Commentary

"EVIDENCE AND VALUES: REQUIREMENTS FOR PUBLIC REIMBURSEMENT OF DRUGS FOR RARE DISEASES - A CASE STUDY IN ONCOLOGY"

Drummond and colleagues have provided a wide ranging, thoughtful, although slightly biased review of many of the important dilemmas faced by those who must make decisions regarding which drugs are reimbursed from the public purse.[1] They focus mostly on drugs for rare diseases, and how scientific evidence and social values can be combined to arrive at the best possible decisions. For those new to the field, this is an excellent introduction. To those with more experience who are looking for practical ways of doing things better, the vagueness of the recommendations may be unsatisfying. Indeed, in the end, it was not clear exactly what the authors w*ere* recommending. In this commentary, I focus on points mentioned in the abstract's conclusions and raise an additional issue that surprisingly was not at all mentioned - the high prices charged for brand name drugs.

The authors call for "…a fair and transparent decision-making process with appropriate community input", but what exactly does it mean? In my opinion, it means that decisions should be made by a group more diverse than experts in drug evaluation and cost-effectiveness analyses, which was the case in Canada until the Canadian Expert Drug Advisory Committee (CEDAC) and the Ontario Committee to Evaluate Drugs (CED) each added two members of the public. It also means that all of the information provided to the reimbursement committees, and the results of the deliberations of those committees, should be made public. It means that reimbursement committees should be influenced by the careful deliberations of members of the public (e.g. the Citizens' Council of the National Institute for Clinical Excellence[2]) about value sensitive issues such as whether reimbursement decisions about drugs for rare diseases should use a different framework than drugs for more common diseases. However, in my opinion, it does not mean that the deliberations of reimbursement committees should occur in public (there is a reason that judges and juries deliberate in private) or that reimbursement committees should be flooded with non-evidence-based testimonials about the benefits or harms of a drug (careful studies of the drug being considered should identify the benefits and harms in an unbiased way). The approach of the Swedish drug reimbursement agency, which has separated reimbursement decisions (which are made by a diverse group of clinicians and members of the public) from the scientific evaluation of the effectiveness and cost-effectiveness of the drug under consideration (which is done by a group of experts, who present their findings to the decision makers) is a good model.[3] This puts the decision making in the hands of a group of individuals who are more representative of the public than is the case in Canada (even with the addition of a couple of public members to CEDAC and CED), yet at the same time recognizes the importance of using rigorously evaluated scientific evidence when making reimbursement decisions.

One of the challenges of assessing drugs for rare diseases is that the small number of patients with the condition makes conducting large randomized trials impossible. The authors therefore call for the development of valid surrogate markers for rare diseases. I support this in principal, but I am not clear how this is to be done for very rare diseases. In order to determine that a surrogate marker truly is valid, one must study a large number of patients who are followed for a long enough time to show that a certain change in the surrogate marker leads to a certain change in the clinically important outcome.[4] The authors argue that some statistical techniques will help increase efficiency, but I remain deeply skeptical that it will be possible to reliably identify valid surrogate markers without long-term follow up of patients. I am also concerned that uncontrolled "registries" of patients receiving a particular drug (e.g. the Canadian registry of

patients with Fabry's disease[5]) may not yield useful scientific information about the effectiveness of the drug. My guess (and it is admittedly only a guess) is that for most patients in the Fabry's registry their disease will slowly progress, and it will be difficult to determine whether the progression is slower than would have been expected without drug treatment. I hope I am wrong, and that the progression of the disease is dramatically slower than historical controls.

The authors suggest that we need to acknowledge "…that the traditional measures of benefit in economic studies do not incorporate all elements of social value." That already occurs and explains why most drug plans do not reimburse sildenafil for erectile dysfunction despite a generally attractive cost-effectiveness ratio[6], and why CEDAC suggested reimbursing erlotinib for advanced lung cancer despite a somewhat unattractive cost-effectiveness ratio.[7] Studies of decision making in Australia and the United Kingdom have shown that the cost-effectiveness ratio is used as a guide to decision making, not an absolute rule.[8,9] The authors suggest that it might be possible to identify a group of diseases that for some reason are viewed as having "higher social value" than others, and thus society would be willing to reimburse drugs for those conditions even if they have a relatively unattractive cost-effectiveness ratio. They suggest that some cancers and rare diseases might have a higher social value. However, it isn't clear to me why these conditions were chosen; why not heart failure or severe depression? Could it be that extremely expensive drugs with unattractive cost-effectiveness ratios have not yet been developed for heart failure and depression? Once they are developed, will we hear similar arguments for the higher social value of those difficult diseases? I think it is dangerous to select one disease over another as having particular social value. This is different from saying that we value life saving drugs more than cosmetic drugs – an approach that does not discriminate for or against a particular disease.

The authors' final conclusion is that one must "….balance equity with an efficient use of resources". The authors define equity as "fairness in access to therapies". But other definitions of equity include "freedom from bias or favouritism" or "fairness; impartiality; justice". I would argue that the use of a cost-effectiveness or cost-utility ratio to guide decision making is extremely equitable because it allocates scarce resources to maximize societal benefit, and it values the health gains of individuals with different diseases equally. This would appear to be more equitable than labeling some disorders as having higher social value than others.

I will now address an important issue that the authors completely and surprisingly ignored – the high (and seemingly never endingly increasing) price charged for drugs. No review of drug reimbursement is complete without recognizing that there are two words in "cost-effectiveness", and that the first word is very much dependent upon the price charged for the drug. Unfortunately, that price usually has very little to do with the drug's incremental benefit, and everything to do with what the major markets (especially the United States) will bear. During the last decade there has been a marked increase in the price of drugs. The median annual price of drugs considered by CEDAC during 2003-06 was approximately $4000 per year, with many greater than $20,000 per year, and a few near $300,000 per year but without a marked increase in effectiveness. Thus, it isn't surprising that many new drugs are not cost-effective.

One approach to this situation is to do what the authors have done - ignore this massive increase in price, consider it part of the price of innovation, and suggest that we should be accepting higher cost-effectiveness ratios for various diseases. This would increasingly take funds away from other valuable investments in health care, and perhaps lead to even more patients without a family physician, and ever longer wait times in over-crowded emergency departments.

Another approach would be to draw a "line in the sand" and indicate to the pharmaceutical industry that they must meet certain standards of efficiency. It is important for the pharmaceutical industry to understand that drug reimbursement committees aren't purchasing drugs; they are purchasing health outcomes. If the industry cannot produce drugs that yield improved health outcomes at a price that is roughly similar to the price of hip arthroplasties, angioplasties, post-heart attack rehabilitation, and other health care

interventions, then those drugs will not be paid for. This is not to say that it isn't legitimate to charge extremely high prices for drugs for extremely rare diseases, like Fabry's disease, because the market is extremely small. However, it is not acceptable when it is argued that the price of a new chemotherapeutic agent must be high because the subset of patients in which it is first tested is small (e.g. trastuzumab for advanced breast cancer), but then the price is not decreased when the same drug is found to be effective in a much broader group of patients with breast cancer. The "rareness" of a disease should not be used as a justification for a high price, only to be followed by a massive market expansion.

To conclude, pharmaceutical reimbursement decisions are a complicated mix of evidence, values and politics. Making the right decision is often not easy and will frequently be controversial no matter how the decision is made. The authors summarize the situation well when they state "Unfortunately, there is no overarching principle for resolving the cluster of value-conflicts that arise when, for example, the incremental cost-effectiveness is high, the evidence is weak, the benefit is small, the cost is high, and the patients have no feasible alternative therapy." This brings back memories of almost every meeting of CEDAC that I attended.

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Declaration of Interests

The author was Chair of CEDAC from 2003-2006, currently serves on Data Safety Monitoring Boards for Novartis, and has consulted for Novartis and Johnson and Johnson during the last year. He received honoraria for all of these commitments. He is has worked with many of the authors of the article that is the subject of this commentary.

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