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REVIEW

Optimizing safety of COPD treatments: role of the nurse practitioner

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Abstract: As the prevalence of chronic obstructive pulmonary disease (COPD) continues to grow, management of the disease still faces considerable challenges. Despite the existence of effective pharmacological treatments, patient adherence is often poor. Side effects of medications and patients' concerns about potential side effects may contribute to poor adherence. Situated as they are at the frontline of patient care in the clinic, nurse practitioners play an important role in the management of COPD. This review discusses the current literature on medications available for management of COPD, focusing primarily on their safety and tolerability. This information can be particularly important for nurse practitioners, who can be invaluable in identifying side effects, and providing education to patients with COPD on the available treatments and the associated side effects. By helping patients to understand the balance of benefits and risks of treatment, nurse practitioners may be able to help improve adherence and thereby improve patient outcomes.

Keywords: chronic obstructive pulmonary disease, safety, treatment, role, nurse practitioner

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death and the fastest growing of the major causes of mortality in the United States.[1] More than 12 million adults were diagnosed with COPD in 2007,[2] and it has been estimated that a similar number of people with the disease remain undiagnosed.[3] Nurse practitioners are ideally placed to play an important role in the early diagnosis and management of COPD. As the prevalence of COPD rises, these patients are likely to make up an increasing proportion of the nurse practitioner's caseload.

Management of COPD involves both pharmacological and nonpharmacological aspects. Pharmacological management can be complex because COPD is a chronic, progressive condition in patients who often suffer from comorbidities.[4] As with many chronic conditions, patients with COPD may require long-term treatment, which may increase the risk of adverse events and raise concerns about adherence to prescribed medication. Chronic disease management increasingly involves a collaborative team approach, with nurse practitioners central to the team, although distribution of tasks between team members varies. The purpose of this review is to discuss the role of nurse practitioners in the management of patients with COPD, with a particular focus on issues concerning the safety and tolerability of pharmacological therapy.

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COPD: an overview

The chronic airway limitation characteristic of COPD is due to inflammation that results in obstruction of the small airways and destruction of lung parenchyma.[4] Common symptoms include chronic cough, sputum production, and progressive, persistent dyspnea that worsens with exertion. COPD can be prevented and existing COPD can be treated, but the disease is incurable and the airway limitation is not fully reversible.[4] As COPD progresses, patients are forced to limit their activities and may experience depression and a decline in their quality of life.[5] Patients with COPD also commonly experience comorbid conditions related to aging and/or smoking, including cardiovascular disease, osteoporosis, and depression.[4]

Smoking is by far the most common risk factor for development of COPD, but other factors such as outdoor, occupational, and indoor air pollution may also cause COPD in the absence of smoking.[4] Factors such as genetics, infections, nutrition, and oxidative stress may also have a role in the development and/or progression of COPD. The prevalence of COPD rises sharply with age;[6] a meta-analysis of studies from 28 countries estimated the prevalence of COPD in individuals aged ≥ 40 years at 9.7% and in individuals aged ≥ 65 years at 15.0%.[7] Furthermore, even if smoking rates were to decline dramatically, the prevalence of COPD may continue to rise over the coming years due to aging of the population and the history of smoking.[8] Historically, the prevalence of COPD has been higher among men than women, although recent trends suggest that this gender difference may be declining in regions where smoking rates are similar between the genders.[9] Despite the existence of risk factors and development of symptoms, many patients may be unaware of existing COPD. For example, a meta-analysis on the global prevalence of the disease estimated that 9.2% of the population met spirometric criteria for COPD but only 4.9% reported a doctor's diagnosis of the disease.[7]

National and international guidelines, including those prepared by the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[4] American Thoracic Society/European Respiratory Society,[10] and Canadian Thoracic Society,[11] provide recommendations for the diagnosis, management, and treatment of COPD. According to the GOLD guidelines updated in December 2011, spirometry is now required to make a confident diagnosis of COPD, whereas previously it was used to support the diagnosis.[4] The fixed ratio of postbronchodilator forced expiratory volume in one second (FEV_1) to the forced vital capacity (FVC), or FEV_1/FVC, needs to be < 70%[4] and the staging system of spirometric classification, which has now been replaced with grading, uses: $FEV_1 \geq 80\%$ predicted (GOLD 1, mild); $50\% \leq FEV_1 < 80\%$ predicted (GOLD 2, moderate); $30\% \leq FEV_1 < 50\%$ predicted (GOLD 3, severe); and $FEV_1 < 30\%$ predicted (GOLD 4, very severe). In order to assess symptoms in patients, the GOLD guidelines suggest the use of the Modified British Medical Research Council questionnaire or the COPD Assessment Test.[4] Canadian Thoracic Society guidelines also suggest incorporating measures of dyspnea and disability into clinical assessment of disease severity to individualize management decisions.[11] It is not always possible to distinguish COPD from chronic asthma in some patients, so it is assumed that the two exist together.[4]

One of the most important initial steps for management of COPD is to reduce exposure to risk factors, including cigarette smoke and/or occupational dusts, fumes, and gases. Given the leading role of smoking as a cause of COPD, it may not be surprising that smoking cessation is the only intervention shown to reduce the rate of disease progression and related mortality.[12] Patient education is a particularly important component of smoking cessation intervention, and education about some aspects of COPD may help patients to cope.[4]

Pharmacological therapies are useful to manage symptoms, and some are indicated to reduce exacerbations, which become increasingly important goals as the disease progresses. Various classes of drugs may be appropriate based on the patient's symptoms, risk of exacerbation, and grade of airflow limitation (Table 1).[4] In general, short-acting bronchodilators are recommended as needed at all stages of the disease, and long-acting bronchodilators may be appropriate as regular maintenance therapy for patients with moderate to severe COPD. The long-acting anticholinergic, tiotropium, was also recently approved for reduction of exacerbations in patients with COPD.

An inhaled corticosteroid (ICS) may be appropriate as add-on therapy to long-acting bronchodilators in patients with severe and very severe COPD. For instance, a combination of the long-acting β-adrenergic, salmeterol, and fluticasone, an ICS, is indicated to reduce exacerbations in patients with COPD with a history of exacerbations.[4] Systemic corticosteroids are recommended in the treatment of acute exacerbations of COPD, but their long-term use is not recommended due to lack of evidence of benefit and side effects.[13]

The 3-year TOwards a Revolution in COPD Health (TORCH)[14] and 4-year Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT)[15] trials

Table 1 Therapy at each grade of chronic obstructive pulmonary disease as recommended by GOLD (Global Initiative for Chronic Obstructive Lung Disease)

Patient group	First choice	Second choice	Alternative choice[b]
Initial pharmacologic management of COPD[a]			
A	Short-acting anticholinergic prn or short-acting beta$_2$-agonist prn	Long-acting anticholinergic or long-acting beta$_2$-agonist or short-acting beta$_2$-agonist and short-acting anticholinergic	Theophylline
B	Long-acting anticholinergic or long-acting beta$_2$-agonist	Long-acting anticholinergic and long-acting beta$_2$-agonist	Short-acting beta$_2$-agonist and/or short-acting anticholinergic Theophylline
C	Inhaled corticosteroid + long-acting beta$_2$-agonist or long-acting anticholinergic	Long-acting anticholinergic and long-acting beta$_2$-agonist	Phosphodiesterase-4 inhibitor Short-acting beta$_2$-agonist and/or short-acting anticholinergic Theophylline
D	Inhaled corticosteroid + long-acting beta$_2$-agonist or long-acting anticholinergic	Inhaled corticosteroid and long-acting anticholinergic or inhaled corticosteroid + long-acting beta$_2$-agonist and long-acting anticholinergic or inhaled corticosteroid + long-acting beta$_2$-agonist and phosphodiesterase-4 inhibitor or long-acting anticholinergic and long-acting beta$_2$-agonist or long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine Short-acting beta$_2$-agonist and/or short-acting anticholinergic Theophylline

Notes: Group A: few symptoms and low risk of exacerbations. GOLD 1 or 2 (mild/moderate airflow limitation) and/or 0–1 exacerbation per year and mMRC grade 0–1 or CAT score < 10. Group B: more significant symptoms; low risk of exacerbations. GOLD 1 or 2 (mild/moderate airflow limitation) and/or 0–1 exacerbation per year and mMRC grade ≥ 2 or CAT score ≥ 10. Group C: few symptoms; high risk of exacerbations. GOLD 3 or 4 (severe/very severe airflow limitation) and/or ≥2 exacerbations per year and mMRC grade 0–1 or CAT score < 10. Group D: many symptoms; high risk of exacerbations. GOLD 3 or 4 (severe/very severe airflow limitation) and/or ≥2 exacerbations per year and mMRC grade ≥ 2 or CAT score ≥ 10. [a]Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference; [b]medications in this column can be used alone or in combination with other options in the first and second columns.

[a]Copyright © 2011, Global Initiative for Chronic Obstructive Lung Disease. Reproduced with permission from Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated Dec 2011. Available from: http://www.goldcopd.org. Accessed July 5, 2012.[4]

Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; mMRC, Modified British Medical Research Council; prn, taken as needed.

both included mortality as an endpoint. In TORCH, the difference in mortality between the salmeterol/fluticasone and placebo treatment groups did not reach statistical significance (salmeterol/fluticasone 12.6%, placebo 15.2%; hazard ratio [HR] 0.825; 95% confidence interval [CI]: 0.681–1.002; $P = 0.052$).[14] In UPLIFT, all-cause mortality was significantly lower in the tiotropium group compared with placebo while patients were receiving treatment (up to day 1440, tiotropium 14.4%, placebo 16.3%; HR 0.87; 95% CI: 0.76–0.99) but not significantly different when data from the following 30 days were included (up to day 1470, tiotropium 14.9%, placebo 16.5%; HR 0.89; 95% CI: 0.79–1.02).[15,16] In both TORCH and UPLIFT, mean FEV_1 was improved.[14,15] A post hoc analysis of TORCH suggested that salmeterol/fluticasone reduced the rate of FEV_1 decline compared with placebo.[17] These treatments and the associated side effects are considered in more detail in the following section.

Safety and tolerability of COPD medications

Table 2 summarizes the side effects of COPD treatments observed in clinical practice, and outlines alerts for nurse practitioners, derived from cautions described in the product prescribing information. Most side effects experienced with medications for COPD are relatively minor, and are bothersome to the patient rather than actually harmful; however, rare side effects that are potentially very serious may occur, and associations with other side effects have been reported, although a definite link to treatment is not proven in all cases (Table 2). Both the experience of unpleasant side effects and a lack of patient knowledge about the disease and treatments can increase the risk of nonadherence.[18] The discussion below addresses side effects frequently encountered in clinical practice, either as actual events experienced by patients or as potential concerns expressed by the patient.

Table 2 Most common potential side effects reported with COPD medications

Drug class	Side effects[a]	Nurse practitioner alert[b]
Inhaled β_2-agonists SABAs (albuterol and levalbuterol) and LABAs (salmeterol and formoterol)	**Headache**[14,19–22] **Pharyngitis**[20,23] **Musculoskeletal pain**[19,20,24,25] Elevated heart rate Elevated blood pressure Hyperglycemia Hypokalemia Palpitation Tremor Cardiovascular adverse effects[c] Increased mortality[c]	Cardiovascular disease, diabetes mellitus, glaucoma, hyperthyroidism, hypokalemia, seizure disorders
Inhaled anticholinergics SAACs (ipratropium) and LAACs (tiotropium)	**Dry mouth**[15,26–28] **Bitter taste**[28] **Constipation**[15,27] Cough Headache Nausea Pain Increased ocular pressure Urinary flow obstruction	Glaucoma, prostatic hyperplasia, or bladder-neck obstruction Avoid spraying aerosol into eyes
Methylxanthines (theophylline)	**Tremor**[29] **Nausea**[29,30] **Vomiting**[29] Arrhythmias Seizures Abdominal pain Diarrhea Hypokalemia Hyperglycemia Sinus tachycardia Nervousness	Use with extreme caution in peptic ulcer disease, seizure disorders, cardiac arrhythmias Need for more intensive monitoring in patients > 60 years, acute pulmonary edema, congestive heart failure, cor pulmonale, fever, hypothyroidism, liver disease, sepsis with multiorgan failure, shock, smoking Care with drug–drug interactions and toxicity
Corticosteroids Inhaled (fluticasone, budesonide, mometasone, beclomethasone, flunisolide, ciclesonide)	**Hoarseness**[31,32] **Oral candidiasis**[14,31–34] **Skin bruising**[31,32] Pneumonia Osteoporosis Cataracts Glaucoma	Patients transferring from oral steroids, emerging allergies, reduced liver function, pulmonary tuberculosis
Oral (prednisone, prednisolone)	**Hyperglycemia**[35–40] **Insomnia**[35,40] **Weight gain**[35,40] Hoarseness Oral candidiasis Skin bruising Myopathy (long-term use) Respiratory failure (long-term use)[c] Facial erythema Fluid retention Headache Hypertension Hypokalemic alkalosis Impaired wound healing Loss of muscle mass Menstrual irregularities Muscle weakness Pathologic fracture Potassium loss	Needs gradual reduction of dosage after prolonged use Enhanced effect on patients with hypothyroidism and cirrhosis Ocular herpes Psychic derangements, emotional instability, psychotic tendencies Ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis, myasthenia gravis Kaposi's sarcoma Discontinuation of corticosteroids may result in clinical remission Drug–drug interaction with cyclosporin

(*Continued*)

Table 2 (*Continued*)

Drug class	Side effects[a]	Nurse practitioner alert[b]
	Sodium retention	
	Tendon rupture	
	Thin fragile skin	
	Abdominal distension	
	Cataracts	
	Convulsions	
	Glaucoma	
	Osteoporosis	
	Pneumonia	
	Vertigo	

Notes: [a]Side effects most commonly identified in randomized clinical trials shown in **bold**; [b]derived from warnings in prescribing information; [c]suggested side effects (cause not proven).
Abbreviations: SABAs, short-acting β_2-agonists; LABAs, long-acting β_2-agonists; SAAC, short-acting anticholinergic; LAAC, long-acting anticholinergic.

Short-acting bronchodilators

Short-acting bronchodilators include short-acting β_2-agonists and the short-acting anticholinergic agent, ipratropium.[4]

Short-acting β_2-agonists

Short-acting β_2-agonists, such as albuterol and levalbuterol, are usually available in a pressurized metered-dose inhaler or as a solution for nebulization, and are recommended for as-needed use to relieve symptoms at all stages of COPD. These agents are generally well tolerated, but patients may suffer from occasional troublesome class side effects, such as hypokalemia, hyperglycemia, elevated heart rate, tremors, headache, and palpitation, which are well established, predictable, and dose related (Table 2).[41,42]

Potential concerns about possible cardiovascular side effects and increased mortality associated with β_2-agonists (particularly fenoterol) used to treat asthma were raised in the late 1980s. Although further studies and meta-analyses have provided conflicting evidence,[43,44] the GOLD guidelines indicate that no association has been found between β_2-agonist use and increased mortality in COPD (Table 3).[4] However, adverse effects may occur more frequently in patients with underlying cardiac comorbidities; therefore, short-acting β_2-agonists should be used with care in patients with cardiovascular disease.

Ipratropium bromide

Ipratropium is well established as a short-acting bronchodilator in COPD, available in a pressurized metered-dose inhaler or as a solution for nebulization, and indicated for regular use four times daily as maintenance therapy for COPD. As with other anticholinergics, dry mouth is the main side effect of this drug.[54] Other side effects include increased intraocular pressure and urinary outflow obstruction (Table 2), so care should be taken with ipratropium in patients with glaucoma or prostatic hyperplasia.[54–56] Some patients complain of a bitter taste, though this may be considered a difference from other treatments rather than a side effect.[55] Some studies have also suggested a possible association between ipratropium and an increase in cardiovascular events and mortality (Table 3).[12,48,49] Evidence from a meta-analysis by Singh et al that considered ipratropium and tiotropium together suggested a possible association between anticholinergic treatment and increased mortality and cardiovascular events (Table 3).[50] However, the United States Food and Drug Administration recently concluded that the available evidence demonstrates that tiotropium does not increase the risk of stroke, heart attack, or death.[57]

Long-acting bronchodilators

Long-acting bronchodilators are recommended as regular maintenance therapy for patients with moderate to severe COPD (Table 1).[4] They include long-acting β_2-agonists (LABAs) and the long-acting anticholinergic agent, tiotropium.

Long-acting β_2-agonists

LABAs are available in the United States as dry powder inhalers (salmeterol and formoterol) or as a solution for nebulization (formoterol and arformoterol), taken twice daily for maintenance therapy. The most common adverse events highlighted in the prescribing information for LABAs are similar to those for short-acting β_2-agonists (Table 2).[58–60] Concerns about rare cardiovascular adverse effects and increased mortality have also been raised for LABAs, especially by studies in patients with asthma, but there is conflicting evidence on these side effects in patients with COPD (Table 3). The Salmeterol Multicenter Asthma Research Trial found a small

Table 3 Conflicting evidence for increased risk of cardiovascular events and mortality with bronchodilators

Drug class	Study description	Outcome	Reference
SABAs	Meta-analysis of randomized, placebo-controlled trials of β_2-agonists in patients with obstructive airways disease (n = 7962)	Increased risk versus placebo of adverse cardiovascular events	Salpeter et al[43]
	Population-based cohort study of patients with COPD (n = 12,090)	No increased risk of fatal or nonfatal acute myocardial infarction	Suissa et al[44]
LABAs	Meta-analysis of randomized, placebo-controlled trials of β_2-agonists in patients with obstructive airways disease (n = 7962)	Increased risk versus placebo of adverse cardiovascular events	Salpeter et al[43]
	Randomized, double-blind, placebo-controlled study of formoterol in patients with COPD (n = 204)	No increased risk versus placebo of adverse cardiovascular events	Campbell et al[45]
	TORCH: randomized, double-blind, placebo- and active-controlled trial of salmeterol and fluticasone in patients with COPD (n = 6112)	No increased risk of mortality for salmeterol or salmeterol-fluticasone combination versus placebo	Calverley et al[14]
	Meta-analysis of randomized, controlled trials of salmeterol and formoterol versus placebo or anticholinergics in patients with COPD (n = 20,527)	No increased risk of respiratory death versus placebo	Rodrigo et al[46]
	Meta-analysis of randomized, double-blind, placebo-controlled trials of salmeterol in patients with COPD (n = 1443)	No increased risk of cardiovascular events versus placebo	Ferguson et al[47]
Anticholinergics	Lung Health Study: randomized, placebo-controlled trial of smoking intervention and ipratropium in patients with mild to moderate lung function impairment (n = 5887)	Increased risk of death and hospitalization for cardiovascular disease and coronary artery disease versus placebo (approached statistical significance)	Anthonisen et al[12]
	Cohort study of ipratropium in patients with COPD (n = 82,717)	Increased risk of cardiovascular events	Ogale et al[48]
	Case–control study of various respiratory medications in patients with COPD (n = 32,130 cases and 320,501 controls)	Increased risk of all-cause and cardiovascular mortality with ipratropium	Lee et al[49]
	Meta-analysis of randomized, controlled trials of anticholinergics in patients with COPD (n = 14,783)	Increased risk of cardiovascular mortality, myocardial infarction, or stroke (composite endpoint)	Singh et al[50]
	Meta-analysis of randomized, double-blind, placebo-controlled trials of tiotropium in patients with obstructive lung disease (n = 7819)	No increased risk of all-cause, respiratory, and cardiovascular mortality	Kesten et al[27]
	Meta-analysis of randomized, placebo-controlled or active-controlled trials of tiotropium in patients with COPD (n = 8002)	No increased risk of pulmonary or all-cause mortality versus placebo	Barr et al[51]
	UPLIFT: randomized, double-blind, placebo-controlled trial of tiotropium (n = 5993)	No increased risk of mortality versus placebo	Tashkin et al[15]
	Meta-analysis following methodology of Singh et al,[50] adding UPLIFT data	No increased risk of cardiovascular mortality, myocardial infarction, or stroke (composite endpoint)	Oba et al[52]
	Pooled analysis of 30 double-blind, placebo-controlled studies (n = 19,545)	Decreased risk of all-cause mortality and cardiovascular events (composite endpoint)	Celli et al[53]

Notes: Shaded areas indicate studies showing increased risk; unshaded areas indicate studies showing no increased risk.
Abbreviations: SABAs, short-acting β_2-agonists; LABAs, long-acting β_2-agonists; TORCH, TOwards a Revolution in COPD Health; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium study.

but significant increased risk of respiratory/asthma-related mortality compared with placebo in patients with asthma[61] and a meta-analysis of studies of LABAs in patients with COPD and asthma found an increased risk of treatment-related cardiovascular events.[43] In contrast, no increased risk compared with placebo was found in two other studies,[14,45] a systematic review,[46] and a pooled analysis[47] that included only patients with COPD. The Food and Drug Administration has now recommended that LABAs should not be used without an asthma controller medication for treatment of patients with asthma,[62] but LABAs are still approved as monotherapy for management of COPD.

Tiotropium bromide

Tiotropium bromide is the only long-acting anticholinergic on the market, and is available in a dry powder inhaler. It is taken once daily as a maintenance bronchodilator therapy and is indicated for reduction of exacerbations in COPD.[63]

Adverse effects associated with tiotropium are similar to those observed with ipratropium, with the most common side effect being dry mouth (Table 2).[52,63] Again, tiotropium should be used with caution in patients with glaucoma or prostatic hyperplasia.

Although the meta-analysis by Singh et al that considered ipratropium and tiotropium together suggested a possible association between anticholinergic treatment and increased mortality and cardiovascular events (Table 3),[50] another meta-analysis[51] and two pooled analyses[27,53] showed no increased risk with tiotropium treatment. Furthermore, results from the UPLIFT study, a large-scale, 4-year, randomized controlled trial, indicated that tiotropium reduced cardiac morbidity.[15] In light of these data, the Food and Drug Administration recently concluded that tiotropium does not increase the risk of stroke, heart attack, or death.[57]

Methylxanthines

Theophylline is the most widely used methylxanthine in the treatment of COPD, but owing to toxicity at higher doses, other bronchodilators are usually preferred.[4] Dose-related adverse effects include nausea, vomiting, seizures, and arrhythmias (Table 2).[64]

Corticosteroids

Inhaled corticosteroids

ICS are recommended as add-on therapy in combination with long-acting bronchodilators for patients with severe and very severe COPD (Table 1).[4] The most commonly prescribed ICS are fluticasone[65] and budesonide.[66] They are available as pressurized metered-dose inhalers or dry powder inhalers, and are usually administered twice daily. ICS are not recommended for monotherapy in COPD.

Common side effects of ICS include bruising of the skin,[31,32] oral candidiasis, and hoarseness (Table 2).[67] More serious side effects that may occur in a small number of patients include pneumonia and a reduction in bone mineral density (a precursor to osteoporosis). An increased risk of pneumonia with ICS in patients with COPD has been shown in several randomized trials[14,68–70] and a meta-analysis.[71] There is evidence both supporting[72–74] and refuting[75,76] the effect of ICS on bone mineral density and/or bone fractures (Table 4). The results from these studies may be confounded by disease severity,[77] but it is still recommended that bone mineral density is assessed prior to prescribing any ICS in COPD and that it is carried out periodically thereafter. There is also a small risk of a dose-dependent increase in cataracts and glaucoma with ICS[67] and it is recommended that regular eye examinations be performed on patients receiving these drugs.

Oral corticosteroids

Oral corticosteroids, prednisone and prednisolone, may be administered in patients with very severe COPD and acute exacerbations, but long-term use is not recommended, especially at the high doses generally required, due to potentially harmful adverse events that may contribute to the development of diabetes, hypertension, osteoporosis, and steroid-induced myopathy (Table 2).[4,13]

Phosphodiesterase-4-inhibitors

The phosphodiesterase-4-inhibitor, roflumilast, was approved by the Food and Drug Administration in 2011 to reduce the frequency of exacerbations in patients with severe COPD. Adverse events associated with roflumilast include diarrhea, weight loss, nausea, insomnia, headache, and back pain.[78] In two clinical trials comparing the effect of salmeterol or

Table 4 Conflicting evidence for increased risk of bone mineral density loss with inhaled corticosteroids

Study description	Outcome	Reference
Lung Health Study: randomized, placebo-controlled study of triamcinolone in patients with COPD (n = 1116)	Significantly lower bone density of the femur and lumbar spine versus placebo, but no increased risk of bone fracture	Lung Health Study Research Group[72]
Case–control analysis of patients with hip fracture in general practice (n = 16,341 cases and 29,899 controls)	Higher risk of hip fracture with inhaled corticosteroids	Hubbard et al[73]
Case–control study in COPD patients of the association between inhaled corticosteroid use and vertebral fractures (n = 1708 cases and 6817 controls)	High doses of inhaled corticosteroid were associated with an increased risk of vertebral fracture	Lee and Weiss[74]
Randomized, placebo-controlled trial of budesonide in patients with COPD (n = 912)	No change in bone mineral density or fracture rates versus placebo	Johnell et al[75]
TORCH: randomized, double-blind, placebo- and active-controlled trial of salmeterol and fluticasone in patients with COPD (n = 658)	No increased risk of bone mineral density loss or fractures with fluticasone or salmeterol-fluticasone combination versus placebo	Ferguson et al[76]

Notes: Shaded areas indicate studies showing increased risk; unshaded areas indicate studies showing no increased risk.
Abbreviations: COPD, chronic obstructive pulmonary disease; TORCH, TOwards a Revolution in COPD Health.

tiotropium in the presence or absence of roflumilast, it was evident that weight loss was greater in patients also experiencing headache and/or gastrointestinal adverse events, indicating a causal relationship between these adverse events.[79] As a consequence of the greater potential for weight loss with roflumilast, regular monitoring of weight should be encouraged in patients treated with this drug.

Combination products

Combination products, including ipratropium plus albuterol,[80] salmeterol plus fluticasone,[81] and formoterol plus budesonide,[82] are commonly prescribed as maintenance therapy for patients with COPD. Salmeterol plus fluticasone is indicated to reduce the risk of exacerbations in patients with a history of exacerbations.[81] Generally, the side effect profiles of the combination products reflect those of the individual components (Table 2),[80–82] and no additional safety concerns have been reported.

Role of the nurse practitioner in COPD

COPD is a chronic disease, often with gradual onset, and is often seen in older patients who may have comorbidities that also require treatment, complicating its diagnosis and management. Limited physician time may lead to inadequacies in the diagnosis and management of COPD.[83] Awareness of COPD and comorbid conditions among patients is low,[84] and communication between patients and health care providers may be poor.[85] Strengthening the role of the nurse practitioner in management of COPD could be an important strategy to improve patient education and communication. The scope of the nurse practitioner's role within the disease management team in COPD may vary between clinics, but could include diagnosis, prescription, patient monitoring, ongoing evaluation of treatment success, and modification of treatment where required (Figure 1). In some clinics, some of these roles may be carried out by other staff, while other tasks, such as writing and modifying prescriptions, are restricted to physicians and nurse practitioners.

As with other chronic diseases, adherence to therapy is often poor among patients with COPD.[18,86] Patients may fail to adhere to treatment because they have inadequate knowledge of the disease and its treatments,[18,86,87] which could potentially result in unrealistic expectations of treatment outcomes. Alternatively, patients may be discouraged by unpleasant side effects[18] or reports of potential side effects. Even if the patient attempts to adhere to therapy, they may underuse, overuse, or improperly use the inhaler devices.[18] Furthermore, patients

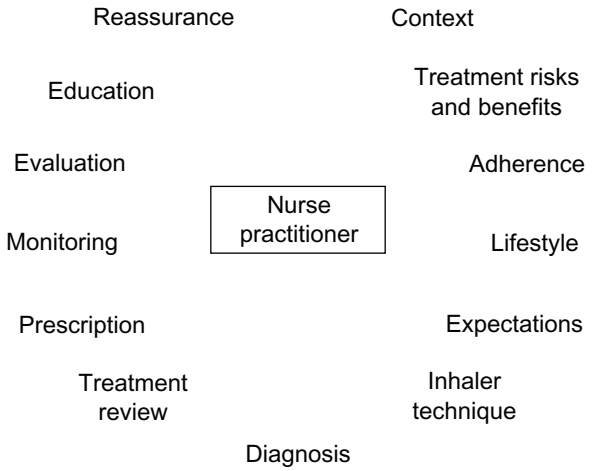

Figure 1 Nurse practitioner's role in management of COPD.

may be prescribed several COPD medications as well as medications for other comorbidities, thus complicating the treatment regimen.[18,87] Because COPD is a chronic disease, patients may receive long-term pharmacologic treatment. Therefore, nurse practitioners should be alert to the possibility of patients developing diseases for which COPD medications can be a risk factor, such as osteoporosis, diabetes, or cataracts. Nurse practitioners can play an important role in addressing and resolving these issues.

Communication between clinic staff and patients is critical to improving adherence and outcomes.[88] The nurse practitioner is ideally situated to educate the patient on the nature of COPD, the lifestyle changes required, and realistic expectations of potential therapeutic benefits. Nurse practitioners can also provide instruction regarding proper use of devices and help patients to understand better the potential benefits and risks of treatments. The nurse practitioner may offer practical advice on the management of multiple therapies, such as creating a medication administration schedule tailored to suit individual lifestyles. In addition, the nurse practitioner can help to educate the patients about self-monitoring of symptoms and can help to determine whether any dosage adjustments or other changes in treatment are required.

Practical considerations for nurse practitioners

Nurse practitioners play a key role in core teams managing the ongoing treatment of COPD. Handling patient concerns about safety and tolerability is an important aspect of the nurse practitioner's responsibilities, and may help to improve adherence to treatment. Therefore, it is important that the nurse practitioner establishes an ongoing dialog with patients,

so as to understand their issues and concerns, and to provide practical education about their illness and its management and treatment.

Nurse practitioners should take a proactive approach to addressing safety and tolerability issues with patients when they are first prescribed a particular medication. Patients should leave the clinic with a good understanding of what side effects may occur, how serious the side effects may be, and what action they should take if a particular side effect occurs. The nurse practitioner should ascertain whether the patient already has any concerns that may prevent him or her from filling the prescription, and try to address them.

When a patient expresses a concern, nurse practitioners must recognize the need for an individual approach to that patient. They need to assess whether the concern stems from a side effect that the patient has actually experienced or a hypothetical concern based on something they have read or heard about. Some patients may be particularly bothered by minor side effects, and adherence is more likely to be a problem in these patients. Some side effects may present a more serious safety concern for certain patients (eg, those with existing cardiovascular disease). The nurse practitioner must assess the best approach, such as continuing with treatment and providing reassurance, continuing with treatment and taking steps to avoid or minimize the side effect, considering other medications or treatment options, or considering whether referral to a specialist is required. Patient concerns should be reassessed regularly. Importantly, the nurse practitioner can help patients to put the side effects they experience or fear into context, helping them to understand that appropriate treatment may be expected to reduce symptoms and exacerbations, and improve their quality of life, whereas they risk continued symptoms and possibly COPD exacerbations in the absence of adherence to treatment.

Conclusion

Despite the growing prevalence of COPD, a lack of knowledge and/or concerns about the side effects of medications can contribute to poor adherence with treatment in these patients. Nurse practitioners can play an important role in the management of the disease by providing patients with education and helping to monitor and individualize their treatments. In particular, nurse practitioners can help to address patients' concerns by providing them with information about the possible occurrence of side effects, advising them on appropriate action, and ensuring that they understand the balance between the potential benefits of treatment and the potential risks of side effects.

Disclosure

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