A clinician's perspective on pharmacoeconomics and rheumatology

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ABSTRACT

This paper provides a brief introduction into pharmacoeconomics and its role in rheumatology from the perspective of a clinician, and is regarded as providing complementary simplified explanations for rheumatologists, which are used in a in much greater sophistication and complexity in other articles in this supplement.

Different definitions of pharmacoeconomics are discussed. In the major part of the article, typical pharmacoeconomic methods are explained and illustrated using examples derived from rheumatology: cost, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis, decision tree analysis, and Markov models. These methods are discussed in terms of strengths and weaknesses and their implications for medical practice.

Definitions of pharmacoeconomics and applications in rheumatology

Pharmacoeconomics is seen as a relatively new discipline that began the mid-1980s (1). Literature typically describes it as a subset of health economics with a focus on pharmaceuticals (2). It studies the value and costs of medication therapies; a typical definition says that it "identifies, measures, and compares costs and consequences of pharmaceutical products and services" (3). It aims at helping decision makers and providers to best allocate scarce resources (4). Some authors also see issues of equity (that is, the "fair" distribution of health care goods) as a task for pharmacoeconomic analysis (5).

Decision makers in the sense of this definition can be clinicians, pharmacists, policy makers, payers, etc., although many authors assume that pharmacoeconomic analysis focuses on consequences of medication to health care systems and society (6).

Many authors interpret the advent of pharmacoeconomics to increases in health care costs, requiring better decision support and higher efficiency (7). One textbook of pharmacoeconomics even states that "society is spending too much on health services" (8). Rheumatic disorders are amongst the most expensive diseases to society, not only because of direct costs, but also extensive indirect costs reflecting work disability. In the US, the total medical care expenditures for adults with rheumatic diseases were estimated at over $300 bn in 2003, approx. 3% of gross domestic product (9). In Canada and the Netherlands, musculoskeletal conditions ranked second in total health care costs by diagnostic category (10). New biological antirheumatic drugs are very expensive (11). In Germany, Adalimumab and Etanercept were number one and two of 2010 top ten drugs by turnover, with sales of €493 and 407 million, respectively (12). Therefore, a typical pharmacoeconomic question is whether all RA patients should receive biologicals, to compare value, side-effects, and costs of methotrexate, biologicals, and other treatments (13).

Pharmacoeconomic methods

This section focuses on what typical textbooks (14) discuss as "pharmacoeconomics", which includes:

- cost, cost-minimisation, cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-utility analysis (CUA);
- modelling techniques (decision trees, Markov modelling).

In addition, other issues that are also connected with "pharma" and "economics" – but not discussed in this article – include:

- national regulation that uses pharmacoeconomical methods and / or influences drug prices (such as the AMNOG legislation in Germany),

- costs of product development (from the perspective of a pharma company),
- the question why drug prices differ from country to country,
- the availability of longitudinal outcomes data; since treatment patterns change over time (15), it would be helpful to get easier access to data on outcomes, especially longitudinally in order to compare the outcomes of different therapies. A good example is the idea to build registries with a high proportion of patients covered,
- even better if a data base covers all consecutive patients with any presumed diagnosis seen at a treatment centre, which can be accomplished using a self-report questionnaire for each patient seen (16),
- study designs (*e.g.* whether to measure costs and outcomes in clinical studies or in real-life settings (17)).

Cost analysis deals with the costs associated with a disease and / or treatment. Since all further types of analysis (cost-benefit analysis, cost-effectiveness analysis etc.) deal with costs, it is fundamental. Costs are calculated in order to estimate the amount of resources used for a certain treatment. They are typically expressed in monetary terms although economists suggest that "true" costs are opportunity costs – that is the value of an alternative use of resources that is forgone. (As an example for the latter concept imagine a decision maker decides to provide access to biological agents for five patients with rheumatoid arthritis – *i.e.*, provides drugs, injections, physician time, etc. -; the "true" cost is the *value* that could have been achieved if the decision maker had provided something else to other patients using the same resources).

Cost-of-illness studies are amongst the earliest applications of pharmacoeconomics (18).

In practice, it is often difficult to decide which costs to consider and how to measure them. Here are some examples:

- Different authors use different definitions of cost categories. There is some inconsistency in the literature on "direct", "indirect" and "intangible" costs. Most authors use the term "direct" costs to denote resources used for treatment (such as drugs, physician time, etc.), whereas "indirect" costs mean disease-related costs (such as loss in worktime). "Intangible" costs are not really costs but rather losses in quality of life, such as pain. Some authors do not use "intangible" costs at all; others do not differentiate between direct and indirect costs (19).
- The perspective of the analyst matters, especially whether he counts costs from the perspective of a single patient, a payer, or the society. For example, a sickness fund that pays for drugs but not for home care will not be interested in the latter costs when calculating the "total cost" of a treatment. By contrast, a health minister will typically require all costs to be included.
- Costs are sometimes difficult to measure. In some instances market prices are simply not available and are replaced by estimates. Another complexity results from overhead costs, which may be difficult to allocate: if, for example, a patient is treated in a hospital, the corresponding part of costs of the hospital administration (including its marketing department) is difficult to allocate correctly to that specific patient.
- Costs may occur over a longer period of time. In this case it must be decided whether the costs are to be discounted. This means that costs occurring in later years are reduced by a certain rate (say, 3% per year). In addition, there is discussion on what rate is appropriate (most authors recommend 3–5% per year). If costs occur in late time periods, discounting can massively influence the total cost calculation.

There have been several attempts to standardise cost measurements. A generic example is Drummond's check list (20). In addition, there are guidelines specifically designed for rheumatic diseases, *e.g.* rheumatoid arthritis (21).

A cost-minimisation study is a rather rare analysis that occurs when different treatment methods yield the same result but at different costs. In this case it may be sufficient for decision makers to choose the method with the lowest costs.

Cost-outcome analysis (22) (used here as the umbrella term for cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis) analyses both outcomes and costs. For example, one treatment method may be more costly than another one but provides better results; in this case it is not sufficient to compare costs only.

Although they may appear similar, CBA on the one hand and CEA/CUA on the other hand are diverse concepts. CBA is based on economic welfare theory. It measures both costs and outcomes in monetary terms (whereas CEA uses medical terms for the outcomes, *e.g.* survival time – see Table I). CBA typically assumes that patients can be modeled as homo economicus type consumers (which can be debated); that is, consumers spend their money so that they buy exactly the bundle of goods that maximises their personal value. It typically uses measuring techniques that are common in economic analysis; one of these is the human capital approach (*i.e.* the benefit of a treatment equals the monetary value of work time gained); other authors use willingness-to-pay techniques (*i.e.* consumers are asked what they would be willing to pay for a specific outcome). As a result of analysis, CBA yields information of the type: "treatment A delivers

Table I. Cost-outcome analysis.

	Costs measured in…	Outcomes measured in…
Cost-benefit analysis (CBA)	Monetary terms (*e.g.* €)	Monetary terms (*e.g.* €)
Cost-effectiveness analysis (CEA)	Monetary terms (*e.g.* €)	Medical or physical terms (*e.g.* blood pressure reduction)
Cost-utility analysis (CUA)	Monetary terms (*e.g.* €)	QALYs or similar terms (*e.g.* HYEs)

a benefit of €X at a cost of €Y". The advantage is that decision-makers can judge directly whether a treatment is worth its costs; in addition, it is easy to compare the outcomes and costs of different treatments.

Some economists suggest that CBA is superior to CEA/CUA also in that it is based on a powerful theory (welfare theory). Whilst it does have merits in theory, CBA is not easily applied in practice. It is often difficult for consumers to reliably estimate the value of a certain treatment ("what would you pay in advance for access to a treatment that increases your survival time by 3 months in a cancer that hits you with a chance of 0.6% in 30 years from now?"). Different techniques do not always yield comparable results (*e.g.* human capital *vs.* willingness-to-pay). Willingness-to-pay, in turn, depends on the ability-to-pay thus the same treatment may be valued at different levels by consumers. For example, RA patients have earnings that are below general population average because they are older, less educated, and more likely to have co-morbidities (23). Finally, if health care is supplied by non-markets (as in most European countries), consumers' willingnesses are difficult to combine to one single measure.

Cost-effectiveness analysis is closer to medical science. It measures outcomes in physical terms, *i.e.* blood pressure reduction, survival rates, etc. It relies on measuring techniques that have been common in medicine for decades. The advantage of nearness to reality comes, however, with the disadvantage that treatments can only be compared directly if they deliver the same type of outcome (*e.g.* blood pressure reduction). By contrast, it is difficult to judge which of two treatments delivers more value if, for example, one decreases blood pressure and the other one the likelihood of infection.

Cost-utility analysis is a means to overcome that problem. It translates physical terms into QALYs – quality-adjusted life years (or comparable figures such as HYEs or DALYs) (24). Thus, if a cancer treatment yields two additional life years in complete health, it is worth 2 QALYs. If it adds two years

in bad health (*e.g.* the health status is calculated as 0.3 on a scale from 0 – death – to 1 – complete health), it gives 2*0.3=0.6 QALYs (25). QALYs can be used to judge on value-cost-tradeoffs. Imagine drug A costs $10,000 more than drug B but is also better in that patients gain 1.5 additional QALYs. In these cases, it is possible to define thresholds of the form: a payer covers the costs for all treatments that cost no more than x$ per QALY gained.

QALYs have attracted health economists since they seem to solve many of the problems of cost-outcome analysis. However, many complexities remain unsolved. One of these is that QALYs do not adjust for the importance of treatment. For example, if tooth replacement increases the quality of life from 0.8 to 0.9 in 1000 patients for one year, 100 QALYs are gained; while a new cancer treatment that saves a 10-year old child who would otherwise die is worth only ~80 QALYs. Based on QALYs, one would conclude that dentistry is "better" than cancer treatment. Another difficulty of all cost-outcome analyses is the unsolved question of how to weight one life against another. Early economic theory assumed that it is best to maximise the sum of utility to society – regardless of who wins and loses. In an extreme case, it is better to sacrifice one person if another person gains more utility than the victim looses. In so-called "welfarist" theory, economists still construct a social welfare function (not necessarily a sum) that is calculated on the basis of individual utility and should be optimised. Other economists, and probably the majority of physicians ("extra-welfarists") do not support the idea of aggregating several personal utilities into one single term. The literature is a bit unclear on these issues since the terminology is not always entirely stable (26). Related questions are whether there is only "demand" in healthcare or "needs" as well (that is, whether patients have a right to get treatment if they need it even if other people have to pay for it), whether the allocation of medical goods, especially the decision to take away from one patient in order to give to another patient, is an ethical question that can

or cannot be solved by mathematical calculation, and others. Some of these questions are discussed in more detail in the last chapter of this article.

Modelling is an analytical tool that simplifies reality to describe the essential events that occur over time. Decision analysis is a systematic quantitative approach analysing clinical and economic consequences of alternative medical treatments under conditions of uncertainty. The uncertainty is described by probabilities that are connected with the occurrence of consequences. Each consequence leads to outcomes that are valued by monetary units, QALYs, or others. Sensitivity analyses are conducted by varying the values of probabilities and outcomes over a certain range in order to determine the robustness of the model structure. A typical way to do so is decision-tree analysis where several treatments and their outcomes are mapped out in a tree-like diagram (Fig. 1).

If outcomes can be expressed in monetary terms (27), treatments can be compared directly. In our example, treatment A yields an expected value of (0.1*400+0.6*300+0.3*100)= 250, whereas treatment B yields 260. However, decision trees are often too simplistic to describe chronic diseases where the same decisions are constantly repeated, probabilities may change over time and the disease is progressing.

In 1983, Beck and Pauker described the use of Markov models for determining prognosis in medical applications (28). Since then, Markov models are increasingly used in economic evaluations of new treatments for repeated events or the progression of chronic diseases. Markov models have the potential to extrapolate efficacy data from short-term clinical trials to longer term cost-effectiveness results and over lifetime, to predict long-term morbidity, mortality, and economics of a diseases, and to identify the optimal initial treatment strategy due to these complex conditions.

In a Markov model, the disease is divided into a finite set of health states from perfect health to death. Individuals move between these health states over discrete time periods (cycles). Transition probabilities describe the

moving from one health state to another. Estimates of resource utilisation and of health outcomes are attached to the health states. Running the model over a large number of cycles, the long-term costs and outcomes of treating patient cohorts with alternative interventions are analysed. Such models provide information to facilitate important decisions on resource allocation. Applying probabilistic sensitivity analyses in a Markov Model provides a useful technique to quantify the level of confidence that a decision-maker has in the conclusions of the model evaluation (Fig. 2). Imagine in this example a cohort of 100 patients starts in disease state A. In the first time period, 60 of them remain in state A whereas 10 die and 30 move to state B. In the second period, out of the 60 who start in A, 36 remain there, whereas 6 die and 18 move to B. From the 30 patients who start in B in this period, 6 die and 24 remain there; together with the new arrivals, 42 are in B at the end of period 2; etc.

Economics and medicine: recent considerations

In recent years, some physicians, especially in Germany, expressed discontent with the application of economics in medicine. Germans tend to see access to medical treatment as a human right (29) that has to be provided by public institutions and that care should be the same for everybody (no "two-classes-medicine"). In this context, the former president of the German chamber of physicians, Hoppe, repeatedly warned of what he called the "economisation of medicine", that is, the shift of power from a traditional one-on-one patient-physician-relationship where the physician would choose the best treatment for this single patient to economists within financial institutions who force physicians to behave along the lines of statistically derived treatment patterns (30). Medical ethicist G. Maio admits that economy is important in medicine. However, it should be the physician to decide; in contrast, today's economists have taken the lead in setting targets and medicine has to follow – to treat what and in a way so that the figures are as expected (31).
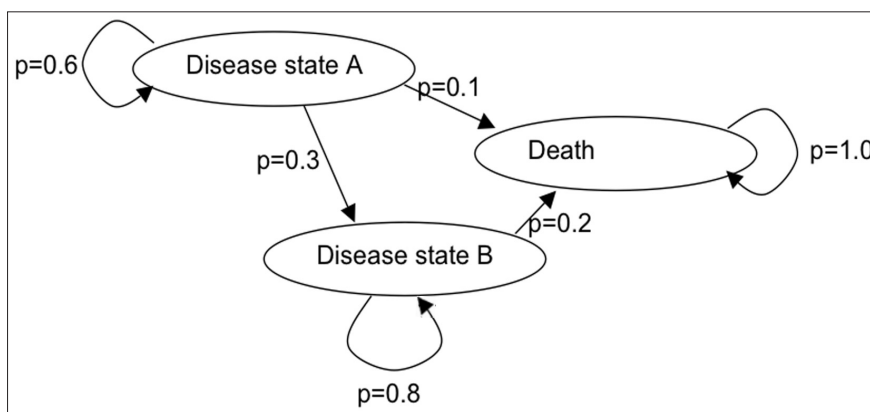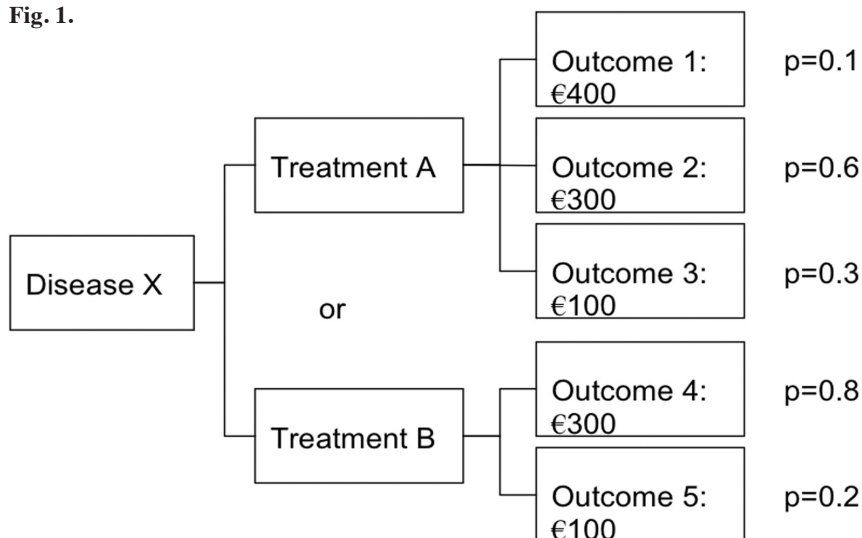
Fig. 1.

Fig. 2.

Obviously, even if physicians (not economists) decide on what and how to treat, there is still a need to allocate scarce resources. Hoppe proposed not to ration but rather to prioritise medical treatment; that is, not to take away potential treatment but rather rank different treatments by severity of disease, inflicted harm, probability of success, available evidence, and others (32). The basic idea is to design a transparent process that would deliver the same treatment to every patient, independent from his personal income, dependent only on his medical need.

From a clinician's perspective, there are several key issues in the relationship between economics, medicine and medical economics (incl. pharmacoeconomics):

- Who has the final decision on the treatment of a patient? If, for example, drug A is better than drug B but much more expensive: is it still possible for the physician to prescribe that drug (and the payer is forced to pay for it) for that specific patient? Or would somebody else decide that drug B is "too expensive" regardless of the specific patient? And based on what targets and data would he decide? Would the decision be transparent or covert?

  Do pharmacoeconomics support the single physician's decision or does is take away the decision from him?

- Are pharmacoeconomic data good enough already to decide on provision of care? For example, real-life patients may behave different from patients in a clinical study and therefore may need different treatment. Another problem is that medical decision making is so complex that easy decision routines fail; e.g. sim-

ple adhering to clinical guidelines in caring for patients with several comorbidities may have undesirable effects from a medical standpoint already; this will become even more complicated if value-cost-tradeoffs are included in the analysis (33).

Taken all together, pharmacoeconomics is a relatively young discipline; its methods have improved considerably over the last years and are of specific interest in rheumatology. They are important tools in many situations where resources are to be allocated. However, there are still important technical questions open for discussion (34).

Acknowledgements

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