AUTHOR COMMENTARIES - FROM Special Topics

Chronic Obstructive Pulmonary Disease (COPD) - Published: January 2010

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Peter Calverley

From the Special Topic of Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition normally related to tobacco smoking. The condition leads to a narrowing of the airways, causing shortness of breath, and there is no cure at present. In the US it is currently the fourth largest cause of death.

A major problem with COPD is the occurrence of exacerbations, the periodic worsening of symptoms and lung function. Exacerbations lead to increased utilization of healthcare services and a decrease in the quality of life.

A Special Topics analysis of COPD research over the past decade shows that the work of Professor Peter Calverley ranks at #2 by total cites and #3 by total papers, based on 87 papers cited 4,763 times. In Essential Science IndicatorsSM from Thomson Reuters, he ranks among the top 1% of scientists in the field of Clinical Medicine.

Calverley is Professor of Respiratory Medicine at the University of Liverpool in the UK. His research interests include the management of COPD, on which he has published extensively. He has been one of the principal investigators in a number of clinical trials that have become highly cited.

In this interview,* ScienceWatch.com *European correspondent Dr. Simon Mitton explores the key contributions made by Professor Calverley and his co-workers on the effective management of COPD.

SW: To start our discussion, would you like to outline how you came to enter the field of respiratory medicine?

I started my medical training at the University of Edinburgh where I met a several inspiring respiratory

physicians, particularly the late Professors John Crofton and David Flemley who were deeply concerned about the problems of respiratory disease and particularly obstructive lung disease.

As a result of that I became a Medical Research Council training fellow, in Edinburgh, with a particular interest in seeing whether oxygen treatment at home would prolong the life of COPD patients, which it did. After the fellowship I pursued my career in Edinburgh, with a period as a visiting fellow in Canada, before taking up my position here in the School of Clinical Sciences at the University of Liverpool. I am also an honorary consultant physician at University Hospital Aintree, Liverpool.

SW: COPD is obviously a horrible condition which must be very distressing. What can you tell me about it?

These papers flagged by your analysis are focused on chronic obstructive pulmonary disease, the term that we now use to describe what people once called chronic bronchitis and emphysema. These are two aspects of the same problem, in one of which the airways in the lungs become inflamed, causing bronchitis, and the substance of the lungs is destroyed, leading to emphysema.

This is a very common problem, originally thought to be confined to western developed countries, but now recognized as having global significance. Rather sadly COPD has steadily increased in importance over the last 20 years.

Patients complain of breathlessness and may have a cough with sputum production. As the disease progresses they tend to be very disabled by the breathlessness, and experience frequent flare-ups, or exacerbations, of the disease. Many of the patients become hospitalized, and many die prematurely. Here in Liverpool we have tried to prevent the exacerbations with various treatment approaches.

SW: What are the main risk factors with COPD?

This condition is mainly due to tobacco smoking, but other factors like health at birth and also occupations through life seem to be important predictors of developing this particular severe illness. Prolonged exposure to workplace dust, particularly in combination with smoking, can lead to airflow obstruction.

SW: Turning to your papers published in the last 10 years, I notice that two of them are clinical guidelines: "Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper," (*Eur. Resp. J*. 23[6]: 932-46, June 2004) with Bart Celli, and "Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease—the GOLD executive summary," (*Am. J. Resp. Crit. Care Med*. 176[6]: 532-55, 15 September 2007) led by Klaus Rabe.

I have conducted many original investigations dealing with both the physiological assessment of the disease and its treatment. These two aspects of my research have meant that I have been involved in panels developing guidelines for the management of COPD.

The 2004 paper publishes the guidelines of the joint American Thoracic Society (ATS) and the European Respiratory Society (ERS) report produced under the leadership of Bart Celli, then at Tufts University in Massachusetts. The 2007 paper gives guidelines from the Global initiative in managing Obstructive Lung Disease

guidelines; that had a wider remit than the 2004 paper, which was limited to COPD management in the most developed economies.

Both of these guidelines were highly cited and had an important impact on how ordinary clinicians managed COPD. In particular, these two evidence-based studies identified what treatment practices were helpful and which ones were not. Defining those things that are not useful is as important in this field as identifying what is positively helpful.

We have set up a classification scheme for COPD severity that is being used by a range of scientists, from clinicians and epidemiologists through to basic scientists, all of whom are striving to understand how this disease impacts on people.

"We demonstrated that a combination treatment of inhaled long-acting beta2 agonists and corticosteroids produces better control of symptoms and lung function, with no greater risk of side effects than that with use of either component alone."

SW: In 2004 the UK National Institute for Clinical Excellence—NICE—published its guidelines on the "Management of chronic obstructive pulmonary disease in adults in primary and secondary care." I believe you contributed to that?

Yes. I was a member of the Guidelines Group, and helped to draft this report. NICE is an independent organization that, among other things, provides best-practice advice to public health authorities the UK, including National Health Service. The clinical research on COPD that we have been pursuing in Liverpool therefore feeds through to healthcare professionals responsible for COPD patients.

SW: Your top papers include several in which you and your colleagues have studied the effectiveness of different treatments available for COPD.

Let me tell you first about the background to these papers.

By the late 1980s, it was recognized that COPD was an inflammatory condition. It seemed sensible then to consider whether existing treatments known to reduce inflammation, particularly inhaled corticosteroids, could modify the natural progression of this condition. This led to a series of studies that were conducted in patients with either very mild or moderate COPD.

The impression was that the rate of decline of lung function was not modified. Unfortunately there were methodological issues in these studies and many clinicians were more concerned about whether these drugs should be added to bronchodilator treatment used to relieve breathlessness.

SW: So the first paper, which ranks at #2 on our list of the top 20 papers published in the past decade, was published in 2000: "Randomised, double-blind, placebo-controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial," (*Brit. Med. J.* 320[7245]: 1297-1303, 13 May 2000). What did you find?

Sherwood Burge and I led this study, which tested the hypothesis that a high dose of the inhaled corticosteroid fluticasone propionate would change the rate of decline of lung function in people with symptomatic and relatively severe COPD. The short answer was that this change did not occur.

However, we did learn (it was the first time this had been looked at) that we could improve people's symptomatology and well-being (expressed via a measure of their quality of life), and also reduce the number of flare-ups, or exacerbations, of the disease. Thus for the first time there was a clinical justification for adding these corticosteroid drugs into the then widely used short-acting bronchodilator

treatment.

SW: In other words, you had found that anti-inflammatory therapy was better than just using short-acting bronchodilators, because you reduced the exacerbations. In 2003 *The Lancet* published your next study in this series, "Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial," (361[9356]: 449-56, 8 February 2003).

That's right. New treatments became available in which inhaled corticosteroids were combined with long-acting inhaled $beta_2$ agonist drugs. These drugs also worked as effective bronchodilators, so there was a reasonable question to ask: could further advantage be gained by adding this extra treatment?

"I have conducted many original investigations dealing with both the physiological assessment of the disease and its treatment."

That question arose on the basis of our study published in *The Lancet* in 2003. This is a four-armed randomized parallel drug trial with a large number of 1,465 participants who were followed for one year. The paper represented a step change in the way studies have been conducted because this was the first time a treatment intervention with different arms to the treatment had been tried in this number of people.

We demonstrated that a combination treatment of inhaled long-acting $beta_2$ agonists and corticosteroids produces better control of symptoms and lung function, with no greater risk of side effects than that with use of either component alone. We said this combination treatment should be considered for patients with COPD.

The paper shaped future clinical practice, because we were able to show that the combination treatment was more effective than the placebo, it improved health, and it reduced exacerbations. That is why it has a high rate of citation.

SW: Your 2007 paper in the *New England Journal of Medicine* completes the trio, "Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease," (356[8]: 775-89, 22 February 2007). What did you find?

The final and largest of this trio of studies was a multinational three-year project in which 6,112 participants were followed. Of these, 875 died within 3 years of the start of the study. We conducted a randomized, double-blind trial administered with a single inhaler that compared a placebo, salmeterol, fluticasone propionate, and salmeterol and fluticasone propionate in combination. We wished to establish whether the combined treatment resulted in a reduction of death.

Unfortunately, the favorable result we found for the combination treatment was not quite large enough to achieve our pre-set level of statistical significance. This probably reflects the large number of people who withdrew when randomized to placebo treatment and hence decreased the power of study to demonstrate a difference.

We confirmed, however, the results of the previous two trials, and showed that even people with mild disease would have benefits from using the combined treatment if they had episodes of exacerbations. Also we resolved our original question: treatment did indeed slow disease progression. Our treatment of symptomatic patients with COPD was beneficial.

This paper has had a widespread impact on the way COPD is managed.

SW: Thank you Peter for those insights into why the papers we have been discussing are high

impact. In conclusion to our interview, would you like to tell me about the future trajectory of your research on COPD?

Yes of course! The clinical studies of the past 10 years that I have been discussing with you have grown out of a better understanding of the scientific aspects of this pulmonary disease. There are now real challenges ahead. Many pharmaceutical companies have developed "me too" versions of the drugs we have tested already.

Although these formulations are likely to produce further improvement of a modest kind, we are thinking about new approaches to COPD management—approaches that maximize physical performance of the patient. We know already that pulmonary rehabilitation is effective. We continue to study and publish about that.

New ways of monitoring rehabilitation will help us classify the performance of our patients better. Similarly, structural measurements like CT scanning to measure the degree of inflammation will also prove to be relevant for defining individual patient groups.

The future for treatment is to develop more specific disease phenotypes that are responsible to particular therapies, rather than offering the one-size-fits-all approach. That's going to be an important challenge for clinical trials and new science.

My group is strongly motivated by that challenge.

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Peter Calverley's current most-cited paper in *Essential Science Indicators*, with 763 cites:

Celli BR, *et al.*, "Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper," *Eur. Resp. J.* 23 (6): 932-46, June 2004. Source: *Essential Science Indicators* from Thomson Reuters.

Additional information:

- From the paper above, also read interviews with **Bartolome Celli**, and **Jørgen Vestbo**.

KEYWORDS: COPD, EMPHYSEMA, SYMPTOMS, RISK FACTORS, MANAGEMENT GUIDELINES, EVIDENCE-BASED STUDIES, TREATMENT PRACTICES, UK NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE), FLUTICASONE PROPIONATE, LUNG FUNCTION, EXACERBATIONS, COMBINATION TREATMENT, LONG-ACTING BETA2 AGONISTS, CORTICOSTEROIDS, SALMETEROL, PULMONARY REHABILITATION, DISEASE PHENOTYPES.

PDF

back to top

Special Topics : Chronic Obstructive Pulmonary Disease (COPD) : Peter Calverley Interview - Special Topic of Chronic Obstructive Pulmonary Disease (COPD)

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