

# COPDX: an update of guidelines for the management of chronic obstructive pulmonary disease with a review of recent evidence

Michael J Abramson, Alan J Crockett, Peter A Frith and Christine F McDonald

Chronic obstructive pulmonary disease (COPD) is a major public health problem. It is the single leading cause of death that is continuing to increase and is now the third largest contributor to the burden of disease in Australia.<sup>1</sup> In response to this challenge, the Australian Lung Foundation and Thoracic Society of Australia and New Zealand developed clinical practice guidelines (COPDX) to improve the diagnosis and management of COPD. These guidelines were published 3 years ago as a supplement to the *Journal*<sup>2</sup> and were based largely on evidence in the Global Initiative for Chronic Obstructive Lung Disease (GOLD).<sup>3</sup> Since then, the Australian Lung Foundation has updated COPDX, incorporating more recently published evidence and systematic reviews in the Cochrane Library. Levels of evidence have been reclassified for this summary in accordance with guidelines from the National Health and Medical Research Council (NHMRC).<sup>4</sup>

## C: Confirm diagnosis and assess severity

Spirometry remains the mainstay of diagnosis of COPD, but is underutilised in Australia. Trials are currently underway to explore barriers to the use of spirometry in general practice, to develop simple reliable questionnaires that may guide general practitioners in screening patients for referral, and to confirm that more widespread application improves outcomes in chronic respiratory diseases. A diagnostic algorithm is under evaluation on the Australian Lung Foundation website (<http://www.lungnet.org.au>) (Box 1).

## O: Optimise function (Box 2)

### Therapeutics

**Long-acting  $\beta_2$  agonists:** Regular treatment with long-acting  $\beta_2$  agonists is more effective and convenient than treatment with short-acting bronchodilators (evidence level I) and is associated with improved quality of life<sup>5</sup> (evidence level II). However, a systematic review of eight randomised controlled trials (RCTs) of long-acting  $\beta_2$  agonists found no overall difference in forced expiratory volume in 1 second ( $FEV_1$ ) when compared with placebo (evidence level I), and only one trial reported less dyspnoea in patients during treatment with these drugs<sup>6</sup> (evidence level II). As the review excluded patients with >15% reversibility after a dose of short-acting  $\beta_2$  agonist, it may underestimate the benefits of long-acting  $\beta_2$  agonists in unselected COPD patients.

**Tiotropium:** This inhaled anticholinergic agent has a duration of effect longer than 24 hours, and so can be taken once daily.<sup>7</sup> Compared with placebo and regular ipratropium, tiotropium reduces exacerbations and improves quality of life.<sup>8</sup> It also decreases exertional dyspnoea and increases endurance by reducing hyperinflation<sup>9</sup> (evidence level II).

**Combination inhalers:** Combinations of an inhaled glucocorticoid and long-acting  $\beta_2$  agonist in a single inhaler are being increasingly used in COPD. A systematic review of six RCTs of combination inhalers for COPD concluded that, compared with placebo, combination therapy led to clinically meaningful differences in quality

## ABSTRACT

- Long-acting  $\beta_2$  agonists are an effective and convenient treatment for chronic obstructive pulmonary disease (COPD), but do not significantly improve lung function.
- The long-acting anticholinergic tiotropium, which can be taken once daily, decreases exertional dyspnoea and increases endurance by reducing hyperinflation.
- The role in COPD of the combination of a long-acting  $\beta_2$  agonist and a glucocorticoid in a single inhaler remains unclear.
- The minimum duration of an effective pulmonary rehabilitation program that includes exercise training is 6 weeks.
- Long-term treatment with inhaled glucocorticoids may reduce the rate of decline in lung function, but the effect is small.
- Aminophylline should no longer be routinely used in acute exacerbations of COPD.
- Non-invasive positive pressure ventilation (NPPV) reduces mortality and hospital stay in patients with acute hypercapnic ventilatory failure; it is also an effective weaning strategy for patients who require intubation.
- Further studies are required to clarify the role of NPPV in the long-term management of stable COPD.

MJA 2006; 184: 342–345

of life, symptoms and frequency of exacerbations<sup>10</sup> (evidence level I). However, comparison of the different combination therapies with their single components gave conflicting results, possibly because of differential drop-out rates in the original studies (Professor Paul Jones, St Georges Hospital, London, personal communication). Again, patients with >12% and 200 mL bronchodilator reversibility were excluded from four of the six trials in this review, potentially reducing the benefits that might be seen in a more general population with COPD. Firmer conclusions about the effects of combination therapy in a single inhaler require more data, including comparison with the effects of the two drugs administered separately in double-dummy trials.

**Oral glucocorticoids:** The use of oral glucocorticoids in stable COPD was recently examined in a systematic review of 24 RCTs.<sup>11</sup> Overall, it would be necessary to treat seven patients (95% CI, 5–12) with oral steroids to achieve one extra case of an increase in  $FEV_1$  greater than 20%. There was no evidence to support the long-term use of oral steroids at daily doses less than 10–15 mg prednisolone, although some evidence that higher doses ( $\geq 30$  mg) improved lung function over a short period. Potentially harmful adverse effects would prevent us recommending long-term use at these high doses in most patients (evidence level I).

### Avoid osteoporosis

In younger patients with asthma or mild COPD, there is no evidence of an effect of inhaled glucocorticoids in daily doses of 1000  $\mu$ g or less of fluticasone or equivalent given for 2–3 years on bone mineral

### 1 Diagnostic algorithm to distinguish chronic obstructive pulmonary disease (COPD) from asthma

The patient's age, height, sex and spirometry results are entered in the left column. A brief questionnaire is completed in the right hand column. The program calculates predicted values and severity, and provides a likely diagnosis. (Available at: <http://www.lungnet.org.au>.)

capacity<sup>22,23</sup> (evidence level II). Although weight loss and low body mass index are both poor prognostic indicators in COPD, there is level I evidence that nutritional supplementation does not alter anthropometric measures, lung function or exercise capacity when nutrition is already depleted.<sup>24</sup>

**Opioids:** These may have a role in the relief of severe intractable dyspnoea<sup>25,26</sup> (evidence level I).

### P: Prevent deterioration (Box 2)

#### Risk factor reduction

The mainstay for preventing deterioration in COPD is complete cessation of smoking, as only complete cessation slows decline in lung function.<sup>27</sup> A combination of psychosocial and pharmacological interventions is superior to no treatment or psychosocial interventions alone for achieving smoking cessation<sup>28</sup> (evidence level I).

#### Vaccinations

Recommended vaccinations in COPDX have been harmonised with NHMRC approved guidelines (<http://immunise.health.gov.au/handbook.htm>). In addition, there is some evidence of a possible benefit from *Haemophilus influenzae* vaccination. Six RCTs of

oral killed non-typable *H. influenzae* vaccine found a significant reduction in the incidence of bronchitic episodes 3 months after vaccination, but the effect had disappeared by 9 months.<sup>29</sup> The severity of exacerbations in the treatment group, as measured by the requirement to prescribe antibiotics, was reduced by 65% at 6 months (evidence level I). However, a larger clinical trial is needed to assess longer term prognosis, and the vaccine is not currently available. Another systematic review of 13, mostly low-quality, trials of oral lyophilised bacterial extracts in COPD found some evidence of symptomatic improvement, but no convincing reduction in exacerbations<sup>30</sup> (evidence level I).

density (BMD) or vertebral fractures<sup>12</sup> (evidence level I). Higher doses are associated with biochemical markers of increased bone turnover, but data on BMD and fractures at these doses are not yet available. In older people, the BMD and fracture safety profile of most inhaled glucocorticoids for the treatment of COPD is not known. However, triamcinolone was associated with reduced BMD in the Lung Health Study<sup>13</sup> (evidence level II). Australian guidelines have been published on the prevention and treatment of osteoporosis, including glucocorticoid-induced osteoporosis.<sup>14</sup>

#### Improve function

**Non-invasive positive pressure ventilation:** Although 12 to 24-month studies in patients with stable COPD with chronic respiratory failure have suggested that the addition of non-invasive positive pressure ventilation (NPPV) may have some beneficial effects,<sup>15,16</sup> its widespread use cannot yet be advocated.<sup>17</sup> Compared with long-term oxygen therapy alone, the addition of NPPV has some beneficial effects on CO<sub>2</sub> retention and shortness of breath.<sup>16</sup> A well powered RCT is near completion in Australia, evaluating NPPV use in COPD patients with hypercapnia.

**Pulmonary rehabilitation:** This reduces dyspnoea, anxiety and depression, improves exercise capacity and quality of life, and may reduce hospitalisation (evidence level I). The minimum duration of an effective rehabilitation program that includes exercise training is 6 weeks; the longer the program continues, the more effective it appears to be<sup>18-20</sup> (evidence level II). However, as yet, effective structures that maintain benefit have not been subjected to robust clinical trials.<sup>21</sup>

**Anabolic steroids and nutritional supplements:** In patients with COPD and weight loss, anabolic steroids may increase body weight and lean body mass, but have little or no effect on exercise

### 2 Therapies to optimise function and prevent deterioration in chronic obstructive pulmonary disease

Established efficacy	Supported by new evidence
<b>To optimise function</b>	
Short-acting $\beta_2$ agonists	Long-acting $\beta_2$ agonists
Ipratropium	Tiotropium
Short-course oral steroids	Combination inhalers
Inhaled steroids	Non-invasive positive pressure ventilation
Pulmonary rehabilitation	Low-dose opioids
<b>To prevent deterioration</b>	
Complete smoking cessation	Inhaled corticosteroids
Influenza and pneumococcal vaccination	<i>Haemophilus influenzae</i> vaccination
Long-term oxygen in patients with hypoxia	Mucolytic agents

### Glucocorticoids

The effect of inhaled glucocorticoids on decline in lung function is controversial. Systematic reviews and meta-analyses of the available RCTs have found a small benefit of uncertain significance when compared with placebo (evidence level I). A 2003 meta-analysis found a combined difference in the rate of decline in FEV<sub>1</sub> of 5.0 mL/year between treatment groups (95% CI, -1.2 to 11.2 mL/year),<sup>31</sup> while a second meta-analysis in the same year found a combined difference of 7.7 mL/year (95% CI, 1.3–14.2 mL/year).<sup>32</sup> The varying conclusions of these reviews would not lead to a recommendation for inhaled glucocorticoids to be used routinely in all patients with COPD. However, these drugs are indicated for patients with a previously documented response and for those who have severe COPD with frequent exacerbations (evidence level II).

### Mucolytic agents

Mucolytic agents may reduce the frequency and duration of exacerbations (evidence level I). A systematic review concluded that, in patients with COPD or chronic bronchitis who have a higher than average rate of exacerbations, treatment with mucolytic agents was associated with a small but significant reduction in acute exacerbations and total days of disability.<sup>33</sup> However, a recent large RCT of *N*-acetylcysteine did not confirm an overall reduction in exacerbations, although a significant reduction was still seen in the subgroup who were not having concomitant treatment with inhaled steroids<sup>34</sup> (evidence level II). Nonetheless, such agents are not available for COPD through the Pharmaceutical Benefits Scheme (PBS) or Repatriation PBS, and are thus currently not widely used in Australia.

### D: Develop a support network and self-management plan

Patients should be encouraged to take appropriate responsibility for their own management (evidence level III-1). However, a systematic review of self-management plans in COPD found no effect on hospital admissions, emergency department visits, days lost from work or lung function.<sup>35</sup> Inconclusive results were observed for health-related quality of life, COPD symptoms and use of other health care resources. Clearly, further well designed RCTs with sufficiently long follow-up are required. Nonetheless, self-management education reduced the need for rescue medication and led to increased use of oral steroids and antibiotics for respiratory symptoms (evidence level I).

### X: manage eXacerbations

**Hospital in the home:** Up to a quarter of carefully selected patients presenting to hospital emergency departments with acute exacerbations of COPD can be safely and successfully treated at home with support from respiratory nurses. A systematic review of seven RCTs of "hospital in the home" schemes found no significant differences in readmission rates or mortality, and a preference for these schemes by patients and carers<sup>36</sup> (evidence level I). However, further research is needed, as the studies reviewed were small and varied in the interventions used.

**Nebulised  $\beta_2$  agonists and anticholinergics:** Hospital management of a severe exacerbation of COPD usually includes nebulised  $\beta_2$  agonist, administered continuously in extremely unwell

patients and intermittently in others. An anticholinergic agent may be delivered together with the nebulised  $\beta_2$  agonist in patients with severe exacerbations or when response to the  $\beta_2$  agonist alone is poor. However, a systematic review that included four RCTs did not demonstrate any additional benefit on FEV<sub>1</sub> of combining an anticholinergic compared with  $\beta_2$  agonists alone<sup>37</sup> (evidence level I).

**Aminophylline:** The routine use of intravenous aminophylline is no longer recommended for acute exacerbations of COPD (evidence level I). A systematic review of four RCTs of methylxanthines found only a transient increase of 101 mL in FEV<sub>1</sub> after 3 days, with a 4.6-fold increased risk of nausea and vomiting.<sup>38</sup> This is confirmed by a recent RCT in patients with non-acidotic acute exacerbations, which found no clinically useful reductions in breathlessness or length of hospital stay and no improvement in lung function, but significantly more nausea among those treated with aminophylline.<sup>39</sup>

**Antibiotic therapy:** Exacerbations with clinical signs of infection benefit from antibiotic therapy. A recent multicentre RCT found that moxifloxacin was equivalent to standard antibiotics (amoxicillin, clarithromycin or cefuroxime) for clinical success, and superior for clinical cure and bacteriological eradication, and reduced the frequency of exacerbations over the following 5 months.<sup>40</sup> These findings applied to patients with milder COPD, most of whom were not prescribed oral steroids (evidence level II).

**Non-invasive positive pressure ventilation:** NPPV is effective for managing acute hypercapnic ventilatory failure in COPD (evidence level I). A systematic review of 14 RCTs found that NPPV resulted in significantly decreased mortality, decreased need for endotracheal intubation, and more rapid improvement in arterial blood gases.<sup>41</sup> Length of hospital stay was reduced by a mean of 3.2 days. When intubation is required, weaning from ventilation is facilitated by NPPV. A systematic review of five RCTs found that the NPPV-weaning strategy was associated with significantly lower mortality and reduced length of hospital stay by a mean of 7.3 days.<sup>42</sup>

### Conclusion

The evidence base for safe and effective management of COPD continues to improve, although there is still a need for well designed RCTs, particularly of non-pharmacological interventions. Further evidence from RCTs and systematic reviews needs to be couched in terms of meaningful outcomes and should provide the numbers needed to treat for benefit and harm. It also needs to be remembered that absence of evidence for a treatment effect is not the same as evidence for absence of an effect. The challenge for the Australian Lung Foundation and the Thoracic Society of Australia and New Zealand is to disseminate COPDX efficiently and to improve the diagnosis and management of COPD in Australia. The most recent approved full version of the guidelines is available at <<http://www.copdx.org.au>>.

### Acknowledgements

The Australian Lung Foundation supported meetings of authors and preparation of this article. We also wish to thank the other members of the COPD Evaluation Committee, Nicholas Glasgow, Susan Jenkins and Richard Wood-Baker, for their helpful comments.

## Competing interests

**Michael Abramson** has served on the scientific advisory committee for the Australian Asthma Study, which was sponsored by GlaxoSmithKline, and received travel assistance from AstraZeneca on one occasion.

**Alan Crockett** has received fees from several pharmaceutical companies for providing training in spirometry for general practitioners and practice nurses.

**Peter Frith** has received honoraria from Boehringer Ingelheim, Pfizer, GlaxoSmithKline and AstraZeneca for delivering lectures and workshops to general practitioners on the use of COPDX, and a grant-in-aid from AltanaPharma for travel to the Thoracic Society of Australia and New Zealand annual scientific meeting.

**Christine McDonald** has received honoraria for speaking at meetings sponsored by Boehringer Ingelheim, Pfizer, GlaxoSmithKline and AstraZeneca, and travel assistance from these companies to attend international respiratory meetings.

## Author details

**Michael J Abramson**, PhD, FRACP, FAFPHM, Professor of Clinical Epidemiology and Deputy Head<sup>1</sup>

**Alan J Crockett**, PSM, PhD, FANZSRS, Director, Primary Care Respiratory Unit<sup>2</sup>

**Peter A Frith**, MD, FRACP, Head of Southern Respiratory Services<sup>3</sup>

**Christine F McDonald**, PhD, FRACP, Deputy Director<sup>4</sup>

<sup>1</sup> Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC.

<sup>2</sup> Discipline of General Practice, University of Adelaide, Adelaide, SA.

<sup>3</sup> Respiratory Department, Repatriation General Hospital, Adelaide, SA.

<sup>4</sup> Department of Respiratory and Sleep Medicine, Austin Health, Melbourne, VIC.

**Correspondence:** michael.abramson@med.monash.edu.au

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(Received 1 Sep 2005, accepted 19 Dec 2005)

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