The schizophrenia drug-treatment paradox: pharmacological treatment based on best possible evidence may be hardest to practise in high-income countries†

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Summary Most people with schizophrenia live in low- and middle-income countries in which clinicians/policy makers are not the first targets of marketing. Because it is years after a drug is first launched that the full effects become known with confidence, the evidence upon which to base practice in low- and middle-income countries may be less biased than that in richer nations.

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The number of trials relevant to people with schizophrenia produced by any one country depends neither on the national population of those with the illness nor on the country's technical sophistication. It is, with a few notable exceptions, much more closely correlated with the gross wealth of the nation, which in itself may be a proxy for the national activity of the pharmaceutical industry (Moll *et al*, 2003). In the past half-century, industry's research activity has led to innovations and revolutions in the care of people with schizophrenia (Freeman, 1958) and has never stood still. Since 1953, the year of the advent of chlorpromazine, many different antipsychotic medications and drug preparations have become available. Drugs, however, have never stopped schizophrenia from being an illness that, for most, seems to require lifelong treatment. This has generated enormous income for companies (IMS Health Inc., 2006). Of course this income and power can be misused (Montgomery *et al*, 2004; Heres *et al*, 2006); nevertheless, industry invests more in research and development than all 'independent' sources, and this is likely to remain the case.

Relentless industry marketing – whether in the form of advertisements, research articles, teaching events, opinion leader talks, guideline lobbying, media seeding, visiting sales representatives or even that not-so-free pizza (Moynihan, 2003*a*,*b*) – fosters hope of the new being better than the old. For about two decades after their patenting, new drug treatments are expensive. Even in countries where generic manufacturing of new drugs occurs through the legal loophole of the 'process patent' – where it is only the process of manufacture that is recognised as patented, allowing the manufacture of a patented drug by altering the process even in a minor way – distribution may not be wide and the drugs can remain inaccessible. For example, owing to loopholes in current patent law, more than 20 brands of olanzapine and risperidone are available in India at a fraction of 'Western' prices. In Bihar, one poor state in India, there are more people with schizophrenia than in the whole of North America. Nevertheless, even these cheaper preparations are not affordable for the poor in Bihar and distribution through the state healthcare system is variable. In any case the World Trade Organisation and the General Agreement on Tariffs and Trade are ensuring that this loophole is being closed and countries are less readily able to exploit the current situation. In Brazil, for example, atypical antipsychotic drugs remain expensive and are only generally affordable if paid for by the state, and this provision varies. Four-fifths of the world's population of people with schizophrenia live in low- or middle-income countries; nevertheless, global marketing relentlessly promotes a collective guilt whereby to advise the use of older, inexpensive drugs is, somehow, to give a second-class service.

COMMERCIAL INTERESTS AND CLINICAL EVIDENCE

It is hard to know the 'objective' facts about the effects of these treatments, and it may be impossible during the period in which large pecuniary interests are heavily involved. As time passes, more complete data from known trials begin to emerge and less-positive studies that had been previously unknown come to light (Easterbrook *et al*, 1991; Gilbody *et al*, 2000). In addition, once a drug is off patent, companies may well be more generous with data. Whether or not this is as it should be, it seems likely that this situation will change only slowly (Chalmers, 2006).

Rich countries develop and evaluate the new drugs, and these same nations are the first focus of the initial decades of marketing. As the battle of the companies is fought out in high-income countries, clouds of dust from marketing obscure the view. Unless effects are dramatic, it takes decades for the dust to settle. For example, in the past 20 years millions of people with schizophrenia in these high-income countries have been caught up in the struggle between companies producing different new antipsychotic drugs. Inevitably there are winners and losers. Many win. Everyone has been forced to be more thoughtful about prescribing, and new compounds have their own effect profiles and are welcome additions to the management of this difficult and damaging illness. On the other hand, some in the rich nations suffer as a result of ill-publicised effects of the new drugs, and have to be compensated (McGough & Abboud, 2005). However, many more are not remunerated for the major or minor ill effects they suffer, save only in the knowledge that evidence of the problems they encountered may be commonly known by the time the medications become available to the other 80% of the world's population.

During this period many in the lower-income countries have to observe the battle from afar and they are forced to use older drugs. On the other hand, much is known about these familiar compounds. The battles that did rage for the first-generation drugs are long over, and much positive and negative data are available. As time passes and newer medication is becoming accessible in less-affluent nations, the second generation of battles have lost some of their urgency and aggression.

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THE SCHIZOPHRENIA TREATMENT PARADOX

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Here is the schizophrenia drug treatment paradox. Evidence-based practice is the judicious use of the best available evidence in patient care or policy making (Sackett *et al*, 1997). Judicious use of best available evidence for the care of people with schizophrenia is possible everywhere. However, by the time drugs are widely accessible in lower-income nations the 'best available evidence' may well be better in these poor countries than was the case when the drugs were first marketed in rich nations.

Recent findings from larger pragmatic and independently funded studies reinforce this argument (Lieberman *et al*, 2005; Lewis *et al*, 2006). If new drugs are compared with haloperidol, an antipsychotic particularly associated with obvious adverse effects, the new experimental compound can hardly fail to seem beneficial in terms of adverse effects (Joy *et al*, 2001). If, however, newer compounds are compared with more benign older drugs there is a consistent finding that there is little to choose between old and new medications, even on adverse effect outcomes. So shocking are these results to a subspecialty convinced by marketing that the trialists themselves are surprised and perplexed at the messages to give, and journals may fail to encourage publication of important results.

In both rich and poor countries, there is no need for collective guilt about use of older treatments. Use of these tried and tested drugs has more chance of being based on really good evidence than that of newcomers for which marketing interests obfuscate fact. There is, however, an enormous need for more independent, well-designed, conducted and reported pragmatic randomised trials in this area. In order to offer people in rich countries more protection from being unofficial participants in enormous post-licensing studies, these pragmatic randomised trials should take place before widespread introduction of the drugs.

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