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Drugs, money and society (Part II)

Tom Walley

Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK

Correspondence
Professor Tom Walley, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool L69 3GF, UK.
Tel: + 44 0151 794 8125
E-mail: twalley@liv.ac.uk

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Pharmacoeconomics started as marketing but has developed into a valuable tool in the fuller assessment of drug therapies. Its principles are now widely accepted, and many countries have government-funded agencies with responsibility for its application, most notably the National Institute for Health and Clinical Excellence in England. Many clinical pharmacologists are active in this area, and the discipline itself is part of the clinical pharmacology trainees' curriculum. Further developments will include value-based pricing and its use in cost sharing arrangements between health service and manufacturers.

Twenty years ago, many clinicians would have rejected the notion that cost of interventions should ever influence their choice of treatment for a patient, emphasizing strongly the Hippocratic view of the primacy of the individual patient over the broader public health view of requiring effective use of the medical commons [1]. This conflicted with the limited resources available, particularly in a publicly funded system like the UK National Health Service (NHS), free at the point of delivery. One result was rationing of the availability of treatments, but often carried out in an uneven and arbitrary manner. The rapidly rising costs of interventions including drugs put greater pressure on this. A decline in acceptance of medical paternalism and better educated patients meant that rationing by 'doctor knows best' was less and less acceptable. Health economists had long argued that all decisions about the use of public funds should be based on careful evaluation of both the effects of an intervention and its costs, so as to inform choice between competing options, but were rarely listened to in practice.

As far back as the 1930s, Archie Cochrane was arguing that 'all effective treatment must be free' [2], but what was effective treatment? In the late 1980s and early 1990s, a movement supporting evidence-based medicine arose, advocating first the evaluation of interventions by clinical trials and then the synthesis of sometimes conflicting information, then basing medical practice on what was proven to be effective. This movement was particularly strong in the UK and some other countries, and led to the creation of the Cochrane Collaboration. The UK Government supported this, in part to increase the effectiveness of healthcare, but also in part because they saw stopping the use of ineffective treatments as a way to cut costs without harming patients.

New information systems designed to pay pharmacists could also be used to examine prescribing by doctors, and revealed wide differences in the costs of prescribing by different doctors in primary care, with no *prima facie* differences in patient outcomes. This supported the view that there were savings to be had without reducing patient care, and led to initiatives such as the advent of drug budgeting for general practitioner fundholders in the NHS in 1991. This and the high cost of many new drugs coming to market at the time focused attention on the costs of drug therapy.

The pharmaceutical industry argued that such a focus was flawed as it considered only the costs of drug therapy (pharmaco-accountancy perhaps) but did not consider the benefits or value of a drug – which might be expensive but either save money elsewhere in the healthcare system or be a better use of limited resources in terms of the health gain achieved than other healthcare interventions. The argument therefore was in favour of the application of health economics measuring costs and benefits to drug therapy, or pharmacoeconomics. This was initially used in promotional activities [3], making some journals reluctant to publish such analyses [4]. There was also evidence of publication bias: for example, 92% of pharmacoeconomics articles in most journals came down in favour of the drug in question, compared with only 30% in the *New England Journal of Medicine* [5].

Some argued, however, that pharmacoeconomics could be used for the public good, in improving the efficiency of healthcare, rather than either merely as advertising (by industry), or even just to contain drug

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expenditure (by government or health authorities), perhaps by a central national agency [6].

I first argued for a pivotal role of clinical pharmacology in such issues in this Journal 14 years ago [7, 8]. Clinical pharmacologists, I argued, had all the key skills in assessing efficacy, safety, and likely effectiveness in everyday practice, but needed to develop their understanding of the basics of health economics if they were to ensure the best treatment for either their own patients, or patients in wider society. I also argued that clinical pharmacologists need to move out of traditional academic pursuits in experimental medicine, and become more engaged in issues of improving prescribing, working with commissioners of service and practitioners, i.e. clinical pharmacology as a practical discipline rather than as a rather more arcane molecule (or now genome) based subject.

How have things progressed since then? The arguments for a broader health economic assessment of interventions or diagnostics, particularly in NHS practice, seem to have been won. Evaluation of interventions is the bread and butter of a large and growing special health authority, the National Institute for Clinical Excellence (NICE), now in existence for 10 years [9]. This has been driven in large part by pharmaceuticals, which account for over two-thirds of appraisals by NICE. NICE was not, of course, the originator of this (the Australian Pharmaceutical Benefits Scheme can claim that credit), but NICE have taken it to a level unseen in other jurisdictions and to great success.

These decisions remain controversial, however: there are always pharmaceutical companies and patient pressure groups willing to attack its judgements, sometimes by attacking its methods. Although an independent health authority, it has seemed sometimes to give way to political pressure. An example of this is the recent decision to increase NICE's commonly interpreted threshold of a cost per quality adjusted life year (QALY) of between £20 000 and £30 000 by an uncertain amount in conditions where there is 'end of life' care. This has a considerable human appeal, but lacks a scientific rationale and indeed undermines the scientific rationale of much else that NICE would do in this area [10]. Successive governments have also been adept at circumscribing other NICE conclusions that they did not like or found particularly unacceptable: for example, when NICE rejected the use of β-interferon for multiple sclerosis except in a trial or other research, the Government responded by announcing the creation of a large 'research' trial that would allow almost free prescribing of β-interferon [11]. Nearly 10 years later, the results of this trial remain unknown and it is unclear that they will ever be published.

It might have been argued that health economics was too theoretical a discipline to allow it to have such a centre stage in decision making in healthcare, but a counter argument was that health economics would be refined by such exposure and its methodologies would become much more robust [6]. This is indeed what has happened. NICE has not just applied health economics, but has also been instrumental in the development of methods that have stood up not only to scientific scrutiny, but also to media and legal examination. The methodology commonly used by NICE is the cost utility study, measuring benefits as a gained QALY and then estimating the NHS and publicly funded social services cost of achieving such a year. In practice, firm evidence on the benefits or likely future benefits measured in this way or on the costs now or in the future is rarely available; therefore, to estimate these it is usually necessary to construct complex economic models, often based on a randomized controlled trial, but inevitably extrapolated from the narrow confines of the trial to everyday practice (and to an NHS setting). The complexity of these models reduces their transparency. A sophisticated industry of creating such models, often from slender data, has arisen to service both the commercial sponsors and the NHS (and sometimes with the same individuals servicing both). The Scottish Medicines Consortium performs a similar role to NICE, but has chosen to adopt a simpler, less expensive approach. However, its deliberations are advisory only, not requiring health authorities to adopt its conclusions as NICE does, and less prominent on the world stage, and can perhaps afford to be less robust. The All Wales Medicines Strategy Group has powers similar to NICE.

One key criticism of this whole process is the spurious level of accuracy it lends to the value of a particular drug therapy based on thin data: it would be desirable that such evaluations be repeated periodically. NICE introduced its 'single technology appraisal' (STA) process in 2006 in response to Government requirements to speed the evaluation of new therapies. This depends on an economic model and clinical evidence submitted by the company sponsor, often based on one large pivotal clinical trial with extensive extrapolation on utilities, and real-world effectiveness and cost-effectiveness in the NHS. There was an undertaking that these STAs would be revisited within 2 years, but this is yet to happen. Also, the pattern of STAs has meant that multiple single drugs are evaluated in independent evaluations, e.g. for several drugs for breast cancer, rather than put together into a single coherent document that would be of most value to the NHS.

For all its difficulties, the work of NICE is rightly applauded. However, it is worth noting that so far it has operated at a time when healthcare budgets were rapidly expanding; how it will deal with budgets contracting – and perhaps the need to make much harsher decisions about the availability of expensive new interventions – from 2011 onwards remains to be seen.

As well as methodological developments, there are also policy developments in pharmacoeconomics. Schemes for sharing the (economic) risks of new drugs with uncertain or limited value based on pharmacoeconomics have been seen recently, e.g. for Velcade (bortezomib), although the history of such schemes has been mixed [12]. Similarly, and following a review by the Office of Fair Trading in the UK of

drug pricing [13], in the near future pharmacoeconomics will be 'reverse engineered' in a move to support 'value-based pricing'. Whereas up to now the flow in pharmacoeconomics in the UK (which allows companies free pricing for innovative drugs) has been:

(Company-determined price)/benefits → modelling → variable [cost/QALY]

in the future, for some products, the process will be

(NHS-determined price)/benefits ← modelling ← fixed/threshold [cost/QALY].

This is a highly controversial and perhaps brave, but logical, next step for pharmacoeconomics [14]. These developments should be regarded as experiments in my view, and we wait to see how they are implemented and firm evidence of their benefits.

Many European countries have also followed the UK lead in setting up agencies to evaluate these issues. Belatedly, the USA has recognized the need to undertake the kind of comparative effectiveness research, with health economics, that has been meat to NICE and NHS research programmes for many years. The Obama administration has invested more than $1 billion in the American Recovery and Reinvestment Act, but at present it is highly controversial as to how this will be used. To many on this side of the Atlantic, it looks like reinventing this particular wheel [15]. But just as health economic studies do not cross borders well because of changing contexts and patterns of healthcare, perhaps each country has to develop its own approach to the organization and administration of pharmacoeconomics.

What about clinical pharmacology in this context? Clinical pharmacologists have been heavily involved in this, including the Chair of NICE (Professor Sir Michael Rawlins) and the initial Chair of the NICE Appraisal Committee (Professor David Barnett). Their views on health economics are worth noting [16]: '..And although neither of us was versed in the black arts of health economics we have acquired sufficient knowledge to both understand the discipline's inherent strengths and weaknesses as well as be wary of the potential biases and prejudices of the health economists themselves'. They also reaffirm the importance of their background in clinical pharmacology in their work for NICE.

Many other senior clinical pharmacologists have been involved in NICE appraisal committees or the appeals committee. It is fair to say that NICE has recognized the skills of clinical pharmacologists in supporting its agenda. Clinical pharmacologists have also been prominent in the set-up and running of the Scottish and Welsh groups.

Clinical pharmacologists have also recognized the importance of this area: pharmacoeconomics is now seen as a key skill for our trainees and is part of the core curriculum. However, opportunities for trainees to engage with this is perhaps limited at present and more could be done, for example, by getting trainee clinical pharmacologists involved with the academic funded teams that conduct assessments on behalf of NICE.

So pharmacoeconomics has grown up in the past 14 years [17]. It started as a bastard science [18] largely driven by the pharmaceutical industry as a means of promoting the value of its products and thereby defending its markets, but has turned into a powerful tool to improve the efficiency of healthcare. It is now accepted as an important discipline, although sometimes based on rather less steady ground than one might wish or that some would acknowledge. I commented in 1995 that 'society expects efficacy, effectiveness and efficiency from drug therapy' – this is more than ever the case today.

I leave the last word to the editor of the *Lancet*, who decried pharmacoeconomics as low-level marketing in 1993 (in the service of patents perhaps) [19], but who, responding to a High Court vindication of NICE's approach in 2007, acknowledged pharmacoeconomics as a science and said 'This decision represents a victory for the way in which science is used in the service of patients' [20].

Competing interests

There are no competing interests to declare.

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