Obtaining evidence for use by healthcare payers on the success of chronic obstructive pulmonary disease management

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Abstract
Healthcare payers make decisions on funding for treatments for diseases, such as chronic obstructive pulmonary disease (COPD), on a population level, so require evidence of treatment success in appropriate populations, using usual routine care as the comparison for alternative management approaches. Such health outcomes evidence can be obtained from a number of sources. The 'gold standard' method for obtaining evidence of treatment success is usually taken as the randomized controlled prospective clinical trial. Yet the value of such studies in providing evidence for decision-makers can be questioned due to the restricted entry criteria limiting the ability to generalize to real life populations, narrow focus on individual parameters, use of placebo for comparison rather than usual therapy and unrealistic intense monitoring of patients. Evidence obtained from retrospective and observational studies can supplement that from randomized clinical trials, providing that care is taken to guard against bias and confounders. However, very large numbers of patients must be investigated if small differences between drugs and treatment approaches are to be detected. Administrative databases from healthcare systems provide an opportunity to obtain observational data on large numbers of patients. Such databases have shown that high healthcare costs in patients with COPD are associated with co-morbid conditions and current smoking status. Analysis of an administrative database has also shown that elderly patients with COPD who received inhaled corticosteroids within 90 days of discharge from hospital had 24% fewer repeat hospitalizations for COPD and were 29% less likely to die during the 1-year follow-up period.

In conclusion, there are a number of sources of meaningful evidence of the health outcomes arising from different therapeutic approaches that should be of value to healthcare payers making decisions on resource allocation.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) imposes a considerable burden on patients, healthcare services and society, yet this is poorly appreciated (1). If management of COPD is to be improved, there has to be greater recognition of the disease and agreement on optimal treatment. Measures of treatment success, as defined in management guidelines, tend to focus on the perspective of physicians or of patients, with little appreciation of the needs of decision-makers for appropriate evidence on health outcomes (2,3). This must be addressed if the profile of COPD is to be improved, and appropriate levels of resources are to be directed at understanding and managing the disease.

Healthcare payers make decisions on a population level, so require evidence of treatment success in comparable populations, using usual routine care as the comparison for alternative management approaches. As COPD cannot be cured, measures of COPD health outcomes that are of relevance to healthcare payers include 'symptom-free days' and 'exacerbation rates', as well as patient satisfaction and impact on quality of life. Use of healthcare resources, particularly hospitalization as a result of exacerbations, and the total costs of management are also of importance to healthcare payers (2). Such health outcomes evidence can be obtained from a number of sources.
PROSPECTIVE CLINICAL TRIALS

The ‘gold standard’ method for obtaining evidence of treatment success is usually taken as the randomized controlled prospective clinical trial. Such studies are highly valued by those seeking best possible evidence as they are designed to test a defined hypothesis in a way that reduces bias and controls for confounders, though at considerable cost. The results from randomized clinical trials often show highly significant differences in treatment approaches. Yet the value of these results as evidence for decision-makers can be questioned. Restricted entry criteria ensure a homogeneous study population but limit the ability to generalize to real life populations. Tightly controlled conditions that allow comparison of one treatment with another may ignore other more relevant issues. Using placebo as a comparison does not usually reflect normal clinical practice. Furthermore, the intense monitoring of patients in clinical trials is unreal and may, in itself, bring patient benefits, irrespective of the treatment modality being evaluated. A clear example of these factors is the mortality rate from acute myocardial infarction in studies of thrombolytic treatment (7%), which was half that usually recorded in cardiac care units (12%) (4).

How do these factors affect clinical trials to obtain evidence of treatment success in COPD? This first consideration is selection of patients for the trials. Definitions of COPD vary between guidelines (1,3), and applying the different criteria may result in very different patient populations included in clinical trials. For example, the patient population in the EUROSCOP trial of inhaled corticosteroids in COPD had an average lung function (FEV₁ 79% predicted) considerably greater than that of the population included in the ISOLDE trial of corticosteroid use (FEV₁ 52% predicted) (5,6). Such differences in patient population may account for differences in study findings. Furthermore, the choice of FEV₁ as the principal characteristic has been questioned – asthma is defined physiologically, chronic bronchitis clinically and emphysema pathologically, so it is difficult to assess COPD only on a measure of lung function. In studies on COPD, patients are often entered into the trials only if other conditions can be excluded (Table 1), raising concerns about the relevance of the study findings if they apply only to a small sub-population of patients.

Once the patient population has been defined, there is then the issue of defining treatment success. There is little agreement on how success in COPD should be defined (Table 2), and views of treatment success vary with the perspective taken (7). In part, the difficulty in defining appropriate measures of treatment success stems from a lack of understanding of the disease. It is agreed that COPD is a chronic disease with a defined pattern (7), but the components of disease pathology vary unpredictably. Furthermore, the factors controlling susceptibility and the rate of decline are not fully established, while the relationship of symptoms to lung function (defined by FEV₁) also varies unpredictably.

Once the measures are defined and the results are obtained, there is the problem of distinguishing between statistically significant results and those that are clinically relevant. Furthermore, averaging the findings for the population blurs the distinction between those who show a good response on the defined criterion and those who do not. For example, 60% of patients may show improvement in FEV₁ with inhaled steroids, while there is little change in 20% and another 20% actually show deterioration in response. The average may suggest that all patients should receive the treatment, but it could be argued that 40% would be better managed by not using the therapy.

Another difficulty in defining appropriate measures of success for assessment in clinical trials is the long-term nature of the disease and treatment goals, while clinical trials are usually of short duration. In prolonged trials that seek to overcome this problem, another difficulty emerges – drop-outs from the trials. These may represent a considerable proportion of the original starting population. How should these be handled? The reasons for dropping out of the study could be highly relevant.

It seems, therefore, that although the results of randomized, prospective clinical trials are highly valued by those compiling best evidence of treatment approaches, they cannot provide a complete picture of

<p>| Table 1. Clinical trials on COPD and its treatment usually exclude patients with co-morbidities |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|</p>
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<tr>
<th>Exclusion</th>
<th>Criteria</th>
<th>Issues to consider</th>
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<tbody>
<tr>
<td>Asthma</td>
<td>Specified levels of reversibility to therapeutic agents used in asthma</td>
<td>Which treatments? What level of reversibility? What proportion of COPD patients is excluded by reversibility criteria?</td>
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<tr>
<td>Cardiovascular problems</td>
<td>Co-morbidities including heart disease, peripheral vascular disease etc</td>
<td>As most patients with COPD are smokers, many also suffer from these concurrent conditions. What proportion of COPD patients is excluded?</td>
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the evidence required by healthcare payers. Clearly, alternative approaches to collecting evidence are required that seek to address some of the short-comings of randomized controlled trials.

RETROSPECTIVE AND OBSERVATIONAL STUDIES

Although the randomized controlled trial is seen as the gold standard, probably the best example of high quality evidence in the respiratory field is the study that demonstrated unequivocally the association between smoking and lung cancer (8). In this epidemiological surveillance study, around 40 000 doctors were studied over a 40-year period. Other surveillance approaches, have produced useful evidence of hitherto unsuspected drug effects (9). Such naturalistic, observational studies do not exclude anyone, so reflect clinical practice more closely than the highly selected patient populations included in clinical trials, but they also contain more potential confounders. They may also take a very long time before results are available. A way to address this problem is by examining data retrospectively.

Retrospective studies run the risk of being seen to be wise after the event, with bias and the selection of favourable cases As a result, compilers of evidence-based guidelines and reviews consider such evidence of lower grade than evidence obtained from clinical trials (3), and may even exclude it from systematic reviews. Yet it is possible to carry out formal structured surveys of unselected patient populations and obtain robust evidence. An example is an audit that was conducted of acute stroke services in the U.K. (10). Collecting data accurately was identified as of critical importance to the robustness of the final results. Consequently, a pilot study was carried out to test the reliability of wording used in the data collection form. Kappa scores were used to test for variability, and the wording modified until data collection was accurate. Hospitals throughout the U.K. were then surveyed for the proportion of patients with acute stroke receiving various assessments and service indicators in the time immediately following the event and before discharge (e.g. assessment of visual fields, ability to swallow, continence care). Feedback was given to the hospitals on performance relative to the total sample (11). When repeated a year later, every region in the country showed improvement on the provision of care for stroke patients (12). Clearly, the evidence collected in the first audit had been of sufficient value to the recipients that behaviour had changed as a result.

A similar approach taken to audit COPD care, found considerable inter-hospital differences in the proportion of patients receiving assessments at initial admission for an acute exacerbation (13). When the death rate from acute exacerbation was examined, a five-fold difference was found between hospitals. Small hospitals were found to have twice the death rate of large hospitals, possibly because of lack of specialist care (14). There was also a clear correlation between mortality rate and poor performance at initial assessment. Such audit data is an essential part of appraisal of clinical practice for individuals and units, and forms the basis of action plans to improve the delivery of care.

Another example of a novel approach to supplement the information from randomized clinical trials comes from an assessment of the leukotriene modifier, montelukast in asthma (15,16). Anecdotal reports suggested that montelukast was less effective in clinical practice than predicted from randomized clinical trials, so a study was designed to understand what happens to the average patient treated with montelukast, without interfering in their management. The approach taken was to identify all patients in a practice or clinic who received the treatment during the defined time period (February 1998 – June 2000). This included all those who started treatment but stopped for any reason, all ages and grades
of asthma, and all those with co-morbidities. Patient consent was obtained for access to records and to send a patient survey form. The only exclusions were patients who did not have a diagnosis of asthma, those who had received montelukast as part of a clinical trial, and patients who were prescribed other leukotriene modifiers. Extensive piloting was carried out to ensure accuracy in data collection, with modification of data collection questions and briefing notes for the investigator, until satisfactory levels of inter-observer agreement could be demonstrably achieved.

Although the study was intensive and required laborious attention to detail, the results seem robust and similar data were obtained from the doctor assessment, the external nurse auditors assessment and from the patients evaluation. These showed that approximately 40% of patients experienced significant benefits from the treatment (i.e. sufficient to be noticeable by the individual), with a similar proportion (40%) showing little change in outcomes and 20% (including all drop-outs — many of whom should probably not have been given the drug at all) experienced worse asthma control. Despite the considerable effort required to obtain robust evidence, the study cost less to carry out than comparable clinical trials.

Thus retrospective, observational studies can provide valuable information on the delivery of care and health outcomes in a way that relates directly to routine clinical practice. As such, the evidence obtained by these methods can supplement that from randomized clinical trials, providing that care is taken to guard against bias and confounders. However, very large numbers of patients must be investigated if small differences between drugs and treatment approaches are to be detected. With large patient numbers, it is also possible to perform subgroup analysis and define, for example, groups of patients who show particularly good or particularly poor responses. This could allow clinicians and healthcare payers to identify those patient groups who could benefit most from treatment, and where cost-effectiveness analyses can be most favourable.

**OBSERVATIONAL DATABASES**

Observational data may be captured by a variety of methods, but commonly it is routinely collected for administrative purposes or as part of epidemiological surveillance (17). Administrative databases are usually built primarily for billing purposes, especially in the U.S.A. where most healthcare is still proved by the traditional fee-for-service systems (e.g. the publicly funded Medicare system). However, most countries with nationalized healthcare systems and most managed-care systems in the U.S.A. also track utilization routinely for auditing purposes and for resource allocation decisions. Epidemiological surveillance databases (such as cancer registries) or public health surveys (such as the National Health and Nutrition Examination Survey) may also contain utilization data (18,19). Although the information from this type of database may be relatively crude or incomplete, the enormous size of some of these databases provides sufficient power for making inferences about health policy. Observational databases vary widely in the type and quality of information they contain, but they provide the outcomes data required by patients, providers and policy makers to inform decisions on the management of COPD (Table 3).

At the Center for Pharmacoeconomic and Outcomes Research (CPOR), a large utilization database based on administrative data from Lovelace Health Systems has been used to examine the costs of healthcare for patients with COPD. Lovelace Health Systems operates a regional staff-and-network model health maintenance organization (HMO) with over 200,000 members. Because Lovelace Health Systems also provides traditional fee-for-service care, it collects very detailed data on all services. Since 1987, the CPOR has captured over 2,000,000 patient-years of utilization from this HMO.

One advantage of using a comprehensive database, such as that of CPOR, is that it allows the use of case-control methods to examine the overall impact of specific illnesses on healthcare costs. Many utilization studies attempt to estimate disease costs by summing costs for hospitalizations, procedures, and drugs that can be directly attributed to the disease of interest. This approach may underestimate costs because it may miss charges in unexpected areas, such laboratory or radiology use, and it overlooks the effects a disease may have on utilization for other illnesses (20). By matching patients with a specific illness to others of the same age and gender without the disease, case-control methods can describe the impact of a disease on overall costs (often referred to as the marginal cost), identify specific areas of increased utilization, and also provide a useful index comparison against normal expected charges.

Recently, CPOR completed a case-control analysis of COPD costs and utilization among patients treated by the Lovelace HMO (21). A total of 1,522 patients with a diagnosis of COPD were enrolled in the health plan for

**Table 3. Information on COPD that may be available from observational databases**

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<tr>
<th>Inpatient admissions and length of stay</th>
<th>Outpatient consultations</th>
<th>Medication use and costs</th>
<th>Direct healthcare costs</th>
<th>COPD exacerbation rates (those that result in a consultation or change in medication)</th>
<th>Survival</th>
<th>Incidence and prevalence of co-morbidities</th>
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EVIDENCE OF TREATMENT SUCCESS IN COPD

Figure 1. Use of outpatient services by patients with COPD and matched controls (21).

the whole of 1997 (i.e. these patients did not die during the period or move to another health plan). A matched group of 4566 control patients were identified with a similar age and gender profile. Medical charts were reviewed from 200 COPD cases and 200 controls to obtain additional information about smoking histories and pulmonary function tests, and to confirm the validity of the diagnoses (22). Patients with COPD were more likely than the control group to smoke during the study period (46.0% vs 13.5%, *P < 0.001), and of those people who had ever smoked, COPD patients had significantly greater smoking exposure than those without COPD (49.5 vs 34.9 pack-years, *P = 0.002). On average, patients with COPD had 3.7 chronic medical conditions (including lung disease), compared with 1.8 for the control group (*P < 0.001), particularly heart disease, cancer, neurological injuries and gastritis. Just 6% of patients with COPD did not have another chronic medical condition.

Patients with COPD had significantly greater use of outpatient services than control cases, with an average of 27.82 outpatient encounters per patient compared with 16.18 for controls (*P < 0.001) (21). Not surprisingly, COPD patients were significantly more likely to use respiratory care services; however, increased utilization was found in almost all service areas, particularly cardiology and emergency services (Fig. 1). Although a similar proportion of both groups used primary care services, the average number of visits made by COPD patients was 54% higher than for the controls. Pharmacy utilization was significantly greater in COPD patients compared with controls (mean prescription fills per patient of 35.48 vs 18.42, *P < 0.001). Only half of the increased pharmacy utilization was for respiratory medications - significant increases were also found in cardiovascular drugs, antibiotics, psychotherapeutic drugs and pain medications. Compared with the control group, patients with COPD were 2.3 times more likely to be admitted to the hospital during the study year, and those admitted had significantly more admissions with longer average duration of stay (Table 4). Overall, healthcare costs among COPD patients were twice those of age- and gender-matched controls (Fig. 2), but half of COPD’s marginal impact would have been lost if the analysis had been limited strictly to respiratory admissions, treatments, and drugs.

The CPOR database is being used for additional studies designed to determine clinical factors related to increased resource utilization. In one study, a total of 302

| Table 4. Hospital admissions in patients with COPD and matched controls (21) |
|---------------------------------|-----------------|-----------------|
|                                 | Patients with COPD (n=1522) | Control patients (n=4566) |
| % of group admitted during 1997 | 25.0%            | 10.6%           |
| Average number of admissions per patient admitted | 1.8             | 1.4*            |
| Average length of stay         | 4.7 days         | 3.9 days**      |

*P=0.01; **P<0.00
patients with a clinical diagnosis of COPD were recruited from the Lovelace Health Plan database (23). Touch-screen computers were used to administer questionnaires on symptoms and quality of life, and lung function was measured before and after a bronchodilator and an exercise test. All inpatient and outpatient resource utilization data for the 12 months prior to the study were obtained. Although only around half of the patients had previously received lung function testing, the diagnosis of COPD was appropriate for all but 3% of the sample, in line with findings from other database studies (22). There appeared to be little correlation between total annual healthcare costs per patient and the stage of COPD, as defined by FEV₁ (24). However, there was a clear correlation between healthcare costs and the number of co-morbid conditions, while there was a weaker correlation with the activity score on the St George's respiratory questionnaire and incidence of wheezing in the previous year.

In another study using the CPOR database, clinical features of 1041 COPD patients treated in 1998 were used to predict healthcare costs and utilization in 1999 (25). In multivariate models, a history of oxygen use, any hospital admission for COPD, and the presence of major
co-morbidity such as heart disease or cancer was a strong predictor of healthcare utilization, while the severity of airflow obstruction as indicated by stage as defined by the American Thoracic Society (24) was not. These preliminary studies suggest that observational databases can provide very good information about the impact of COPD on healthcare costs and utilization, even when pulmonary function test results are not included in the data.

Analysis of an administrative database has also thrown light on the use of inhaled corticosteroids in patients with COPD (26), a therapeutic approach that has received only ambiguous support from clinical trials (5,6). A database of 22,620 patients in Ontario, Canada, was used to identify patients aged 65 years or older discharged from hospital with a diagnosis of COPD. After adjusting for possible confounding factors, those who received inhaled corticosteroids within 90 days of discharge had 24% fewer repeat hospitalizations for COPD and were 29% less likely to die during the 1-year follow-up period (Fig. 3). The association between use of inhaled corticosteroids and improved healthcare outcomes remained, irrespective of the number of co-morbid conditions and age. Similar results on improved survival with fluticasone propionate and combined fluticasone propionate/salmeterol have been found from a study of a British hospital database (27). Clearly, analysis of observational databases has revealed meaningful results on a therapeutic approach, in a way that randomized controlled clinical trials have been unable to demonstrate unequivocally.

CONCLUSIONS

It is apparent that meaningful evidence on the health outcomes arising from different therapeutic approaches can be obtained from a range of sources. While randomized, prospective, controlled clinical trials have long been viewed as the 'gold standard' of evidence, this approach alone may not provide sufficient information from which healthcare payers can make decisions about resource allocation. Retrospective and observational studies in all-inclusive patient populations, investigating different therapeutic approaches within routine clinical care, may give data that more closely reflects the real-life situations of relevance to healthcare payers. Analysis of administrative databases may give invaluable insight into the health outcomes of most importance to healthcare payers – population-based requirement for healthcare services and mortality.

REFERENCES


