Amid the gloom, however, there is some light. Simply collecting data and presenting it to governments can stimulate action. (Many governments are unaware of what its citizens pay for drugs, two of the report's authors told the *BMJ*.) In the Lebanon, the survey included in the report was done by the Ministry of Health, and in response it reduced a number of fixed drug prices. In Kuwait, access to free essential medicines was extended to non-Kuwaitis after its survey was published. Current efforts to develop new drugs for neglected diseases offer further encouragement. Research undertaken by the public-private partnerships set up over the past five years has a good chance of delivering eight or nine new chemical entities within the next five years.[6]

Furthermore, thanks to persistent and passionate lobbying by Kenya and Brazil, augmented by the input and signatures of 5000 eminent scientists, physicians, policy makers, Nobel prize winners, MEPs (members of the European Parliament), and industry representatives, a landmark resolution was adopted at last week's World Health Assembly. This commits the World Health Organization to producing a blueprint for a new system of prioritising and financing pharmaceutical research aimed at stimulating the development of drugs, vaccines, and diagnostics for diseases that member states identify as health priorities: a marked contrast to the status quo, where priorities and prices depend primarily on Western based industries. One of the most important suggestions of the resolution is that incentives for research and development should be linked to health outcomes.

Shock and sadness at Dr Lee Jong-wook's untimely death permeated this year's World Health Assembly. If WHO's commitment to redress the research imbalance delivers on its promise to provide more effective and affordable medicines for the most disadvantaged sick people in the global village, there can be no more fitting legacy.

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Competing interests: None declared.

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doi 10.1136/bmj.38868.651736.47

Are older antipsychotic drugs obsolete?

No

Antipsychotic drugs have been essential in treating schizophrenia since chlorpromazine was introduced in the mid 1950s. By 1980 over 20 other antipsychotic medications were available, and all of them are now sold as generics. Ever since clozapine was shown in the late 1980s to be more effective for treatment resistant patients with schizophrenia than the older antipsychotic agents,[1] numerous new antipsychotic drugs have been synthesised and released, with claims of greater efficacy and better tolerability than the older generic agents. Are these claims true, and how should clinicians go about choosing the appropriate drug for their patients with schizophrenia?

Several authoritative and widely adopted treatment guidelines for the use of antipsychotics, such as the TIMA algorithm (Texas Implementation of Medication Algorithms), recommend only the newer antipsychotic drugs as first and second line treatments, reinforcing the perception that the older drugs are therapeutically inferior. These new antipsychotics are often referred to as "atypical" or "novel" agents, suggesting that their mechanism of antipsychotic action is different from that of the older drugs. Yet both old and new medications appear to exert antipsychotic effects via blockade of dopamine D2 receptors in the brain.[2]

With regard to efficacy, an early meta-analysis conducted by Leucht et al found no significant advantage of risperidone, olanzapine, or quetiapine over the older drug haloperidol, despite the data being from studies funded by the manufacturers of the new agents.[3] Leucht et al did, however, find a lower incidence of extrapyramidal side effects associated with the newer drugs. Davis et al, on the other hand, in a separate meta-analysis of all available studies purporting to examine the differences between novel and conventional agents concluded that the newer agents had both efficacy and tolerability benefits over the older ones.[4]

A more wide ranging meta-analysis comparing low potency, older antipsychotics with newer agents found little or no difference in either efficacy or tolerability, including extrapyramidal side effects.[5] Similarly, the few independently sponsored head to head studies found no differences in therapeutic benefits between olanzapine and chlorpromazine[6] or between olanzapine and haloperidol (with prophylactic benztropine).[7]

Starting in December 2000 the National Institutes of Mental Health sponsored a large randomised controlled trial of over 1400 patients with schizophrenia, comparing the effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone with that of a conventional antipsychotic, perphenazine (Clinical Antipsychotic Trials of Intervention Effectiveness, CATIE).[8] Surprisingly, perphenazine was not only as effective as three of the four newer agents but also did not cause more extrapyramidal side effects. Olanzapine alone showed marginally higher effectiveness, but it was associated with a significantly greater risk of weight gain and other adverse metabolic changes.

The results of the CATIE study permit a range of interpretations, depending on one's priorities or biases. Thus, one might argue that ziprasidone is the "best" drug because its effectiveness is in the middle of the

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pack and its side effects are among the lowest. Alternatively, olanzapine was the most effective agent, even though it was associated with the most weight gain and other metabolic side effects. Others might consider that perphenazine, which was in the middle range in effectiveness and side effects but cost much less than the others, is the best in terms of cost effectiveness.

Drug companies might be expected to selectively focus on the small marginal benefits of drugs they manufacture and sell. But pharmaceutical giants are not the only parties with financial conflicts of interest. Government agencies and insurance companies, with vested interests in paying as little as possible for care, might choose to focus on the lack of significant difference between older and newer agents, since the older ones have a clear cost advantage, and recommend the older agents as the best initial choice for patients.

Many questions remain.[9] In the CATIE trial the dosing of all agents except olanzapine was set at or below that recommended by the Food and Drug Administration, while olanzapine could be given at 50% above the recommended dose. Could the (slight) advantage of olanzapine be a function of the higher dose? The study was not long enough to adequately assess the true health consequences of the metabolic changes, even though these adverse effects, as opposed to more immediate neurological problems, might be life shortening in the long run. Clozapine, which, yet again, turned out to be the best choice for those who did not respond to another agent,[10] also produced troubling metabolic effects. Thus, choosing among the available antipsychotic agents involves difficult trade-offs. Truly novel agents are still needed.

What are clinicians to make of all this, in terms of selecting an antipsychotic drug for their patients? Patients themselves (and their care givers) need to be involved in the choice and informed about data that might help them with the decision. Such information should include the fact that efficacy differences between older and newer drugs (with the exception of clozapine) are small, if they exist at all. Patients and care givers should also be aware of the trade-offs between fewer neurological side effects (including akathisia, parkinsonism, or tardive dyskinesia) and more adverse metabolic effects (such as weight gain, hyperlipidaemia, and hyperglycaemia).

For patients who do not respond well to one antipsychotic drug the evidence is consistently in favour of clozapine as the agent most likely to be effective. Yet the rates of clozapine prescribing appear to be far below what would be expected if this was being recommended for all patients who do not respond to treatment. Not only clinicians but patients and families may need to be better educated about clozapine, and treatment guidelines need to be revised to reinforce this.

Cost may be a critical barrier to accessing medication, particularly for long term treatment. Clinicians and patients for whom cost is a key concern should be relieved to know that the cheaper older antipsychotics have not become obsolete.

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Competing interests: In the past five years RG has received research project grants from Lilly, Janssen, Pfizer, and Bristol-Myers Squibb and honorariums for speaking from AstraZeneca, Bristol-Myers Squibb, and Janssen.

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Should UK allergy services focus on primary care?

The time is ripe to rise to this challenge

The marked increase in the prevalence of allergic disease over the past few decades has left the NHS ill prepared. In response to the Health Select Committee's damning report in 2004 on allergy services,[1] the Department of Health and the Scottish Executive are currently reviewing all aspects of provision of allergy care. Their separate reports will be published shortly. A key question is whether it would be more effective for the NHS to emulate the model used in other parts of Europe and North America and invest in expanding specialist services for allergy or—more controversially—to concentrate efforts on developing primary care services. This choice will have substantial and lasting implications for people with allergies in the United Kingdom and will probably affect the thinking of policy makers in other parts of the world who are grappling with similar rapid increases in the prevalence of allergic disease.

Around one in three of the UK population have allergic symptoms at some point in their lives.[2] Localised or organ specific allergic disorders such as atopic eczema, allergic rhinitis, and asthma are

BMJ 2006;332:1347–8