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What's 'atypical' about the newer antipsychotics?

The volume of prescriptions for atypical antipsychotics continues to increase and in general practice they are now prescribed for schizophrenia twice as often as conventional antipsychotics.* While these newer drugs appear less likely to cause movement disorders, recent findings have highlighted adverse effects (including sudden cardiovascular death and diabetes), and challenged preconceptions about the differences between new and old drugs.

What CATIE did

Adverse effects have a major impact on the clinical effectiveness of both old and new antipsychotics, as observed in 2 recent large-scale, publicly funded trials.^{1,2} The trials, part of the US National Institute of Mental Health CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) program, were designed to look at real-life conditions and outcomes.

The largest CATIE study enrolled almost 1500 participants with chronic schizophrenia.¹ Participants were randomised to 18 months' treatment with perphenazine (a conventional antipsychotic related to fluphenazine and no longer marketed in Australia) or an atypical (see Table 1, over). The primary endpoint was the discontinuation rate, a measure of overall clinical effectiveness reflecting the balance of therapeutic benefits and undesirable effects.

With all drugs, a strikingly large proportion of participants discontinued early because of intolerable side effects or a lack of efficacy (see Table 1). Olanzapine had lower rates of discontinuation and hospitalisation for exacerbations of schizophrenia than other drugs, but was associated with significantly worse weight gain and elevations in glycated haemoglobin (HbA_{1c}) and lipid concentrations. Some commentators have pointed out that olanzapine may have been advantaged by a higher maximum allowed dose than the other drugs in the study.³

Despite expectations that newer drugs would be superior to an older one, perphenazine was similar to quetiapine, risperidone and ziprasidone in terms of discontinuation rates, hospitalisation for exacerbation of schizophrenia, and on rating scales of schizophrenia symptoms and illness severity. There were significantly more discontinuations due to extrapyramidal symptoms with perphenazine, although the proportion of patients with extrapyramidal symptoms did not differ significantly between drugs.

Antipsychotics and Alzheimer's

A second CATIE study investigated olanzapine, quetiapine, risperidone or placebo for psychosis, aggression or agitation in 421 people with Alzheimer's disease.² The trial found no significant difference between any drug and placebo in ratings of clinical improvement. Patients discontinued all treatments at similar rates, after about 8 weeks on average. While they more often discontinued placebo for lack of efficacy, they discontinued drug therapy because of adverse effects or intolerability (for example, extrapyramidal side effects in the risperidone and olanzapine arms). Other drug-related adverse effects included sedation, confusion and cognitive disturbances.

* source: BEACH data, Australian General Practice Statistics and Classification Centre, a collaborating unit of the Family Medicine Research Centre, University of Sydney and the Australian Institute of Health and Welfare

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Table 1. Selected results from the main CATIE schizophrenia trial¹

Drug	Discontinuations			Hospitalisation for exacerbations of schizophrenia (per 100 patient–years)	Significant weight gain (>7% of baseline)	Elevated serum prolactin level
	Lack of efficacy	Adverse effects*	Extrapyramidal symptoms			
olanzapine Zyprexa	15% [†]	19%	2%	29 [†]	30% [†]	No
quetiapine Seroquel	28%	15%	3%	66	16%	No
risperidone Risperdal	27%	10%	3%	45	14%	Yes
ziprasidone Zeldox	24%	15%	4%	57	7%	No
perphenazine [‡]	25%	16%	8% [§]	51	12%	No

Note: shaded areas indicate significant differences from other antipsychotics

* includes extrapyramidal symptoms

[†] p <0.001 (group comparison)

[‡] a conventional antipsychotic not currently marketed in Australia (previously marketed as Trilafon)

[§] p = 0.002 (group comparison)

What's in a name? Atypical antipsychotics

Soon after its introduction overseas in the early 1970s, clozapine was labelled an 'atypical' antipsychotic — one with the unprecedented characteristic that it produced markedly fewer extrapyramidal side effects. The pharmacology of clozapine differs from that of the conventional antipsychotics — another aspect that is atypical.

Drug development efforts have since focussed on matching clozapine's reduced propensity to cause movement disorders. The resulting 'atypicals' (or 'second-generation antipsychotics') are an improvement in this respect, but rather than forming a true class, they encompass a variety of chemical structures, receptor affinities and, as is becoming clearer with time, adverse-effect profiles.

While the label 'atypical' has stuck, it is worth noting that these drugs differ as much from each other as they do from the older antipsychotics. Atypical doesn't simply mean better — each drug has its individual combination of benefits and harms.

Serious adverse events in dementia trials

Atypical antipsychotics are poorly tolerated in behavioural disturbances of dementia, as highlighted by the CATIE Alzheimer's disease trial (see p.1).² In addition, they have been associated with small but significant risks of death and stroke.

An increased death rate was found in an analysis of placebo-controlled trials of aripiprazole, olanzapine, quetiapine and risperidone in dementia patients, mostly due to cardiovascular events (e.g. heart failure, sudden death) or infections (e.g. pneumonia).⁴ Use of atypicals was associated with 1 death for every 100 patients treated over 10–12 weeks.⁵ Additionally, both olanzapine and risperidone were associated with an increased risk of fatal and non-fatal strokes and

transient ischaemic attacks.^{6,7} Conventional antipsychotics may carry similar risks, but there is insufficient evidence to draw conclusions.^{4,5}

If behavioural disturbances mean there is a risk of harm to the person with dementia or to others, or if the symptoms are significantly distressing, a trial of an antipsychotic may be necessary, but efficacy, adverse effects and ongoing need must be monitored. Review after 3 months at most and discontinue if treatment is ineffective.⁸ Always manage underlying causes and try non-drug strategies first.

Managing behavioural disturbances of dementia will be the topic of the May issue of *Prescribing Practice Review*.

Long-term adverse effects in perspective

Trial results quantify the prevalence of short-term or common adverse events from antipsychotics as well as the overall effect of these adverse events on discontinuations. Unfortunately, clinical trials are still too small or too short to measure the rates of adverse events that are less common or slow in onset, such as diabetes or tardive dyskinesia. Epidemiological studies can give estimates of risk but cannot establish that drug effects are the cause. Because of these uncertainties, comparing the balance of benefits and harms of different drugs in long-term antipsychotic treatment remains a challenge.

Diabetes and metabolic syndrome

Epidemiological studies have found an association between the onset of type 2 diabetes and using clozapine or olanzapine, or, in some studies, risperidone or quetiapine.^{9,10} Trial data show that clozapine and olanzapine are more likely to cause weight gain and metabolic disturbances (hyperglycaemia and hyperlipidaemia) than other antipsychotics.⁹ This is in addition to any background increase in patients with schizophrenia. There are few data on the incidence of weight gain or diabetes in people with dementia who are using antipsychotics.

One observational study of people with schizophrenia found that the adjusted risk of diabetes was 60% higher for users of olanzapine, risperidone or quetiapine than for users of haloperidol and that the newer drugs were associated with about 1 new case of diabetes per 100 patient-years of use.¹⁰ Substantial risks have been observed with clozapine; a 5 year study found that one-third of users were diagnosed with new-onset diabetes in this period.¹¹

People using antipsychotics require close monitoring for diabetes risk factors.¹² Check fasting plasma glucose, lipids and body mass index (BMI) when starting any antipsychotic, and on a regular basis. Measure at least 6 monthly with clozapine or olanzapine and annually for others.¹³ Manage cardiovascular risk factors (including smoking and blood pressure). Lifestyle interventions to manage weight may be appropriate (see over). Consider switching antipsychotics if there is a significant metabolic disturbance.¹³

Tardive dyskinesia

Evidence suggests that the risks of tardive dyskinesia (TD) are lower with atypical antipsychotics than conventional antipsychotics; nevertheless, some risk appears to remain with all antipsychotics except clozapine.^{14,15} Clinicians need to be vigilant for emerging TD no matter what antipsychotic the patient receives. Although there is no established relationship between dose and TD, use the lowest effective dose to minimise adverse effects.

The annual incidence of TD with conventional antipsychotics is around 5% (including non-persistent cases) in adults under 65 years.¹⁵ Older patients are at particular risk of TD; one study in patients with a mean age of 65 years found an incidence of about 25% per year during continuous exposure.¹⁶ Data on the incidence of TD with non-clozapine atypicals are relatively scarce, but it is estimated at 0.8% per year in non-elderly adults.¹⁷ In 1 study, elderly patients who received an average of 1 mg/day of risperidone for dementia had a 1 year cumulative incidence of persistent TD of 2.6% (95% CI 0.5% to 4.6%).¹⁸

Counselling points for people using antipsychotics^{13,19}

- Explain that reducing, stopping or missing doses can lead to relapse.
- Counsel patients to avoid illicit drugs; using cannabis or amphetamine, even intermittently, can worsen symptoms.
- Explain the need for regular medical monitoring to manage the risks of antipsychotic therapy, and to deal with problems quickly.
- Encourage patients to report troublesome adverse effects, so that these can be responded to appropriately (e.g. by dose reduction, a change in drug or reassurance).
- Explain that stopping an antipsychotic suddenly can lead to withdrawal symptoms (e.g. nausea, vomiting, restlessness and mild influenza-like symptoms) for up to several weeks.

Weight gain with antipsychotics: can diet and exercise help?

Several trials have now demonstrated that behavioural interventions can assist people with schizophrenia in managing their weight.²¹ These used programs of group or individual sessions with a health professional, focussing on diet and exercise to prevent weight gain or promote weight loss. Typically, the average improvement in weight relative to the non-intervention group was modest — about 2–3 kg after 3 months. Follow-up over several years is still needed to determine if weight loss is sustainable and to assess the effect on morbidity and mortality.

One trial involving 51 outpatients at a Victorian psychiatric hospital who had recently started olanzapine for various indications found that a course of six 1 hour individual education sessions with a dietitian over 3 months prevented weight gain.²² At 3 months, 64% of the control group had gained > 7% of their initial body weight, compared with 13% of the intervention group. A serious limitation of the study was that one-third of the study participants were lost to follow-up at 3 months, and almost two-thirds by 6 months.

As in the general population, weight management is more difficult in real life than in a trial. Nonetheless, consider intensive lifestyle intervention if a patient taking an antipsychotic experiences significant weight gain or metabolic effects. Enhanced Primary Care (EPC) Team Care Arrangements (TCA) are intended for people with chronic conditions who have complex care needs. Patients may be referred for help with weight management under EPC arrangements as part of comprehensive multidisciplinary care for their mental illness and comorbidities. Patients require both an EPC GP Management Plan and a TCA to be eligible for a Medicare rebate when consulting an allied health provider (such as a dietitian, exercise physiologist or psychologist). Consult the Department of Health and Ageing's website at www.health.gov.au/epc for more information.

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References

1. Lieberman JA, et al. N Engl J Med 2005;353:1209–23.
2. Schneider LS, et al. N Engl J Med 2006;355:1525–38.
3. Dettling M, Angelescu IG. N Engl J Med 2006;354:298–300; author reply 298–300.
4. US Food and Drug Administration. FDA Public Health Advisory. Deaths with antipsychotics in elderly patients with behavioral disturbances. <http://www.fda.gov/cder/drug/advisory/antipsychotics.htm> (accessed 7 December 2006).
5. Schneider LS, et al. JAMA 2005;294:1934–43.
6. Janssen-Cilag Pty Ltd. Risperdal product information. 29 September 2006.
7. Eli Lilly Australia Pty Ltd. Zyprexa product information. 3 August 2006.
8. National Institute for Health and Clinical Excellence. Dementia: supporting people with dementia and their carers in health and social care. Clinical Guideline No. 42. 2006. <http://www.nice.org.uk/download.aspx?o=CG042NICGuideline> (accessed 21 February 2007).
9. Newcomer JW, Haupt DW. Can J Psychiatry 2006;51:480–91.
10. Lambert BL, et al. Am J Epidemiol 2006;164:672–81.
11. Henderson DC, et al. Am J Psychiatry 2000;157:975–81.
12. Proietto J. Aust Prescriber 2004;27:118–9.
13. Therapeutic Guidelines: Psychotropic. Version 5, 2003.
14. Novartis Pharmaceuticals Australia Pty Ltd. Clozaril product information. 16 September 2005.
15. Tarsy D, Baldessarini RJ. Mov Disord 2006;21:589–98.
16. Jeste DV, et al. Arch Gen Psychiatry 1995;52:756–65.
17. Correll CU, et al. Am J Psychiatry 2004;161:414–25.
18. Jeste DV, et al. Am J Psychiatry 2000;157:1150–5.
19. Australian Medicines Handbook, 2006.
20. Wahlbeck K, et al. Cochrane Database Syst Rev 1999;(4):CD000059.
21. Faulkner G, et al. Cochrane Database Syst Rev 2007;(1):CD005148.
22. Evans S, et al. Aust NZ J Psychiatry 2005;39:479–86.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



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