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DRUGS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability.[4,7] This major airflow obstruction affects over 10 million Americans and costs over $18 billion annually.[16] Exacerbations are associated with 50-70% of these costs.[2] Smoking contributes to 80% of COPD.[9] People with COPD have increased risk of cardiovascular disease, osteoporosis, and muscle wasting.[20]

Evidence-based treatment guidelines include the Global Initiative for Chronic Obstructive Lung Disease (GOLD), and the joint American Thoracic Society (ATS) and European Respiratory Society (ERS) position paper.[2,5] GOLD acknowledges COPD is not easy to differentiate from chronic asthma. Management of COPD is guided by assessing an individual's disease severity and then implementing a stepwise treatment plan (see Table 1). No treatment has been proven to reduce the rate of decline in lung function.[2]

A COPD management program includes four components: assess and monitor disease, reduce risk factors, manage stable COPD, and manage exacerbations. Smoking cessation is the only proven way to delay progression of COPD, as well as the most cost effective.[5] Influenza vaccination reduces serious illness and death in COPD by 50%.[9] Routine pneumococcal vaccination is of controversial benefit.[5,9]

Pharmacological treatment can improve and prevent symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance.

BRONCHODILATORS

Once mild COPD is present, a short-acting bronchodilator is indicated to use as needed for rescue.[2,5] A Cochrane review found ipratropium and short-acting B-2 agonists were similarly safe and effective for bronchodilation in COPD.[15] GOLD indicates that initial therapy needs to be tailored to the situation. Improved physiologic capacity may occur, even for the sedentary, despite unmeasurable changes in lung function.[9] Patients with loss of skeletal muscle mass may not benefit from bronchodilators.[9]

BETA-2-AGONISTS

Short-acting inhaled B2-agonists include albuterol, levalbuterol, pirbuterol, and terbutaline. A Cochrane review found regular use of short-acting beta-agonists associate with improved lung function and decreased breathlessness in stable COPD.[12] Regular use of short-acting B2-agonists over three months associates with slight, but significant, loss of effectiveness.[9] Adverse effects include palpitations, arrhythmias, hypokalemia, and muscle cramps.[8,9] Paradoxical bronchospasm, sometimes life-threatening, may occur with B2-agonists.[13] Most studies comparing albuterol (equal parts R and S isomers) to levalbuterol (R isomer) concerned asthma in children. A few involved COPD. A randomized, double-blind, placebo-controlled trial that compared nebulized levalbuterol and racemeic albuterol in 30 patients with stable COPD found single-dose, as needed levalbuterol offered no advantage over albuterol.[23]

Large studies show long-acting B2-agonists improve bronchodilation, reduce symptoms, and improve quality of life.[8] Meta-analysis of nine controlled clinical trials shows a 21% decline in exacerbation rates in COPD.[27] Gold recommends adding a routine long-acting bronchodilator to a short-acting agent in moderate COPD.[5] Long-acting inhaled B2-agonists last over 12 hours and are not effective for acute episodes. Adverse effects rise with over 50 mcg BID for salmeterol; 12 mcg BID for formoterol.[8]

If a patient has COPD co-existing with asthma, beware of the boxed warning stating that a small, but significant increase in serious asthma episodes or asthma-related deaths is associated with salmeterol. FDA added the warning due to results from a large placebo-controlled safety study that was stopped early. Post-marketing surveys prompted FDA to suggest serious adverse effects are less likely with salmeterol when also using an ICS.[8, 14]

ANTICHOLINERGICS

Inhaled anticholinergics are an alternative to long-acting B2-agonists for moderate COPD.[5] These drugs block acetylcholine, resulting in site-specific bronchodilation and minimal systemic absorption.[9] The short-acting anticholinergic ipratopium (Atrovent) acts within 10 to 15 minutes.

The long-acting anticholinergic tiotropium (Spiriva) is used once daily for COPD. Studies submitted to the FDA showed tiotropium significantly improved bronchodilation over placebo.[11] However, results for reduction of dyspnea, exacerbations, less rescue medication, and QOL were not deemed clinically meaningful. Dry mouth, the most common adverse effect, occurs more in women and the elderly. Phase 4 studies will investigate the effect of tiotropium on the QT interval.[11] Tiotropium costs three fold more than ipratropium. Tiotropium does not consistently show superiority over ipratropium in the amount of rescue medication used.[11] Although recent reviews suggest the combination of long-acting anticholinergics with long-acting B2-agonists in severe COPD, studies of this combination have not been published. Effects of tiotropium on exercise tolerance await study.[10]

THEOPHYLLINE

A narrow therapeutic window and numerous drug interactions compromises the usefulness of the bronchodilator theophylline.[9] The lowest effective dose should be used.[2] Meta-analysis of 4 randomized, controlled trials found theophylline did not improve clinical variables or symptom scores and was associated with more adverse effects, including arrhythmias.[7] A Cochrane review recommends xanthines not be used for COPD exacerbations, due to modest, inconsistent endpoints and significantly more adverse effects.[18]

STEROIDS

Inhaled corticosteroids (ICS) include beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone. The mechanism responsible for the persistence of the inflammatory response in COPD is not well understood and poorly responsive to glucocorticosteroids.[5]

Evidence from four large prospective 3-year studies failed to show an effect of ICS on the rate of change of FEV1 (Forced Expiratory Volume) in any severity of COPD.[2] Several large studies also showed no improvement in mortality or slowing the rate of decline in lung function with ICS in COPD.[3] Slight improvement in airflow and fewer exacerbations may occur.[2,9]

In advanced COPD, there is evidence the number of exacerbations a year and rate of deterioration in health status are reduced with ICS.[2] Consider ICS when maximum combination of bronchodilators is inadequate, use of antibiotics is frequent, or spirometry shows improvement with ICS. GOLD recommends ICS in severe COPD for repeated exacerbations and when FEV is under 50% predicted.[5] Some clinicians withdraw ICS, then if exacerbations recur, reinstitute ICS.[2]

ICS can induce oral Candid infections, a risk lowered by rinsing the mouth after using dry powder inhalers (DIPs) and using spacers with metered dose inhalers (MDIs).[3] Epidemiological evidence suggests ICS increases risk of hip fracture in a dose-related manner.[3] Lifetime cumulative doses over 2000mg of beclomethasone is associated with development of posterior subcapsular and nuclear cataracts in adults and elderly.[24] Susceptibility to effects on hypothalamic-pituitary-adrenal function, long-term effect on lungs in children, and effects of ICS over decades awaits research.[3, 4]

Six of seven randomized, placebo-controlled trials show benefit with oral and intravenous steroids in COPD exacerbations.[7] Four to seven day courses are effective, but longer than 14 days is of no benefit.[9] Regular use of systemic glucocorticoids increases mortality in stable COPD, and long-term use doubles fracture risk in dose-related manner.[3, 9] Hyperglycemia is a common adverse effect.

COMBINATION THERAPY

GOLD notes that combining drugs with different mechanisms and durations of action may increase bronchodilation for equivalent or lesser adverse effects.[5] ATS/ERS adds that combining inhaled B-2 agonists and corticosteroids is clearly better than monotherapy when FEV is under 50% predicted.[2]

The fixed combination of albuterol/ipratropium (Combivent), is used in COPD when a second bronchodilator is required. No convincing data shows this combination is superior to either drug alone.[7, 25]

The combination of fluticasone/salmeterol (Advair) is approved for COPD associated with chronic bronchitis and is not recommended as initial COPD therapy. It should only be used in patients whose COPD is stable, but severe. Advair in COPD has not been evaluated beyond 6 months.

DEVICES

Proper use of devices is essential. A recent newsletter of The Institute for Safe Medicine Practice carries an article about a patient swallowing formoterol capsules, instead of inserting these into the inhaler.[20] Instructions for most devices are available from http://www.goldcopd.com under resources for inhalers and spacers. Consider spacer devices for outpatients.[2]

CONCLUSION

Much about the treatment of COPD will remain controversial until there is a better understanding of the causal mechanisms and its relationship to other obstructive airway diseases. No current drug therapies prevent the progression of COPD. The recommended management of COPD is based on a step approach related to disease severity. Long-acting bronchodilators are of some clinical benefit for moderate to severe disease, but come at a significant cost. ICS use is of controversial benefit for severe disease. New treatments being explored for COPD include phosphodiesterases, now in clinical trials. The TORCH study of survival in COPD is due in 2006.[21] The best treatment remains prevention.[16]

Reviewed by Chris Blem, PharmD, Legacy Health Systems, and Molly Osborne, MD, PhD, Oregon Health Sciences University.

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Table 1 – COPD Drug Options & Cost Comparisons

Disease Severity[2]	Recommended Treatment	Drug Options	OHP Avg 30-day Cost*
Mild Mild airflow limitation (FEV1/FVC < 70% but FEV1 ≥80% predicted) and usually chronic, productive cough. At this stage, the individual may not be aware that his or her lung function is abnormal.	Begin **Short-acting Bronchodilator PRN** (B-2 Agonist or Anticholinergic) Combination therapy may improve symptoms if monotherapy is insufficient.	**albuterol**	$20
		Atrovent (ipratropium)	$90
		Combivent (albuterol/ipratropium)	$95
		Maxair (pirbuterol)	$100
		Xopenex (levalbuterol)	$235
Moderate Worsening airflow limitation (50% ≤FEV1 < 80% predicted), and usually the progression of symptoms, with shortness of breath typically developing on exertion.	Add **Routine Long-acting Beta-agonist**	Foradil (formoterol)	$85
		Serevent (salmeterol)	$95
Severe Further worsening of airflow limitation (30% ≤FEV1 < 50% predicted), increased shortness of breath, and repeated exacerbations that have an impact on patients' quality of life. If severe, but stable, and chronic bronchitis, consider combination products.	Add **Routine Long-acting Anticholinergic Or Substitute combination of Long-acting B-2 agonist with corticosteroid.**	Spiriva (tritropium)	$110
Very Severe Severe airflow limitation (FEV1 < 30% or FEV1 < 50% predicted) plus chronic respiratory failure. At this stage, quality of life is very appreciably impaired and exacerbations may be life threatening.	Add **Routine Inhaled Corticosteroid**	QVAR (beclomethasone)	$55
		Azmacort (triamcinolone)	$95
		Flovent (fluticasone)	$110
		Aerobid (flunisolide)	$120
		Advair (fluticasone/salmeterol)	$150
		Pulmicort (budesonide)	$215
Inadequate Response To above	Add or substitute **Low-dose theophylline**	**theophylline ER**	$30

*Data from SYBASE Drug2004; 9/1/04-10/31/04;Ingredient costs before rebate. **Bolded** drugs are available generically and have lower copays.

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