Are atypical antipsychotics advantageous? – the case for

Nicholas A. Keks, Professor and Director of Psychiatry, Box Hill Hospital, Eastern Health, and Monash University, Melbourne

Summary

Atypical antipsychotics are a diverse group of drugs. Their widespread use has significantly improved the treatment of schizophrenia. Most patients no longer experience extrapyramidal adverse effects from drugs, including the often irreversible tardive dyskinesia. However, serious adverse reactions can occur with atypical antipsychotics. While atypical antipsychotics have modest efficacy advantages over typical antipsychotics, the efficacy varies between drugs and from patient to patient. Many patients still do not respond adequately to drug treatment of their psychosis. Despite their cost, the atypical antipsychotic drugs are preferred because of their better adverse effect profile and efficacy advantages in some patients.

Key words: schizophrenia, adverse effects.

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Introduction

Antipsychotics were originally called 'neuroleptics' (from the Latin, to grasp the neuron) because extrapyramidal adverse effects were thought to be essential for their therapeutic efficacy. Typical antipsychotics, such as chlorpromazine, improved the outcome by about 50% compared to the pre-neuroleptic era. Many patients who had previously been institutionalised were enabled to live in the community.

There were significant problems with neuroleptic treatment because many patients experienced extrapyramidal adverse effects (Table 1). These included tardive dyskinesia, a disfiguring, stigmatising and often irreversible problem. The prevalence of tardive dyskinesia was estimated to be approximately 20% of patients, but it significantly affected more than 39% of those on long-term treatment with depot neuroleptics.[1] Clearly, there was a need for drugs which were better tolerated than the typical antipsychotics.

Characteristics of atypical antipsychotic drugs

The term 'atypical' refers primarily to the low propensity of an antipsychotic to induce extrapyramidal adverse effects, compared to typical antipsychotics. Clozapine, which was developed in the 1960s, was the first drug to be recognised as atypical, although thioridazine (which is no longer widely used due to its association with QT_c prolongation) also had moderate atypical characteristics. As clozapine was associated with serious toxicity, similar antipsychotics (serotonin-dopamine antagonists) were developed and risperidone, olanzapine and quetiapine became available. Despite some similar characteristics, these drugs are clinically quite different from each other in their adverse effect profiles (Table 2). Key associations are hyperprolactinaemia with risperidone, weight gain with olanzapine and sedation with quetiapine.

Amisulpride, a benzamide, comes from a different direction in atypical antipsychotic development. It is a highly selective dopamine D2 receptor blocker, unrelated to the serotonin-dopamine antagonists. Its main adverse effect is hyperprolactinaemia. More recently aripiprazole, the first partial dopamine agonist to prove to be an effective atypical antipsychotic, has become available. Its adverse effects are primarily nausea and insomnia.

Extrapyramidal adverse effects

The key characteristic of atypical antipsychotics is that the drugs effectively treat psychoses at doses which do not induce extrapyramidal adverse effects. In contrast, the typical drugs tend to cause extrapyramidal adverse effects at the doses which are effective for psychotic symptoms. Extrapyramidal

Table 1

Extrapyramidal adverse effects

Dystonias – oculogyric crisis – torticollis – opisthotonus – laryngeal dystonia	Terrifying, occur soon after starting drug. (Laryngeal dystonia can be life-threatening.)
Parkinsonism	Occurs in days to weeks after starting drug. Primarily rigidity; may worsen negative symptoms and depression.
Akathisia	Restless legs; tormenting and associated with suicide. An emotional sense of agitation or restlessness even in the absence of motor movements.
Tardive dyskinesia	Repetitive involuntary movements, especially seen around mouth and tongue, but can affect any part of body. Often irreversible.

Table 2

Relative frequency of common adverse effects of antipsychotics at usual therapeutic doses

Note: this is the frequency of occurrence of adverse effects, not the intensity with which they occur

Drug	Usual daily oral dose range (mg)	Sedation	Postural hypotension	Anticholinergic	Extrapyramidal	Weight gain
Atypical drugs						
amisulpride	400-1000 (acute psychosis) 100-300 (negative symptoms)	+	+	0	++ *	+
aripiprazole	10-30	++	+	0	+	+
clozapine	200-600	+++	+++	+++	+	+++
olanzapine	5-20	+++	+	++	+	+++
quetiapine	300-750	+++	++	+	+ *	++
risperidone	2-6	++ (initially)	+++ (initially)	0	++	++
ziprasidone	80-160	++	+	+	+	+
Typical drugs						
chlorpromazine	75-500	+++	+++	+++	++	+++
droperidol	5-10 (intramuscular) †	++	+	+	+++	+
fluphenazine	5-20	+	+	+	+++	+++
haloperidol	1-7.5	+	+	+	+++	++
pericyazine	15-75	+++	++	+++	+	++
pimozide	2-12 ‡	++	+	+	+++	+
thioridazine	300-600	+++	+++	+++	+	+++
trifluoperazine	5-20	+	++	+	+++	++
zuclopenthixol acetate	50-150 (intramuscular) §	+++	+	++	+++	++
zuclopenthixol dihydrochloride	10-75	+++	+	++	+++	++

Approximate frequencies of adverse effects:

0 (<2%) = negligible or absent; + (>2%) infrequent; ++ (>10%) = moderately frequent; +++ (>30%) = frequent

* rarely a problem at usual therapeutic doses

† doses >5 mg should not be given without immediate access to ECG monitoring and resuscitation facilities

‡ use doses >12 mg only under specialist supervision

§ single dose, not to be repeated for 2 to 3 days

Table reprinted with permission from Table 8.6, Therapeutic Guidelines: Psychotropic. Version 5. Melbourne: Therapeutic Guidelines Limited; 2003.

adverse effects still occur with risperidone, olanzapine and amisulpride if the dose is increased beyond the therapeutic range. Clozapine and quetiapine rarely cause extrapyramidal adverse effects at any dose, unless the patient has Parkinson's disease. Aripiprazole causes extrapyramidal adverse effects at a comparable rate to placebo, although a small proportion of patients may experience akathisia.

Meta-analyses confirm that atypical antipsychotics cause fewer extrapyramidal adverse effects than typical drugs, particularly haloperidol.[2] It has been strongly suggested that this advantage disappears for risperidone, olanzapine and amisulpride if low doses of typical antipsychotics are used in comparison.[3] However, even at low doses typical drugs will cause extrapyramidal adverse effects in a proportion of patients, while for practical purposes clozapine and quetiapine do not cause extrapyramidal adverse effects.

In clinical practice extrapyramidal adverse effects are now seen infrequently. The contrast with the past, when many patients were affected by Parkinsonism and tardive dyskinesia, is striking in settings such as psychiatric inpatient units where it is now hard to find a case for teaching purposes. Tardive dyskinesia is now seen mainly in patients on long-term therapy with depot formulations of typical antipsychotics.

Other adverse effects

All typical antipsychotics, risperidone, amisulpride and to a small extent olanzapine, cause hyperprolactinaemia. Consequences include amenorrhoea, sexual dysfunction, galactorrhoea and gynaecomastia. In contrast, clozapine, quetiapine and aripiprazole do not elevate serum prolactin concentrations.

Table 3

Symptoms of schizophrenia

Positive	- delusions - hallucinations - thought disorder	Symptoms which are more responsive to antipsychotic medication than negative symptoms.
Negative	- flat affect - poverty of thought - amotivation - social withdrawal	Develop with progression of illness, cause disability, persistence signifies onset of chronic illness.
Cognitive	- distractibility - impaired working memory - impaired executive function	Dysfunction tends to occur in association with negative symptoms.
Mood	- mania - depression	Mood disorder often occurs in schizophrenia. Anxiety can occur at any stage of illness.

Atypical antipsychotics can cause other serious adverse effects (as can typical antipsychotics). Clozapine is associated with agranulocytosis, myocarditis/cardiomyopathy and convulsions. Due to its toxicity, only specialists can prescribe clozapine and close monitoring is required. Clozapine and olanzapine are particularly prone to cause weight gain and may be associated with increased risk of diabetes mellitus and hyperlipidaemias.[4,5] Periodic physical evaluation of patients with schizophrenia and related psychoses is therefore an increasingly important part of management, especially in general practice.

Efficacy of atypical versus typical antipsychotics

The symptoms of psychosis can be divided into a number of treatment-relevant dimensions (Table 3). Clozapine, amisulpride, risperidone and olanzapine have consistently established superiority over typical drugs for the treatment of positive symptoms.[6] The effects are modest and may not be seen in some patients. However, the symptom benefits many patients obtain are frequently translated into significant improvements in functioning and quality of life. All atypical antipsychotics reduce negative symptoms and clozapine, risperidone, olanzapine and amisulpride have established superiority over typical drugs.[2] It is possible that the benefits for negative symptoms occur at least partly through the reduction in extrapyramidal adverse effects. Atypical antipsychotics are also more beneficial than conventional drugs for cognitive dysfunction.

Long-term treatment

The treatment of schizophrenia and related psychoses is often lifelong. A vital dimension of therapeutic efficacy is therefore relapse prevention over long periods of time. Studies of adequate duration in relapse prevention have not been carried out. The major exception is a double-blind study which compared risperidone and haloperidol at usual clinical doses for over two years. Risperidone was associated with lower rates of relapse, and fewer extrapyramidal adverse effects, including tardive dyskinesia.[7] An editorial accompanying these results declared that evidence now supported the use of risperidone over haloperidol in relapse prevention. It is not certain whether the results of this study can be generalised to other atypical antipsychotics; similar trials are needed for the other drugs.[8]

Mood disorders

Interestingly, all atypical antipsychotics have a greater antidepressant efficacy than typical drugs and may be beneficial as adjunctive therapy to antidepressants in some patients. Olanzapine has demonstrated efficacy as monotherapy in mania, risperidone has been effective in combination with a mood stabiliser, and clozapine can be helpful in treatment-resistant mania. Evidence has emerged about the efficacy of quetiapine and aripiprazole in mania and quetiapine in depression. In contrast, the effectiveness of typical antipsychotics in mood disorders can be regarded as partial, at best.

Effectiveness

In community settings, treatment with clozapine has consistently shown superiority over typical drugs in areas such as suicidal behaviour, cognition and aggression. Among authoritative clinical guidelines for the management of schizophrenia, there is uniform agreement that patients who have not responded to other treatments should receive a trial of clozapine.

Evidence for other atypical antipsychotics is less consistent. A recent study comparing long-term treatment with olanzapine versus haloperidol plus benztropine demonstrated only minor benefits for olanzapine, with no differences on many outcome measures despite much higher cost.[9]

Promising developments

A long-acting injectable formulation of risperidone is now available. This is comparable in efficacy to oral risperidone, and may cause fewer and less severe extrapyramidal adverse effects.

Olanzapine is also available in a short-acting injectable formulation. This is being used primarily for management of acutely disturbed patients. Its safety profile is superior to that of intramuscular droperidol and haloperidol.

Aripiprazole differs from all previous typical and atypical drugs, which are dopamine antagonists. Partial dopamine agonism may theoretically assist both hyper- and hypo-dopaminergic dysfunction in different brain areas. Aripiprazole has shown efficacy and a favourable adverse effect profile in studies in schizophrenia.

Conclusion

Atypical antipsychotics are a heterogenous 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.

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Are atypical antipsychotics advantageous? – the case against

Vaughan Carr, Professor of Psychiatry, University of Newcastle, New South Wales

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.