

Selective polypharmacy for chronic obstructive pulmonary disease

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We must admit that we don't understand chronic obstructive pulmonary disease's (COPD) pathogenic mechanism, nor do we know how to change the downhill course of the disease, except for smoking cessation and for certain patients who need oxygen. But that shouldn't stop us from trying to improve COPD patients' quality of life and reduce the number of COPD exacerbations they experience. However, the approach to accomplish this without causing pneumonia, possible cardiac complications, financial hardships, and other side effects of drug therapy is not entirely clear.

ICC, in a recent article (1), urgently suggested that pulmonary experts provide recommendations for approaches to COPD therapy that would improve quality of life and reduce exacerbations while keeping costs and other side effects of therapy down. Currently, therapies such as long-acting muscarinic agonists (LAMA), long-acting beta agonists (LABA), short-acting beta agonists (SABA), inhaled corticosteroids (ICS), long-acting theophylline, acetylcysteine, azithromycin, influenza and pneumococcal vaccines, and roflumilast are all being promoted as useful for these indications. Some have been found to improve both quality of life and reduce exacerbations (e.g., LABA, LAMA), others just reduce exacerbations or increase the time to next exacerbation (roflumilast). Each drug has its own side effects that have to be considered; one of the most important side effects is excessive cost since it is the most common reason that patients can't obtain needed medications (2).

Many COPD patients receive combinations of the agents listed above, but since most of the medications have similar indications for COPD, it is not clear which of the multiple medications patients should take. The GOLD guidelines suggest that adding a bronchodilator of a different class may improve the clinical response obtained with a single

bronchodilator. But which therapy should be started first, and what should be next, and how can cost be kept to a minimum while still obtaining the desired results? There are few studies that deal with these issues, so physicians and patients are left to conduct expensive experiments to guess what works best within the patient's budget.

A recent article (3) by Magnussen and his colleagues looked at the treatment of exacerbations of severe COPD in patients being treated with tiotropium, salmeterol, and fluticasone (a LAMA, a LABA, and an ICS) and found that the occurrence moderate or severe exacerbations were similar among those who discontinued inhaled ICS to those who continued their use. An accompanying editorial (4) concluded that ICS should only be given in patients receiving long-acting bronchodilators if patients had symptomatic improvement related to the ICS and not for the prevention of exacerbation, even in patients with severe COPD.

This is a useful study to help clarify the need for the polypharmacy that COPD patients often receive, since 70% of the patients in the study were receiving ICS (4), many of whom had no indication for the ICS. Many were not benefitting from the medication. However, the study does not go far enough in clarifying which medications will benefit patients at a feasible cost.

I looked at the costs of the drugs at the doses used in the Magnussen *et al.* study, based on local costs in the US state of Washington, obtained from multiple pharmacies using a website with a large data base of pharmacy costs (<https://www.rxpricequotes.com/>). The monthly costs were approximately: tiotropium \$520 for 30 days, salmeterol \$310 for 30 days, and fluticasone \$530 for 30 days. Just for these three medications, taken individually, the cost would be \$1,360 per month or \$16,320 yearly.

Discontinuing the ICS if it did not improve the patient's symptoms would save \$6,360 yearly—a substantial savings. However, many patients who receive both salmeterol and fluticasone do not take these agents separately; they take Advair[®], which contains both. This preparation would cost \$509 for twice daily dosage for 30 days, making the monthly cost \$1,029 or \$12,348 yearly. Substituting fluticasone for Advair[®] would only save \$2,388 per year. In some countries, the cost of these medications would be less. Some countries have universal health care programs that would cover some or all of the cost of the medications. However, in the unmanaged health care of the US with payment caps, high deductible rates, and limited health insurance coverage, most of the drug costs are paid by COPD patients and their families. Since patients with severe COPD are not likely to be employed and are often living at the poverty level, these enormous drug costs either deprive the patient of food, clothing, and shelter or else make it impossible for them to receive health care, a very painful choice.

The Magnussen *et al.* study considered medications that are among the most expensive in their therapeutic categories, presumably because the company that makes one of the agents used in the study paid for the study. This decreases the usefulness of the study, as does the fact that of the 13 listed authors of the study, 12 either work for the company directly or else receive payments from the company sponsoring the study and many other companies.

It would be of great practical interest to know whether multiple bronchodilators are always indicated or is the patient's improvement with an additional bronchodilator the only deciding factor? It would also be valuable to know if less expensive LAMA, LABA, and theophylline preparations would substitute for the expensive branded bronchodilator medications. For example, a month's generic ipratropium (15 cc of 0.06% nasal spray) costs \$23.01 as determined by <http://www.goodrx.com/> and even though it would require more frequent dosing than tiotropium, the yearly savings of \$5,964 might be crucial for COPD patients.

Similarly, generic ICS and generic formoterol could save a great deal of the \$16,320 drug cost burden that COPD patients have to bear if they are on the regimen included in the current study (3). I know of no studies that prove the branded drugs provide clinically significant improvements in patient quality of life or greater reduction in exacerbations of COPD than the less expensive generic LAMA, ICS, and LABA medications. Data concerning the role of long-acting theophylline would also be of practical interest.

A month's supply of a branded long-acting theophylline (Theo-24) is only \$69.39 in the US, and it might improve the action of another bronchodilator or even be a sufficient bronchodilator by itself in certain patients.

Acetylcysteine (generic, 30 mL, 20% solution) only costs \$12.10 (<http://www.goodrx.com/>) and reduces exacerbations of COPD and improves patient quality of life (1). How much more do additional drugs add to the benefits of acetylcysteine? Unfortunately, such studies are also not available.

More studies should be required by drug regulatory organizations concerning indications for new medications in circumstances where polypharmacy is common and the usefulness and cost-effectiveness of a new medication in conjunction with other medications in common use is not clear, which is certainly the case with COPD medications. In patients with hypertension, for example, the use of a new anti-hypertensive medication is only approved with a clearly defined context for its use. The same situation should apply for COPD medications. Other government and regulatory actions would also help COPD patients. For example, assuring that lower cost generic medications are available would allow many more patients to receive therapy.

Although the costs shown above reflect costs in the US, which are likely to be higher than in most countries, it is very likely that branded drugs, which are heavily promoted, will be much more expensive and not necessarily better for patients than less expensive generic drugs in the same therapeutic categories in all countries. When pharmaceutical companies provide bribes to physicians to prescribe their expensive drugs and pay other companies not to produce inexpensive generic medications (5), patients who cannot afford the high costs must suffer. Such activities indicate that the companies know that their medications are not worth their extra cost compared to generic medications. As physicians, our responsibility is to our patients, not to the drug companies that seek to influence us by their payments to harm our patients! In the absence of needed data, it makes sense to initiate therapy with the less expensive generic medications in the different therapeutic categories, as needed, to achieve the best clinical results.

A recent analysis of access to care among 11 high-income countries (6) showed that the US is by far the worst country in providing equitable access to care for all its patients, with striking inequality among adults with incomes below or well below their countries' median income. The cost

of prescriptions was a major cause of inequitable care for the US patients. About twice as many US patients did not receive their prescribed medications because of cost than the mean number of patients in all the other ten countries. Physicians must not only ensure that patients are prescribed medications that will benefit their medical condition. They must work with their patients to find the medication that will benefit them at the cost they can afford!

The public trust in physicians in many parts of the world is at an all-time low. In 1966 in the US, 73% of Americans said they had great confidence in the leaders of the medical profession. In 2012, only 34% expressed this view. In a recent measurement of public trust of physicians in a 29-country survey, the US was 24th with only 58% of the people believing that physicians could be trusted. Only 23% of people in the US have confidence in the US health care system (7). When patients see that their physicians are receiving large payments from drug companies and then see that they are prescribing the most expensive medications, which their patients cannot afford, when less expensive alternatives that are also effective are available, the respect for physicians worldwide will continue to fall.

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