

Conclusion

Atypical antipsychotics are a heterogeneous group of drugs and generalisations about the group are only sometimes justifiable. A number of atypical antipsychotics have superior efficacy with respect to typical drugs in positive, negative, cognitive and mood symptoms. All atypical antipsychotics are associated with a lower risk of extrapyramidal adverse effects, a characteristic of major significance to patient outcomes. In addition, several atypical antipsychotics do not cause the hyperprolactinaemia associated with all typical compounds. The benefits of reduced extrapyramidal adverse effects justify the cost of prescribing atypical instead of typical antipsychotics.

References

1. Hope JD, Keks NA, Sacks TL, Freer T. Abnormal involuntary movements in people with schizophrenia in the community. *Med J Aust* 1999;171:111-2.
2. Leucht S, Pitschel-Walz G, Abraham D, Kissling W. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res* 1999;35:51-68.
3. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *Br Med J* 2000;321:1371-6.
4. Henderson DC. Atypical antipsychotic-induced diabetes mellitus: how strong is the evidence? *CNS Drugs* 2002;16:77-89.
5. Koro CE, Fedder DO, L'Italien GJ, Weiss SS, Magder LS, Kreyenbuhl J, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *Br Med J* 2002;325:1-5.
6. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry* 2003;60:553-64.
7. Csernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 2002;346:16-22.
8. Geddes J. Prevention of relapse in schizophrenia. *N Engl J Med* 2002;346:56-8.
9. Rosenheck R, Perlick D, Bingham S, Liu-Mares W, Collins J, Warren S, et al. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. *JAMA* 2003;290:2693-702.

Professor Keks has received research funding from, or has been a consultant to, all pharmaceutical companies marketing atypical antipsychotic drugs in Australia.



Are atypical antipsychotics advantageous? – the case against

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Summary

Conventional antipsychotic drugs are just as effective as atypical antipsychotics. Some of the atypical drugs appear to have an efficacy advantage, but it is small and of marginal clinical significance. The apparent better tolerability of the atypical antipsychotics in terms of extrapyramidal symptoms is variable and dose-dependent. It needs to be balanced against the problems of weight gain and metabolic adverse effects that are likely to contribute to long-term morbidity and mortality. Atypical antipsychotics are far more expensive than conventional drugs. Whatever modest benefits some of them may appear to have are outweighed by their high costs.

Key words: cost-effectiveness, schizophrenia.

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Introduction

There is a tendency for Australian doctors to prescribe newer and more expensive drugs. In psychiatry this is reflected in the dramatic increase in prescriptions for so-called 'atypical' antipsychotic drugs in preference to 'conventional' or 'typical' antipsychotics. Atypical antipsychotics account for over two-thirds of all antipsychotic drug prescriptions, and in 2003 the most commonly prescribed atypical antipsychotics (olanzapine, risperidone and quetiapine) accounted for a million prescriptions at a cost to government of \$197 million. However, do these drugs offer significant clinical advantages that make them good value for money?

What is an atypical antipsychotic?

All currently available antipsychotic drugs competitively block dopamine D2 receptors. This is the basis of their antipsychotic efficacy, but it is also the mechanism by which they induce extrapyramidal adverse effects and increase prolactin concentrations.

Atypical antipsychotics are defined by an absence or marked reduction of extrapyramidal effects and prolactin elevation. These characteristics are probably due to a lower affinity for D2 receptors, compared to most typical antipsychotics.

However, using these defining criteria, there is no clear boundary between typical and atypical drugs. All antipsychotics have the potential to produce extrapyramidal adverse effects in a dose-dependent manner and most increase prolactin. The other pharmacological properties of the typical and atypical drugs also overlap, for example, their capacities to block various monoamine and acetylcholine receptors and produce other adverse effects. Neither group is homogenous with respect to its adverse effect profile.

Clinical trials of comparative efficacy

Studies comparing typical and atypical antipsychotics usually show equal efficacy or, at most, modest therapeutic superiority for the atypical drug. There is usually an advantage for atypical antipsychotics with respect to extrapyramidal adverse effects. However, the randomised controlled trials, from which such results are derived, need to be interpreted with caution.

Selection of comparator

The choice and dose of the comparator (typical) drug is one that usually gives the atypical drug the best chance of appearing in a favourable light. In particular, the dose of the comparator is frequently higher than would be required for optimal therapeutic blockade of D2 receptors. This can have a number of effects:

- the rate and severity of adverse effects produced by the typical drug are greater than for the atypical drug
- secondary negative symptoms and cognitive impairment are likely to be greater with the typical than with the atypical drug.

Under these conditions the high rate of dropout from trials, which is often as much as 50–60% over six weeks or so, is not likely to be random. This can further bias results in favour of the atypical drug.

Selection of patients and outcomes

Controlled trials usually measure only symptoms, adverse effects and relapse/remission indicators. They fail to provide a broader perspective using more comprehensive measures such as social and occupational function, quality of life, and health utility indices that would make cost-effectiveness analyses easier to undertake. The nature of randomised clinical trials is such that large numbers of potentially eligible patients are excluded for various reasons such as inability to give consent, and comorbid substance abuse. These and other factors contribute to selection bias. Likewise, patients having their first episode of psychosis

are rarely explicitly identified and studied in phase II or III clinical trials. Schizophrenia is not a homogenous disease and different patients may respond differently to the same drug, but this is not knowable in advance and thus clinical trials cannot yet be designed to take this into account.

Duration of trials

Most therapeutic trials are brief (about 6–8 weeks) and there is a relative paucity of long duration trials (six months to one year or more). This is not just a function of the difficulties in retaining participants in clinical trials, but relates to industry's imperative to demonstrate efficacy and satisfy the requirements of regulatory agencies. Given that schizophrenia, the primary indication for atypical antipsychotics, is a chronic or relapsing condition, long-term study data are especially important. The absence of these data leaves large gaps in our knowledge about long-term efficacy and safety.

Sponsorship

To these methodological shortcomings and sources of bias in comparative efficacy studies should be added the bias inherent in clinical trials sponsored by the pharmaceutical industry. Although this bias has not been directly addressed in schizophrenia, there is evidence to suggest that trials sponsored by pharmaceutical companies are 3–4 times more likely than non-industry sponsored trials to report results in favour of the company's product.^{1,2}

Comparative effectiveness

A number of meta-analyses have been published comparing the efficacy of typical and atypical antipsychotics. One much criticised systematic review reported that there was no clear evidence that atypical drugs were more effective or better tolerated.³ Another found a 'modest' advantage for atypical antipsychotics in relapse prevention.⁴ A further study reported that, while the atypical antipsychotics aripiprazole, quetiapine and ziprasidone had no greater efficacy than typical drugs, there was a statistically significant but small advantage (effect size 0.21–0.29) for amisulpride, olanzapine and risperidone.⁵ The same study reported a moderate advantage (effect size 0.49) for clozapine relative to typical drugs. This study highlights the fact that, in terms of efficacy, the atypical drugs are clearly heterogeneous.

While clozapine has generally been regarded as effective for treatment-resistant schizophrenia, another recent meta-analysis did not find it had a substantial advantage.⁶ The meta-analysis noted that where a greater advantage was found for clozapine it was associated with short duration studies, financial support from a drug company and higher baseline symptom score. However, there is evidence that clozapine can be effective in reducing suicidal ideation and improving negative symptoms.

In relation to cognitive function, it seems likely that atypical drugs do not have significant advantages when compared to low therapeutic doses of a typical antipsychotic.⁷ Even with respect to extrapyramidal adverse effects atypical antipsychotics appear to have no advantages over low-potency antipsychotics such as chlorpromazine.⁸

It seems reasonable to conclude that:

- atypical antipsychotics are not all the same and should not be regarded as a homogenous class in terms of efficacy and adverse effects
- if there are any efficacy advantages for some atypical antipsychotics, they are small, with the possible exception of clozapine
- there is as yet no consistently demonstrated advantage for atypical antipsychotics in terms of negative symptoms or cognitive function
- there is a tolerability advantage for atypical antipsychotics as far as extrapyramidal adverse effects are concerned, but this is dose-dependent and most antipsychotics, if given at sufficiently high doses, will cause these adverse effects in a substantial proportion of patients.

While tardive dyskinesia is less likely to occur with atypical drugs, weight gain, obesity, hyperlipidaemia, impaired glucose tolerance and diabetes mellitus have been associated with atypical antipsychotics, most notably clozapine, olanzapine and, to a lesser extent, quetiapine. In some cases there may therefore have to be a trade-off between the short-term tolerability of atypical drugs and the potential long-term morbidity or mortality due to metabolic and cardiovascular diseases.

Cost-effectiveness of atypical antipsychotics

If there is a small efficacy advantage for at least some atypical antipsychotics (excluding clozapine as a special case with particular indications), is this advantage worth the large additional cost? For example, if the average cost of haloperidol is about 2 cents per day and that of olanzapine \$11 per day, does olanzapine confer an additional benefit commensurate with its greater cost? Few adequately designed independent studies have tried to address these questions.

One randomised controlled trial of 12 months used a comprehensive set of outcome measures in comparing olanzapine and haloperidol (with prophylactic benztropine). It found no advantages for olanzapine in compliance, symptoms, extrapyramidal symptoms or overall quality of life. A small benefit for olanzapine in improving cognition and reducing akathisia had to be balanced against weight gain and vastly greater costs of the order of US\$3–9000 per year.⁹

An Australian cost-modelling study has also looked at the issues. It reported that the relatively modest health benefits

of risperidone and olanzapine were associated with an unfavourable cost-effectiveness profile compared to typical antipsychotics, unless the typical drugs caused moderate to severe adverse effects.¹⁰

Conclusion

Are atypical antipsychotics advantageous? The short answer is perhaps sometimes, but not much. Atypical antipsychotics are not a homogenous class. There may be an efficacy advantage for some of these drugs, but this is small, of marginal clinical significance, and vastly outweighed by their very high cost. Insufficient attention is being paid to their weight gain and metabolic adverse effects, with attendant implications for long-term morbidity and mortality, in favour of emphasising short-term tolerability advantages.

References

1. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003;289:454-65.
2. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *Br Med J* 2003;326:1167-70.
3. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *Br Med J* 2000;321:1371-6.
4. Leucht S, Barnes TR, Kissling W, Engel RR, Correll C, Kane JM. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry* 2003;160:1209-22.
5. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry* 2003;60:553-64.
6. Moncrieff J. Clozapine v. conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination. *Br J Psychiatry* 2003;183:161-6.
7. Green MF, Marder SR, Glynn SM, McGurk SR, Wirshing WC, Wirshing DA, et al. The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. *Biol Psychiatry* 2002;51:972-8.
8. Leucht S, Wahlbeck K, Hamann J, Kissling W. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet* 2003;361:1581-9.
9. Rosenheck R, Perlick D, Bingham S, Liu-Mares W, Collins J, Warren S, et al. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. *JAMA* 2003;290:2693-702.
10. Magnus A, Carr V, Mihalopoulos C, Carter R, Vos T. Assessing cost-effectiveness of drug interventions for schizophrenia. *Aust N Z J Psychiatry*. In press 2005.

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