Stepping patients through COPD management

Commentary by
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A 74-year-old man with a history of inhaler use presents for evaluation of his medications. A diagnosis of COPD is confirmed. Current Australian guidelines are available to guide assessment and treatment of patients with respiratory conditions.

Case scenario

Thomas, aged 74 years, comes to see you today. He is taking fluticasone propionate 500 mcg and salmeterol xinafoate 50 mcg one inhalation twice daily and tiotropium bromide via an inhalation device for 'emphysema', which was diagnosed during a 'nasty chest infection' when he was in his mid-60s. He recalls that his chest x-ray showed 'large lungs', but he does not remember having any lung function tests at that time.

Thomas started smoking when he was 17 years old and finally gave up about six years ago when they 'just got too expensive!' He had accumulated about 60 pack-years. Other than a couple of episodes of bronchitis and a 'smoker's cough', he has had no other respiratory symptoms and has never been hospitalised. Thomas worked as an accounts clerk for most of his working life and had no hobbies that exposed him to noxious agents.

Thomas has hypertension that is well controlled with olmesartan 20 mg once daily. He plays golf once a week and manages to walk around all 18 holes despite having 'creaky knees', and he is otherwise well and not taking any other regular medications.

He asks if he still needs to be using the inhalers for his 'emphysema' and whether he still has 'large lungs', although he is unsure what this means. You arrange for him to have pre- and postbronchodilator spirometry, which shows a postbronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio of 0.63 and a FEV_1 of 68% predicted (and no bronchodilator responsiveness). A diagnosis of chronic obstructive pulmonary disease (COPD) is confirmed as the FEV_1/FVC ratio is below 0.70; the FEV_1 value indicates mild airflow limitation (FEV_1 >60% predicted).

Should further investigations be performed? Where can current Australian guidelines be found to guide assessment and treatment of patients with respiratory conditions such as Thomas?

Commentary

Diagnosis

Thomas is a past smoker with an onset of respiratory symptoms in middle age. This leads to consideration of a diagnosis of COPD, with a differential diagnosis of adult-onset asthma or mild heart failure, although there are no signs of heart failure on examination.

Spirometry results show mild airflow limitation (FEV_1/FVC <0.7; FEV_1 between 60% and 79%) after administration of a short-acting bronchodilator. If asthma was present,

Key points

- **In patients with stable COPD, the severity of airflow limitation should be measured by spirometry.**
- **The next step in assessing a patient with COPD is to ascertain how greatly the symptoms impact on their activity and quality of life.**
- **A stepwise introduction of a drug from one of the two classes of long-acting bronchodilators – long-acting muscarinic antagonists (LAMAs) or long-acting beta-agonists (LABAs) – is encouraged.**
- **A combination long-acting bronchodilator (LAMA plus LABA) would be the next step in treatment for patients with severe symptoms who fail to respond satisfactorily to a single bronchodilator, or who have a history of exacerbations.**

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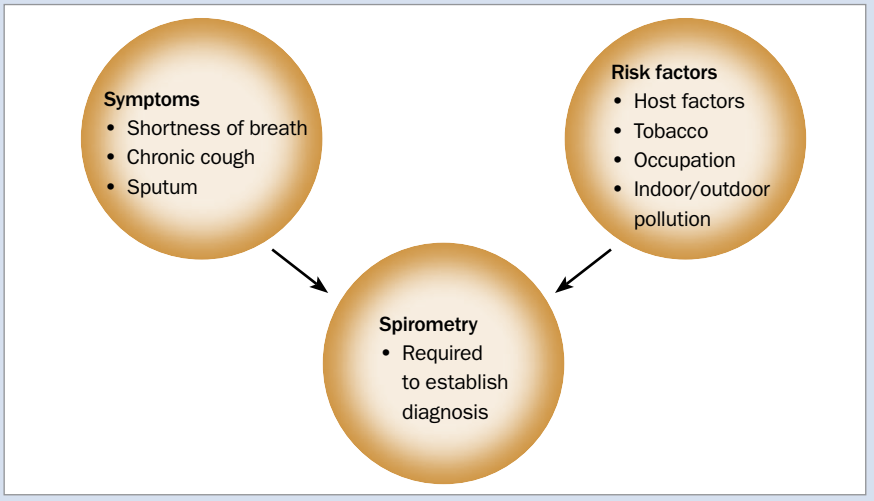

Figure 1. Pathways to the diagnosis of chronic obstructive pulmonary disease (COPD).
Reproduced with permission from Global Initiative for Chronic Obstructive Lung Disease (GOLD).[1]

the results would often show a complete reversibility or substantial improvement in FEV_1 (e.g. by 20% or 400 mL); there may also be asthma symptoms or allergic traits from childhood.

Thomas has the trifecta of exposure to recognised risk factors (cigarette smoke), relevant respiratory symptoms (cough/'bronchitis') and airflow limitation after bronchodilator use, which leads to a definite diagnosis of COPD (Figure 1).[1] Asthma is highly unlikely. This distinction is important because treatments for each condition target different pathophysiologies and outcomes.

COPD guidelines and management plans

Expert bodies in Australia have provided recommended assessments that can assist in the management of patients with COPD. *The COPD-X plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease*, as well as a compendium of helpful tools, including the *COPD-X concise guide for primary care* and the *Stepwise management of stable chronic obstructive pulmonary disease (COPD)*, are available (Figure 2).[2-4]

The COPD-X guidelines have been updated regularly since their first edition in 2003.[2] There are now three to four reviews conducted each year, undertaken by an expert panel that includes Australian clinicians, researchers and academics from the fields of respiratory medicine, general practice, physiotherapy, nursing and pharmaceutical science who systematically examine the worldwide literature for relevant new evidence, and online updates are published shortly after. Each review is approved by the Lung Foundation Australia (LFA) and Thoracic Society of Australia and New Zealand (TSANZ). Every few years the COPD-X concise guide is updated by the COPD-X Guidelines Committee and reviewed by a panel of GPs and provides focused advice suitable for GPs.[3] The stepwise guide is also reviewed whenever the full evidence search is undertaken.[4] Other clinical tools are also available through the LFA (https://lungfoundation.com.au) and TSANZ (www.thoracic.org.au), and are regularly updated.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) produces yearly reports on the prevention, diagnosis and management of COPD.[1] These are written by an independent scientific committee comprising expert respiratory physicians, researchers and academics who review the evidence twice each year. The GOLD report reflects this evidence but also provides clinical interpretation and suggestions for diagnostic and treatment interventions. The global report is not a guideline and is not specifically developed for any one country. Not surprisingly, GOLD and the COPD-X committee have evolved similar approaches to producing their reports, but there are Australian-specific recommendations in the COPD-X concise guide applicable to clinical practice in Australia.

Other assessments and investigations

In patients with stable COPD, it is important to first have an idea of the severity of airflow limitation – in this case scenario spirometry confirms that Thomas' airflow limitation is mild. This is relevant when judging if symptoms match objective measures – and in Thomas' case they do. The result also categorises his risk of respiratory and all-cause mortality as being relatively low. Although the level of airflow limitation has no particular therapeutic relevance, the FEV_1 does determine the PBS eligibility for ICS-containing combination therapies in patients with COPD. The more important characteristics to guide therapy are how troubled the patient is by his symptoms and presence or absence of exacerbations.

The next step in assessing a patient with COPD is therefore to ascertain how greatly the symptoms impact on their activity and quality of life, as this knowledge helps to guide the choice of therapy between single or dual long-acting bronchodilators. This can be usefully formalised in a COPD assessment test (CAT), an easily completed test of eight questions marked on a scale of one to five (www.catestonline.org). The Modified Medical Research Council Dyspnoea Scale (https://pulmonaryrehab.com.au/patient-assessment/resources/) can be completed by simply asking the patient how much activity is required to make them breathless.

Finally, in Thomas' case, it would be helpful to classify the 'nasty chest infection' and 'episodes of bronchitis' as mild or moderate exacerbations, because this history would heighten the likelihood of future exacerbations and therefore more rapid disease progression or death. Consequently, this is also relevant to the choice of drug treatments.

In summary, a thorough assessment for COPD requires documentation of a patient's smoking and exposure history, lung function, severity of symptoms, functional impairment and exacerbation history.

Therapeutic decisions

In all patients with COPD, especially older patients such as Thomas, annual influenza vaccination and the recommended pneumococcal vaccinations should be provided.

STEPWISE MANAGEMENT OF STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

	MILD	MODERATE	SEVERE
Typical symptoms	◦ few symptoms ◦ breathless on moderate exertion ◦ recurrent chest infections ◦ little or no effect on daily activities	◦ breathless walking on level ground ◦ increasing limitation of daily activities ◦ cough and sputum production ◦ exacerbations requiring oral corticosteroids and/or antibiotics	◦ breathless on minimal exertion ◦ daily activities severely curtailed ◦ experiencing regular sputum production ◦ chronic cough ◦ exacerbations of increasing frequency and severity
Typical lung function	**FEV_1 ≈ 60-80% predicted**	**FEV_1 ≈ 40-59% predicted**	**FEV_1 < 40% predicted**
Non-pharmacological interventions	**RISK REDUCTION** Check smoking status, support smoking cessation, recommend annual influenza vaccine and pneumococcal vaccine according to immunisation handbook		
	OPTIMISE FUNCTION Encourage regular exercise and physical activity, review nutrition, provide education, develop GP management plan and written COPD action plan (and initiate regular review)		
	CONSIDER CO-MORBIDITIES especially cardiovascular disease, anxiety, depression, lung cancer and osteoporosis		
	REFER symptomatic patients to pulmonary rehabilitation		
		Consider oxygen therapy for hypoxaemia, surgery, bronchoscopic interventions, palliative care services and advanced care planning	
Stepwise pharmacological interventions (inhaled medicines)*	**START with short-acting relievers:** (used as needed)		
	SABA (short-acting $beta_2$-agonist) OR **SAMA** (short-acting muscarinic antagonist)		
	ADD long-acting bronchodilators: **LAMA** (long-acting muscarinic antagonist) OR **LABA** (long-acting $beta_2$-agonist) Single inhaler dual therapy (**LAMA**/**LABA**) may be suitable		
		CONSIDER adding ICS (inhaled corticosteroids) FEV_1 ≤50% predicted AND ≥two exacerbations in last 12 months AND significant symptoms despite LAMA and LABA therapy*	**ICS**/**LABA** and **LAMA** Single inhaler triple therapy (**ICS**/**LAMA**/**LABA**) may be suitable
	Assess and optimise inhaler device technique at each visit		

REFER PATIENTS TO LUNG FOUNDATION AUSTRALIA FOR INFORMATION AND SUPPORT - FREECALL 1800 654 301

Lung Foundation Australia has a range of resources to promote understanding of COPD and assist with management.

Based on The COPD-X Plan: Australian and New Zealand Guidelines for the Management of COPD and COPD-X Concise Guide for Primary Care

*Refer to PBS criteria: www.pbs.gov.au

Register at www.copdx.org.au to receive an alert when the COPD-X Guidelines are updated

Lung Foundation Australia

1800 654 301 | Lungfoundation.com.au

Figure 2. Stepwise management of stable chronic obstructive pulmonary disease (COPD). (Information on inhalers is provided on page 2 of this two-page reference guide.)

Reproduced with permission from Lung Foundation Australia.[4]

Thomas' smoking status should be reassessed. If he still smokes socially or is exposed to side-stream or second-hand smoke, he will need counselling and advice. He may also benefit from counselling about recommended activity levels – at least 30 minutes of moderate-to-vigorous exercise four to five times per week (https://pulmonaryrehab.com.au/importance-of-exercise/exercise-prescription-table). His weekly golf game is probably not enough.

Pulmonary rehabilitation

Referral to a pulmonary rehabilitation program for assessment of Thomas' exercise capacity, nutritional status, diet and muscle strength should be considered. A formal rehabilitation course usually involves patients visiting a gym over six to 12 weeks, where several combined information classes improve their understanding of the disease, its effects, its treatments and any other potential effects. Emphasis is placed on guiding self-management to ensure continuing healthy lifestyles, correct use of inhaled and other medications and responding to symptom flare-ups (or exacerbations) appropriately. Exercise classes supervised by a physiotherapist and/or exercise scientist are provided two or three times each week. Most patients can expect to experience improved fitness, strength, health-related quality of life and nutrition, leading to a healthier lifestyle. They also have a better understanding of mental health implications and their condition, so preventive actions can be undertaken and they can respond quickly to early symptoms of exacerbations.

Inhaler therapy

Thomas's current inhaler therapy can now be assessed. He is using an inhaler with a combined inhaled corticosteroid (ICS; fluticasone propionate)/long-acting beta-agonist (LABA; salmeterol xinafoate) taken from a metered-dose inhaler (MDI) and an inhaled long-acting muscarinic antagonist (LAMA; tiotropium bromide) from a capsulated dry-powder inhaler. The COPD-X guidelines recommend stepwise incrementing of therapy, beginning with a LAMA alone, according to symptoms and exacerbation responses (Figure 2).[4] Thomas has mild airflow limitation and symptoms, and is active, and any exacerbations he has experienced have been mild, with the exception of one possible 'moderate' exacerbation.

Recommendations from COPD-X are based on strong evidence from large randomised controlled trials and meta-analyses. They encourage a stepwise introduction of a drug from one of the two classes of long-acting bronchodilators, LAMAs and LABAs. LAMAs and LABAs have equivalent efficacy for controlling symptoms, but LAMAs are superior for improving quality of life and exercise capacity, as well as having a slightly greater ability to reduce exacerbation frequency.

A combination long-acting bronchodilator (LAMA plus LABA) would be the next step in treatment for patients with severe symptoms who fail to respond satisfactorily to a single bronchodilator, or who have a history of exacerbations.

Although ICSs are essential drugs for controlling asthma, they have a much smaller role in treating COPD. If an ICS is prescribed, it needs to be in combination with a LABA (a distinguishing feature from asthma treatment, as most asthma patients will do well with an ICS alone). Evidence from comparative trials and meta-analyses that have led to COPD-X guidelines, as well as TGA and PBS recommendations, confirms that ICS combination therapies may be indicated in patients in the following scenarios only:

- combined COPD and asthma when COPD and asthma coexist
- moderate-to-severe airflow limitation with a history of proven exacerbations (e.g. one hospitalisation in the past year, or more than two exacerbations requiring treatment with an antibiotic and/or oral corticosteroids in the past year)
- COPD with a blood eosinophil count above 300 cells/mcL, i.e. above 0.3 x 10^9/L.

Mounting evidence is now suggesting that an ICS in combination with a LABA would be appropriate if there were continuing exacerbations in spite of treatment with a LAMA/LABA combination.

Some years ago, Thomas was prescribed inhaled therapy with what was then considered standard treatment – that is, fluticasone propionate 500 mcg and salmeterol xinafoate 50 mcg one inhalation twice daily. Mounting evidence from large clinical trials has led to changes in prescribing recommendations. Observations over the past 10 years have shown that ICS use, especially in high doses, is associated with an increased likelihood of pneumonia, skin thinning, oral candidiasis, hoarseness, increased risk of osteoporosis and increased likelihood of poor diabetes control, and these should make one wary of initiating an ICS in a patient with COPD without clear-cut reasons.[3]

Many trials over the past 20 years have shown that an ICS/LABA combination reduces the likelihood of COPD exacerbations in patients with a history of exacerbations and lower lung function (e.g. an FEV_1 <50% predicted). Some recent trials have demonstrated, however, that LAMA/LABA combinations are at least as effective as ICS/LABA combinations in reducing exacerbation frequency. Nevertheless, it is acknowledged that there are definitely patients with COPD who benefit from an ICS/LABA. The characteristics cited above help to delineate in which patients ICS/LABA treatment should be considered, and this emphasises how important good patient assessment is before initial therapeutic decisions are made.

Reviewing Thomas' medications

Given his level of symptoms, mild airflow limitation, absence of asthma and low risk of exacerbations, Thomas should not require an ICS. Several recent trials have demonstrated that, in such patients, it is safe to stop the ICS and maintain the patient on a LAMA alone or a LAMA/LABA combination. (Figures 3 and 4).[5,6] In this case scenario, it is feasible for Thomas to discontinue use of fluticasone propionate 500 mcg and salmeterol xinafoate 50 mcg and continue just the tiotropium bromide. When he is reviewed, Thomas is relieved about the suggestion to stop the ICS/LABA combination, revealing that it makes his mouth uncomfortable, and that he has had some hoarseness since it was first prescribed. He also does not like the idea that muscle weakness and osteoporosis might interfere with his golfing.

Thomas returns to your practice after four weeks of taking only the LAMA tiotropium

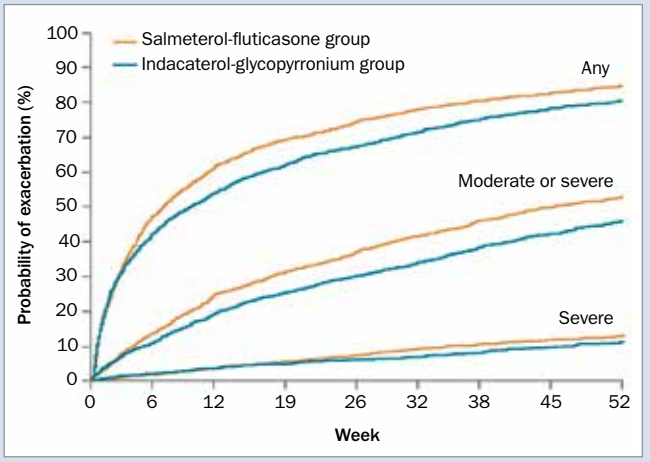

Figure 3. The time to first exacerbation of any severity, time to the first moderate or severe exacerbation and time to the first severe exacerbation in a group of patients receiving treatment with indacaterol and glycopyrronium (LABA plus LAMA) and another group of patients receiving treatment with salmeterol and fluticasone (LABA plus ICS).
Reproduced with permission from Wedzicha JA, et al; FLAME Investigators. N Engl J Med 2016; 374: 2222-2234.[5]

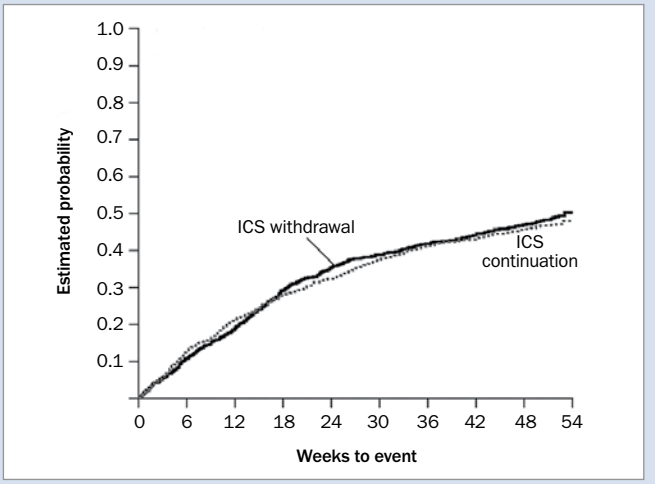

Figure 4. A Kaplan-Meier curve for the estimated probability of moderate or severe exacerbations of chronic obstructive pulmonary disease (COPD) showing no significant difference between a group assigned to withdrawal of inhaled corticosteroids (ICS) and a group assigned to continued ICS treatment.
Reproduced with permission from Magnussen H, et al. N Engl J Med 2014; 371: 1285-1294.[6]

bromide. He has noticed a small increase in breathlessness with exercise restriction, despite his device technique being good. According to the COPD-X guidelines, a LABA should now be added to the LAMA he is already taking. This cannot be achieved with the HandiHaler device he is using, but a combination form of tiotropium with the LABA olodaterol can be administered via the Respimat device. An alternative would be to switch to a different LAMA/LABA combination. Another available capsulated dry-powder inhaler is indacaterol and glycopyrronium administered via the Breezhaler device. Other alternatives are vilanterol trifenatate and umeclidinium bromide via the Ellipta device or formoterol (eformoterol) fumarate dihydrate and aclidinium bromide via the Genuair device.

Further investigations

The description of Thomas' previous chest x-ray indicates that either he had taken a very large inspiration (as instructed) or he has lung hyperinflation. Repeating the chest x-ray may be appropriate to check for signs of cardiac enlargement and/or cardiac failure, given Thomas' longstanding history of hypertension and high level of smoking in the past. His smoking history also raises the risk of lung cancer. Other respiratory diagnoses that could emerge from the chest x-ray are bronchiectasis (although it is not usually evident unless severe) or interstitial lung disease, particularly if chest examination reveals basal crackles or crepitation. Seeking these interpretations from the reporting radiologist in the request form would be helpful. Alternatively, if crackles are present or if Thomas reports a chronic cough that produces sputum or blood, a CT chest scan and referral to a respiratory physician would be highly recommended. **RMT**

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COMPETING INTERESTS: Professor Frith has received honoraria for advising on treatment of COPD, particularly the role of ICS, for Boehringer Ingelheim, Menarini and Novartis; and has received expenses and speaker fees for lectures about ICS use in COPD from Lung Foundation Australia, Boehringer Ingelheim, Optimum Patient Care (Australia) and Novartis. Dr Hancock has received honoraria or speaker's fees and expenses in the past five years from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Teva, Lung Foundation Australia, International Primary Care Respiratory Society and Optimum Patient Care (Australia).