovascular and peripheral vascular disease; (5) were not undergoing active treatment for another medical condition that required hospitalization; (6) were not undergoing active treatment for another medical condition that required hospitalization; (7) had no plans to move from the area within the next 15 months; (8) were willing to accept random assignment to either one of the intervention arms.

Outcome (blinding of outcome)

1. Case control
2. Single-blinded (retrospective) 1 Enrolled in outpatient rehabilitation, attended at least one session (reference 5 for inclusion criteria)
3. Other

Attendance

1. Completed a 3 months supervised, center-based exercise program; attended at least 60% of exercise sessions before randomization and agreed to continue regardless of allocation AND attended at least one session (reference 5 for inclusion criteria)
2. Probably single-blinded 1 1 1 1 1 1 Disability associated with SOB or diagnosis of CB and/or emphysema, ambulatory, 55-80 years, FEV1/FVC <70% and FEV1 >20% predicted; (2) reported difficulty in performing at least one of the following activities as a result of their condition: walking upstairs, walking 200 meters, or doing housework; (3) self-reported smoking status: current, former, or never; (4) presence of major co-morbidities, such as diabetes, coronary artery disease, stroke, or severe cardiovascular and peripheral vascular disease; (5) were not undergoing active treatment for another medical condition that required hospitalization; (6) were not undergoing active treatment for another medical condition that required hospitalization; (7) had no plans to move from the area within the next 15 months; (8) were willing to accept random assignment to either one of the intervention arms.

Side effects

Not reported Men in the LT group reported significantly 2=Other 1=B, 2=Other improvements in self-reported disability and benefits for men but added other benefits for women but added more favorable scores than men in the ST group for dyspnea, fatigue, emotional function, and (13) long (18 week) or short (6 week) exercise program.

Results (signif)

None This is the same trial as Berry trial
None Fits research question very well; None Fits research question very well

Comments

No impact on overhead task 8% faster. Walked 6% farther during 6MWT, climbed stairs 15% faster, and performed cognitive tasks 8% faster. Improvement in cognition and physical function in COPD compared to 3 months before intervention.

Some patients had difficulty completing the long program, but after 3 months, they continued to show improvements in self-reported disability and benefits for men but added other benefits for women but added more favorable scores than men in the ST group for dyspnea, fatigue, emotional function, and (13) long (18 week) or short (6 week) exercise program.

Not reported LT reported 12% less disability than ST, not reported LT reported 12% less disability than ST, not reported LT reported 12% less disability than ST. Not reported Men in the LT group reported significantly improvements in self-reported disability and benefits for men but added other benefits for women but added more favorable scores than men in the ST group for dyspnea, fatigue, emotional function, and (13) long (18 week) or short (6 week) exercise program.
Excluded Studies

Bibliographic Citation

1st Author, Year
Does not meet the C of PICO
Comparison group received no exercise/rehab

Lacasse et al., Swiss Med Wkly, 2004 Does not answer our question. Editorial review; no original data.


Salman et al., J Gen Intern Med 2003 Metanalysis on effectives of rehabilitation. Can we still use their findings? They showed that the effect of rehab in severe patients was only significant if program lasted 6 months or longer. However, not sure that meets the C of the PICO question.

Does not meet the C or I of PICO
Compared cost-effectiveness of 6 months of rehab versus usual care (no rehab)

Does not meet the C of PICO. Maintenance study instead of duration study
Comparison group received no exercise/rehab

Does not meet the C or I of PICO
Did not measure the effect of extending the program to 6 months + the comparison group received no exercise

Does not meet the C or I of PICO
Did not measure the effect of extending the program to 2 years + no comparison group

Extended the follow-up, but not the intervention + no comparison group (longitudinal study)

Does not meet the C of PICO
Comparison group received no exercise/rehab

Does not meet the C or I of PICO
Compared standard-length rehab program to no exercise/rehab

Does not meet the C or I of PICO
Comparison group received no exercise/rehab + intervention group received standard-length rehab

Does not meet the C or I of PICO
Comparison group received no exercise/rehab + did not measure the effect of extending the rehab program to 12 months

Abramson et al., MJA, 2006 Unrelated (review article on management of COPD)

Elliott et al., Respirology, 2004 Compared setting rather than duration. Data from long term maintenance not analyzed because of drop out

Spencer et al. BMC Pulmonary Medicine, 2007 Only a protocol - no data

Romagnoli et al., Respiration, 2006 This examines repeating PR at 6 and 12 months, not prolonging the PR.

Does not meet the C of PICO
Compared supervised PR plus maintenance to non supervise PR + maintenance

Does not meet C or I

3 interventions: 1) dyspnea self management with home exercise program (DM); 2) DM + 4 supervised treadmill exercise every other week for 2 months; 3) DM + 24 supervised treadmill exercise sessions 3x/week over 2 months - so more about volume rather than duration.

Brooks et al., Eur Respir J, 2002 Does not meet the C of PICO. Maintenance study instead of duration study

Moullec et al., Respiratory Med, 2008 Does not meet the C of PICO. Maintenance study instead of duration study

Ries et al., Am J Respir Crit Care Med., 2003 Does not meet the C of PICO. Maintenance study instead of duration study

Rossi et al., Chest 2005 Does not meet the the C of the PICO. Clinic et al., Chest 2001 This study did not isolate program duration (different setting, different volumes)

Green et al., Thorax 2001 Relates to effect of a shortened program

Carrieri et al., 2005

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Puente- Maestu et al., Lung, 2003

Trooster et al., 2000

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Guell et al., Chest, 2000

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Pitta et al., Chest 2008,

Goldstein et al., Chest 1997

Heppner et al., JCPR 2006
<table>
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<tr>
<th></th>
<th>Study Design</th>
<th>FEV1/FVC &lt; 0.65, FEV1 &lt; 70%, nonsmoking for at least 8 weeks of rehab: Group A - Increased peak watts in both groups; Group B = No change in peak watts.</th>
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<td>2</td>
<td>Vogiantis, 1999</td>
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</tr>
<tr>
<td>3</td>
<td>Garuti, 2003</td>
<td>(ref 184)</td>
<td></td>
</tr>
</tbody>
</table>

**Inclusion Criteria**
- COPD patients admitted into rehab following acute exacerbation, history of smoking current non-smokers for at least 2 months, optimized medical therapy, no exacerbation in the past 6 months, absence of musculo-skeletal problems and willingness to participate, no active exercise blocks of four.

**Exclusion Criteria**
- Unstable medical condition, inpatient for disease severity >40; Severe FEV1 < 40%

**Eligibility Criteria**
- Inpatient for disease severity: Mild/Moderate (FEV1 40-59%) n=7, Severe (FEV1 < 40%) n=17
- Outpatient for disease severity: Mild/Moderate (FEV1 30-40%) n=36, Severe (FEV1 < 35%) n=99

**Outcome(s)**
- Improved exercise capacity
- Reduced Borg leg fatigue in Mild (7.5 to 5.5), Severe (8.0 to 6.5)
- Increased 6MWD in Mild/Moderate (89 to 105), Severe (111 to 137)
- Improved SGRQ in Mild/Moderate (9.4 to 7.7), Severe (10.0 to 6.7)
- Improved HAD-depression in Mild/Moderate (6.0 to 4.8), Severe (6.4 to 4.6)
- Cost-utility

**Drug / Dosage / Regimen**
- Reduction in dyspnea in Mild/Moderate (4.9 to 3.5), Severe (8.0 to 5.5), 6MWD statistically significant change in Mild/Moderate (7.7 to 5.0), 6MWD statistically significant change in Severe (6.0 to 3.5)
- Severe (5.3 to 5.4), no difference in Very Severe (5.6 to 5.5)

**Participants**
- **Group A** = Reduction in dyspnea in Mild/Moderate (4.9 to 3.5), Severe (8.0 to 5.5), 6MWD statistically significant change in Mild/Moderate (7.7 to 5.0), 6MWD statistically significant change in Severe (6.0 to 3.5)
- **Group B** = No change in peak watts.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Reason for Exclusion</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>167 Franssen 2004</td>
<td>Effects of whole-body exercise</td>
<td></td>
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<tr>
<td>419 Rossi 2005</td>
<td>Length and clinical effectiveness of</td>
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</tr>
<tr>
<td>248 Karapolat 2007</td>
<td>Do the benefits gained using a short-</td>
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<tr>
<td>487 Vallet 1994</td>
<td>Value of individualized rehabilitation</td>
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<tr>
<td>177 Garcia-Aymerich 2007</td>
<td>Regular physical activity modifies</td>
<td></td>
</tr>
<tr>
<td>292 Maltais 1997</td>
<td>Intensity of training and physiologic</td>
<td></td>
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<tr>
<td>408 Ries 1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>76 Carter 2003</td>
<td>Peak physiologic responses to arm</td>
<td></td>
</tr>
<tr>
<td>53 Borghi-Silva 2006</td>
<td>L-carnitine as an ergogenic aid for</td>
<td></td>
</tr>
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</table>

The table above lists studies with reasons for their exclusion from a systematic review. It includes details on the effects of physical activity, rehabilitation strategies, and specific interventions like L-carnitine usage. The studies vary in their focus, from the impact of exercise on physical capacity to the utility of rehabilitation programs for patients with chronic obstructive pulmonary disease (COPD).
## Comorbidities that were currently diagnosed with COPD within 6 hours travel to RTOT

<table>
<thead>
<tr>
<th>Study Source</th>
<th>Study Design</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Industry Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>FOY, 2001</td>
<td>RCT</td>
<td>Expiratory airflow</td>
<td>Not specifically stated</td>
<td>COPD/Asthma</td>
<td>Heart health issues, psychologic disorder</td>
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<td>SABIT, 2008</td>
<td>RCT</td>
<td>Not specifically stated</td>
<td>COPD</td>
<td>Published elsewhere</td>
<td>Single center Outpatient PRP with either 6 weeks [3x per wk]</td>
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<tr>
<td>LAVIOLETTE, 2007</td>
<td>retro</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No active Cardiovascular, Neuro testing, done at start. Same number of women and post PR, and at 6 months post PR.</td>
<td>awaiting PR between sites. Gender analysis done.</td>
</tr>
</tbody>
</table>
| SKUMLIEN, 2006 | RCT | Not specifically stated | COPD              | Cannot comment | 12MD declined post PR but remained significantly better than baseline, however, not obviously enhanced 

## Bold Primary Outcomes

- **Distance improved with intervention in both genders but did not achieve statistical significance:**
  - Δ Distance improved with intervention in both genders but did not achieve statistical significance.

- **Similar improvement in 6MWD:**
  - Similar improvement in 6MWD [47.8mF vs. 43.6mM] Not evaluated 

- **CRQ improved significantly for both genders although difference in change 6MWD between genders was negative:**
  - CRQ improved significantly for both genders although difference in change 6MWD between genders was negative.

- **Women had higher FEV1%:**
  - Women had higher FEV1% 44% vs. 39.6%. Similar mortality for women and men.

- **Dyspnea statistically improved in women:**
  - Dyspnea statistically improved in women.

- **MRC score improved significantly:**
  - MRC score improved significantly.

- **Dyspnea assessed by SOBQ statistically improved in women:**
  - Dyspnea assessed by SOBQ statistically improved in women.

- **No significant gender difference in BPQ [respiratory symptoms] over time adjusted for FEV1:**
  - No significant gender difference in BPQ [respiratory symptoms] over time adjusted for FEV1.

- **Not analyzed for gender:**
  - Not analyzed for gender.

## Data Registry and Similar Assessments

- **Complete post PR 12WT and QoL assessment:**
  - Complete post PR 12WT and QoL assessment.

- **Gender analysis done:**
  - Gender analysis done.

## Table

<table>
<thead>
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</tbody>
</table>
| SKUMLIEN, 2006 | RCT | Not specifically stated | COPD              | Cannot comment | 12MD declined post PR but remained significantly better than baseline, however, not obviously enhanced 

## Attendance and exercise predictors.

- **No significant gender difference in BPQ [respiratory symptoms] over time adjusted for FEV1:**
  - No significant gender difference in BPQ [respiratory symptoms] over time adjusted for FEV1.

- **Not evaluated for gender:**
  - Not evaluated for gender.
<table>
<thead>
<tr>
<th>Bibliographic Citation</th>
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<tr>
<td>Berry MJ_2003</td>
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<td>Clini E_2001</td>
<td>Not Relevant</td>
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<td>Gadoury MA_2005</td>
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<tr>
<td>Garcia-Aymerich J_2006</td>
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<td>Grodner S_1996</td>
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<td>Heppner PS_2006</td>
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<tr>
<td>Kayahan B_2006</td>
<td>Not Relevant</td>
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<td>Leung ACSC_2006</td>
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<td>Low G_2006</td>
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<td>Maltais F_2008</td>
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<td>O'Donnell DE_2007</td>
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<td>Puhan MA_2008</td>
<td>Not Relevant</td>
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<td>Rajendran AJ_1998</td>
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<td>Ries AL_2003</td>
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<td>Spruit MA_2005</td>
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<td>Theander K_2009</td>
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<td>Varkey AB_2004</td>
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<td>Wilson DH_2004</td>
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In summary, early PR post-AECOPD is safe and effective in improving exercise tolerance and dyspnea. Home-based PR is possible, but adherence is limited. Further research is needed to improve exercise compliance and long-term outcomes.
<table>
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<td>Riario-Sforza GG_2005</td>
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