The use of atypical antipsychotics in the management of schizophrenia

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Long-term drug treatment of schizophrenia with conventional antipsychotics has limitations: an estimated quarter to one third of patients are treatment-resistant; conventional antipsychotics have only a modest impact upon negative symptoms (poverty of thought, social withdrawal and loss of affect); and adverse effects, particularly extrapyramidal symptoms (EPS). Newer, so-called atypical, antipsychotics such as olanzapine, risperidone, sertindole and clozapine (an old drug which was re-introduced in 1990) are claimed to address these limitations. Atypical agents are, at a minimum, at least as effective as conventional drugs such as haloperidol. They also cause substantially fewer extrapyramidal symptoms. However, some other adverse effects are more common than with conventional drugs. For example, clozapine carries a significant risk of serious blood disorders, for which special monitoring is mandatory; it also causes troublesome drowsiness and increased salivation more often than conventional agents. Some atypical agents cause more weight gain or QT prolongation than older agents. The choice of therapy is, therefore, not straightforward. At present, atypical agents represent an advance for patients with severe or intolerable EPS. Most published evidence exists to support the use of clozapine, which has also been shown to be effective in schizophrenia refractory to conventional agents. However, the need for compliance with blood count monitoring and its sedative properties make careful patient selection important. The extent of any additional direct benefit offered by atypical agents on negative symptoms is not yet clear. The lack of a depot formulation for atypical drugs may pose a significant practical problem. To date, only two double-blind studies in which atypical agents were compared directly have been published. Neither provides compelling evidence for the choice of one agent over another. Atypical agents are many times more expensive than conventional drugs. Although drug treatment constitutes only a small proportion of the costs of managing schizophrenia, the additional annual cost of the use of atypical agents in, say, a quarter of the likely U.K. schizophrenic population would be about £56 M. There is only limited evidence of cost-effectiveness. Atypical antipsychotics are not currently licensed for other conditions where conventional antipsychotics are commonly used, such as behavioural disturbance or dementia in the elderly. Their dose, and place in treatment in such cases have yet to be determined.

Keywords: schizophrenia antipsychotics
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Introduction

Schizophrenia

Schizophrenia normally begins in late adolescence or early adulthood. It is a chronic disease, often severe and disabling, and is characterised by acute episodes, with varying periods of remission between these. Acute episodes may present with positive symptoms including delusions, hallucinations, thought disorders, changing mood, and often catatonic phenomena. Patients with chronic disease may also have negative symptoms including lack of drive and initiative, social withdrawal and blunting of emotional expression. There is a high mortality amongst schizophrenics and about 10% overall commit suicide [1, 2].

Schizophrenia is common with an incidence of 10–70 per 100,000, a prevalence of 3–4 per 1000, and a lifetime risk of 1% [3, 4]. Thus, at any time, there may be upwards of about 110,000 sufferers in the UK, with perhaps 16,500 new cases each year. In 1994/95, there were almost 25,000 hospital episodes for schizophrenia and a further 23,000 for other affective disorders in England [5]. Schizophrenia and allied disorders therefore represent a very substantial disease burden for sufferers and their families and carers, and a significant resource commitment for health and social services.

A number of factors may predispose to schizophrenia, including a possible genetic component, possible environmental hazards (particularly obstetric complications and maternal influenza), and the season of birth. The detailed pathophysiology of schizophrenia has not been determined, but it may result from dopaminergic overactivity. Evidence for this includes: the antagonism of dopamine receptors by antipsychotics both in vivo and in vitro; the association of antipsychotic efficacy with antagonism of D2-receptors; exacerbation of signs and symptoms by dopamine agonists; and autopsy reports showing increased D2-receptor densities in schizophrenics. Recent research has investigated whether dysfunction of other neurotransmitters leads to abnormal dopamine function; for example, clozapine has affinity for many receptors, including the subtypes D1, 5-HT2 and 5-HT3 [6].

Current management options

Although psychosocial treatment, including counselling, education, and family interventions, is important, long-term drug treatment is the mainstay of management for schizophrenia in most patients. The first effective drugs, the phenothiazines, have been available since the 1950s. Their antipsychotic effect manifests in two ways; control of agitation and aggression, taking between a few minutes and a few hours, and alleviation of psychotic symptoms, after days or weeks of treatment. Maintenance treatment is usually continued with oral or depot formulations for at least 1 year after the first episode. However, approximately 75% of patients will relapse within 12 to 18 months of discontinuation of treatment [7, 8]. Recurrent disease should therefore be treated indefinitely.

Many drugs are currently available for the oral treatment of schizophrenia and related disorders. The most notable differences between these are the incidence of adverse effects and cost. Adverse effects may be serious and irreversible, the most troublesome being extrapyramidal side-effects (EPS), including acute dystonia, akathisia, parkinsonism, and tardive dyskinesia. Patients on long-term treatment and/or receiving high doses are thought to be at highest risk of EPS.

The British National Formulary (BNF) classifies the drugs into three groups according to the pattern and frequency of adverse reactions:

- **Group 1:** chlorpromazine, methotrimeprazine, and promazine; generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal side-effects.
- **Group 2:** pericyazine, piperoxazine, and thioridazine; generally characterised by moderate sedative effects, marked antimuscarinic effects, but fewer extrapyramidal side-effects than Groups 1 or 3.
- **Group 3:** fluphenazine, perphenazine, prochlorperazine, and trifluoperazine; generally characterised by fewer sedative effects, fewer antimuscarinic effects, but more pronounced mental hazards (particularly obstetric complications and extrapyramidal side-effects). Rarely, neuroleptic malignant syndrome, a potentially fatal complication, may develop [9].

Many patients with schizophrenia are deemed resistant or refractory, and either gain little benefit from standard treatment or cannot tolerate the extrapyramidal side-effects of conventional antipsychotics. However, the clinical situation is difficult to define precisely. Thus, about 30% of patients (with acute episodes) in trials show only limited improvement. Operational definitions of treatment-resistance vary, from failure to respond to two conventional antipsychotics given for 6 weeks, to more formal grading systems involving assessments over 1 week to 6 months [10]. In the UK, the number of patients who could be classed as treatment-resistant might be around 33,000 to 44,000 (i.e., between 600 and 800 per million population).
A number of studies of antipsychotic utilisation have been published. Among the concerns raised in a recent UK study was the frequent use of antipsychotics at higher than recommended doses [11]. Of 192 psychiatric inpatients studied 89% were receiving antipsychotics, 54% of whom received depot preparations; 41% of those on treatment were prescribed two or more antipsychotics concurrently. The mean dose was 1262 mg of chlorpromazine (CPZ) equivalents, almost half of patients were receiving more than the usual upper treatment limit of 1000 mg CPZ equivalents daily, though the number of patients receiving greater than 4000 mg CPZ equivalents daily had fallen since a similar audit in 1991 (3% vs 12%).

The authors stress the difficulties for clinicians in deciding what is a ‘high’ dose for a particular drug (and, by implication, for any individual patient).

The last decade has seen the introduction of so-called atypical antipsychotics including remoxipride, olanzapine, risperidone and sertindole, and also the re-introduction of the atypical agent clozapine in 1990. Remoxipride was withdrawn in 1993 due to reports of aplastic anaemia. The newer agents are variously claimed to reduce the incidence and severity of adverse effects, to be superior in improving negative symptoms, and to be more effective in refractory patients. This report reviews their clinical efficacy and safety and considers their place in therapy.

Clinical rating scales

The clinical diagnosis and objective assessment of patients with schizophrenia is difficult in practice, not least because patients may be unable to give a reliable clinical history necessary for an optimal assessment of their status. A number of rating scales have therefore been developed for use both in clinical studies and in routine practice. In addition to scales employed as measures of efficacy and safety, almost all clinical trials also used the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for schizophrenia. This provides a means for the uniform diagnosis of psychiatric conditions, first developed by the American Psychiatric Association in 1952.

The European Medicines Evaluation Agency (EMEA) has recently published a detailed account of the issues and difficulties in assessing antipsychotics [12]. In views, and those of psychiatrists generally, appear to be that clinical rating scales such as Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Symptom Scale (PANSS) (Table 1) are appropriate and valid and that changes shown are likely to translate into clinical benefits for patients. However, the EMEA report also includes general advice on the interpretation of clinical trial results and guidance on the following points in particular:

1. Efficacy of individual drugs: efficacy and safety benefits from studies in patients with acute exacerbations cannot be assumed to extend to maintenance treatment and vice versa.

2. Assessment of negative symptoms: a specific, valid scale is needed (e.g., PANSS or Scale for Assessment of Negative Symptoms (SANS)) but assessment of improvement remains difficult because:

   - Negative symptoms may be secondary to other causes, e.g., psychotic symptoms, depression, extrapyramidal effects, hospitalisation. Thus a favourable change in symptom scores does not, by itself, confirm a direct effect upon negative symptoms.

   - Therapeutic effects on negative symptoms are expected to take more time to develop; the EMEA recommends that trials last at least 8 weeks (many published studies last 6 weeks or less).

   - In an acute episode of schizophrenia, it is difficult to distinguish negative symptoms from other phenomena. Therefore, results from trials in patients experiencing acute episodes provide less direct evidence of effect on negative symptoms.

The interpretation and presentation of clinical trials is therefore not straightforward. For clozapine and risperidone, we have relied upon two systematic reviews. For other drugs, original trial data are mainly presented as it is commonly reported, as the mean change from baseline in the various clinical rating scales. Table 2 shows a summary of comparative trials reviewed.

Clinical efficacy and adverse effects of individual drugs

Clozapine

Clozapine (Clozaril®, Sandoz) is a dibenzodiazepine and has dopamine, 5-HT, histamine and adrenergic receptor antagonist properties. It is licensed in the UK for patients resistant to, or intolerant of, other agents.

The UK Cochrane Collaboration has recently published a systematic review of clozapine vs typical neuroleptics in schizophrenia in which the results of 27 controlled trials, 23 of which were less than 13 weeks duration, were assessed [13]. Key findings included:

1. There were no significant differences in efficacy for broad outcomes such as mortality, patient dissatisfaction, working ability or suitability for discharge from hospital at the end of the study.

2. In the short term (generally, studies of less than 13 weeks duration), patients on clozapine had fewer relapses (odds ratio (OR) 0.5, 95% CI 0.3–0.7, number needed to treat (NNT) 17), and more frequent clinically-important
Table 1 Clinical rating scales for schizophrenia.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full description</th>
<th>Method of assessment</th>
<th>Number of items</th>
<th>Points per item</th>
<th>Score range</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
<td>Interview</td>
<td>18</td>
<td>7</td>
<td>18–126</td>
<td>Originally developed in 1962 to provide a rapid assessment of change in disease, whilst also describing major symptoms.</td>
</tr>
<tr>
<td>CGI-S</td>
<td>Clinical Global Impression of Severity</td>
<td>Interview</td>
<td>nk</td>
<td>nk</td>
<td>0–6</td>
<td>Used in a wide range of conditions including psychoses. The score indicates the direction and extent of change, e.g., 0 = marked improvement, 6 = marked worsening.</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Symptom Scale</td>
<td>Interview</td>
<td>30</td>
<td>7</td>
<td>30–210</td>
<td></td>
</tr>
<tr>
<td>SANS</td>
<td>Scale for the Assessment of Negative Symptoms</td>
<td>Interview</td>
<td>5</td>
<td>6</td>
<td>0–30</td>
<td>Requires the clinician to assign ratings of severity to well-defined features of the disorder, and assess negative symptoms only.</td>
</tr>
</tbody>
</table>

Table 2 Summary of randomised comparative studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient number</th>
<th>Inclusion criteria</th>
<th>Study length (weeks)</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beasley 1996 [18]</td>
<td>335</td>
<td>Acute schizophrenia</td>
<td>6</td>
<td>olanzapine, haloperidol</td>
</tr>
<tr>
<td>Beasley 1997 [19]</td>
<td>431</td>
<td>Acute schizophrenia</td>
<td>6</td>
<td>olanzapine, haloperidol</td>
</tr>
<tr>
<td>Zimbroff 1997 [22]</td>
<td>497</td>
<td>Schizophrenia</td>
<td>8</td>
<td>sertindole, haloperidol</td>
</tr>
<tr>
<td>Pfückers 1997 [23]</td>
<td>201</td>
<td>Acute schizophrenia</td>
<td>6</td>
<td>quetiapine, chlorpromazine</td>
</tr>
<tr>
<td>Arvanitis 1997 [24]</td>
<td>266</td>
<td>Acute schizophrenia</td>
<td>6</td>
<td>quetiapine, haloperidol</td>
</tr>
<tr>
<td>Klieser 1995 [26]</td>
<td>59</td>
<td>Schizophrenia</td>
<td>4</td>
<td>clozapine, risperidone</td>
</tr>
<tr>
<td>Tran 1997 [27]</td>
<td>339</td>
<td>Schizophrenia</td>
<td>28</td>
<td>olanzapine, risperidone</td>
</tr>
</tbody>
</table>

improvement (OR 0.4, CI 0.2–0.7, NNT 6). In treatment-resistant patients, there was no difference in relapse rate across four studies while in two short-term studies there was a better clinical response to clozapine compared with conventional antipsychotics (OR 0.14, CI 0.06–0.25, NNT 4).

- Dry mouth (OR 0.3, CI 0.2–0.4, NNT 6) and extrapyramidal effects (OR 0.4, CI 0.2–0.8, NNT 6) were less frequent with clozapine while increased salivation, increased temperature and troublesome drowsiness were more frequent with clozapine. However, clozapine causes agranulocytosis in between 0.05% and 2% of patients, substantially higher than with standard antipsychotics, and because of this increased risk it was withdrawn from use soon after its introduction in the 1970s. In 1989 a relaunch was approved but supply of the drug was conditional upon a stringent programme of white cell count monitoring being carried out (Clozaril Patient Monitoring Scheme). The cost of these tests is included in the price of the drug.

A study has been published analysing the results of the monitoring scheme for the first year of the drug’s reintroduction in the US [14]. In 11,555 patients who received clozapine, the incidence of agranulocytosis after 1, and 1.5 years of treatment, was 0.80% and 0.91% respectively. Most cases occurred within the first 3 months of treatment (84%). The risk increased with age, and was higher in women.

In addition to bone marrow depression, seizures are reported to occur in 14% of those treated with high doses of clozapine (over 600 mg day$^{-1}$; normal maintenance dose range 150–300 mg day$^{-1}$).
Risperidone

Risperidone (Risperdal®, Janssen) is a benzisoxazole derivative which combines potent 5-HT₂ and dopamine receptor antagonist. It is licensed for the treatment of acute and chronic schizophrenia.

The NHS Centre for Reviews and Dissemination has recently published a meta-analysis of eleven randomised controlled trials of risperidone and conventional antipsychotics in a total of 2513 patients (range 35 to 1362) [15]. Key findings included:

- Overall, the proportion of patients showing clinical improvement (defined as a 20% reduction from baseline BPRS or PANSS scores) was higher for risperidone (OR 1.27, CI 1.04–1.56, NNT 20) though the absolute difference was modest (57% vs 52%).
- Patients receiving risperidone were less likely to require medication for extrapyramidal symptoms (22.9% vs 38.4%, OR 0.51, CI 0.41–0.63, NNT 7), though the incidence increased with higher doses (>8 mg) of risperidone.
- The drop-out rate was lower in the risperidone-treated patients (29.1% vs 32.9%, OR 0.75, CI 0.61–0.94, NNT 20) though the drop-out rate due to adverse experiences or treatment inefficacy showed no improvement.
- In one study where the Scale for the Assessment of Negative Symptoms (SANS) was used to assess the change in negative symptoms, there was no significant difference between risperidone and haloperidol. Eight further studies used the negative PANSS rating; only one showed risperidone to be significantly better than conventional antipsychotics (haloperidol in this study).
- When the results of all eight studies are considered, the difference in changes in PANSS scores was −0.74 (CI −1.50–0.02) which almost reaches statistical significance (P=0.058).
- Weight gain and palpitations/tachycardia were significantly more common with risperidone (P<0.05).
- The neuroleptic malignant syndrome (NMS) has been described during risperidone treatment [16]. Two patients, both over 80 years of age, were originally treated with sulpiride (one was also taking trifluoperazine) and developed EPS. Sulpiride was stopped and both patients were commenced on risperidone 2 mg daily. One developed symptoms of NMS within 12 h of the first dose, and the other within 5 days of starting treatment. Both patients recovered after withdrawal of risperidone.

Olanzapine

Olanzapine (Zyprexa®, Lilly) is a thienobenzodiazepine, and is a potent 5-HT₂ and dopamine antagonist, with anticholinergic activity, an activity profile very similar to that of clozapine. It is licensed for the treatment of all forms of schizophrenia. The published evidence for olanzapine, all of which originates from the clinical research department of the manufacturer, amounts to one placebo-controlled study, three randomised double-blind comparative studies with haloperidol (all lasting 6 weeks) and a 28-week comparison with risperidone.

In a study of 152 patients, those given olanzapine 10 mg day⁻¹ had significantly better improvements in BPRS and PANSS scores than either placebo or olanzapine 1 mg day⁻¹, while olanzapine 1 mg day⁻¹ was no better than placebo [17].

Two trials have compared three doses of olanzapine with haloperidol and placebo.

In the North American study, 335 patients were treated for 6 weeks; the mean changes from baseline in total BPRS scores for placebo, low, medium and high dose olanzapine and haloperidol (mean dose 16.4 mg daily) were −3.1, −6.7, −12.6, −15.2 and −12.9 respectively [18]. Thus, all active groups were superior to placebo and haloperidol and olanzapine had similar efficacy. Only high-dose olanzapine (15 mg daily) was significantly better than haloperidol in terms of the mean change in negative symptoms (SANS) scores; the mean baseline and change for high-dose olanzapine were 13.4 and −4.1 respectively and 13.2 and −2.0 for haloperidol.

Medium (but not low- or high-) dose olanzapine produced significantly less deterioration in two of three extrapyramidal symptom scales. The mean change from baseline in extrapyramidal symptom scores (Simpson-Angus, Barnes and AIMS scales) was, respectively, −0.3, −0.3 and −0.8 for medium-dose olanzapine and 1.0, 0.4 and −0.2 for haloperidol. There were no other significant differences in adverse reaction rates between olanzapine and haloperidol.

In a similar study outside North America, 431 patients received 1 mg (fixed dose), 5, 10 or 15 mg (all ± 2.5 mg) olanzapine, haloperidol (mean dose 13.8 mg daily) or placebo for 6 weeks [19]. There were no significant differences in any efficacy outcome measure between olanzapine and haloperidol. The mean changes in extrapyramidal symptom scores were significantly better for olanzapine compared with haloperidol, though baseline scores were not reported.

Most recently, a large international study has been published in which 1996 patients in 174 centres were randomised to receive either olanzapine or haloperidol for 6 weeks (each at 5 mg daily increasing to 20 mg daily if necessary) [20]. Overall, 60% of patients completed the trial; the proportion was significantly higher in those given olanzapine (66% vs 47%, P<0.001). The mean changes in most measures of primary efficacy were significantly greater for olanzapine-treated patients though
in all cases, the absolute difference was modest. For example, the mean difference in BPRS score in the olanzapine group was \(-10.9\) compared with \(-7.9\) with haloperidol \((P<0.02)\); mean baseline scores were 33.1 and 34.1 respectively.

There were significantly fewer extrapyramidal events in the olanzapine group \(19.2\% \text{ vs } 45.2\%, P<0.001\); this was reflected in significantly better EPS rating scale scores and lower use of benztpine amongst patients receiving olanzapine. The mean increase in weight was significantly higher with olanzapine \((1.88 \text{ kg vs } 0.02 \text{ kg}, P<0.001)\).

**Sertindole**

Sertindole (Serdolect®; Lundbeck) is a selective antagonist of dopamine and 5-HT₂ receptors. It is licensed for the treatment of schizophrenia.

Two studies of sertindole have been published.

In 205 patients, sertindole at doses of 8 mg and 12 mg for 40 days was no more effective than placebo, but sertindole 20 mg produced significantly better improvements in PANSS and BPRS scores \([21]\).

A double-blind study in 43 patients evaluated three doses of sertindole \((12–24 \text{ mg daily}), \text{ haloperidol (4–16 mg daily), and placebo (22)}\). Sertindole was no more effective than haloperidol for all measurements of psychosis. There were significantly fewer extrapyramidal events with any dose of sertindole compared with haloperidol.

Many drugs, including antipsychotics and antidepressants, cause QT interval prolongation \((>500 \text{ ms})\) and in placebo-controlled studies of sertindole, QT prolongation was reported in 1.6% of patients \((\text{personal communication, Lundbeck, 1997)}\). The manufacturer recommends that patients receiving sertindole have a minimum of four ECGs in the first 12 months of treatment.

For other adverse effects, nasal congestion and reduced ejaculatory volume \((\text{in men})\) were significantly more common with sertindole compared with placebo \([22]\).

**Quetiapine**

Quetiapine (Seroquel®; Zeneca) was launched in the UK in October 1997 and is licensed for the treatment of schizophrenia. Three placebo-controlled trials have been published confirming its efficacy. Quetiapine has also been compared in patients with acute exacerbations of schizophrenia with both chlorpromazine and haloperidol in studies lasting 6 weeks \([23, 24]\). No significant differences in efficacy between quetiapine and the conventional drugs were found but there were significantly fewer, or less deterioration in, extrapyramidal symptoms in the quetiapine groups.

**Amisulpride**

Amisulpride (Solian®, Lorenz Syntheclabo) has also been launched in the UK \((\text{November 1997)}\), and is licensed for acute or chronic schizophrenia where positive and/or negative symptoms are prominent. Several placebo-controlled trials have been published but, to date, only one comparative study with conventional antipsychotics. In a comparison with haloperidol over 6 weeks in 191 patients, both drugs were similarly effective as judged by improvement in BPRS scores \([25]\). Patients given amisulpride had slightly greater improvement in the PANSS negative symptoms subscale \((P<0.038)\) and also had fewer extrapyramidal effects \((P=0.009)\).

**Comparisons of atypical antipsychotics**

Only two double-blind controlled studies have so far been published in which the efficacy and safety of these agents has been compared directly. In a study of very limited power, Klieser and colleagues studied 59 patients who received either risperidone \((4 \text{ mg or } 8 \text{ mg daily})\) or clozapine \(400 \text{ mg daily}\) for 28 days \([26]\). The main findings were that both drugs were equally effective as assessed by BPRS and the global impression scale \((\text{Clinical Global Impressions of Severity, CGI-S)}\). Similarly there was no significant difference in adverse events except for increased or excess salivation which was more frequent with clozapine than with either dose of risperidone.

In a larger study, 339 patients \((\text{in 35 centres})\) with schizophrenia, schizoaffective disorder or schizoaffective disorder were randomised to olanzapine or risperidone for 28 weeks \([27]\). One hundred and seventy-eight patients \((52.5\%)\) completed the trial \((57.6\% \text{ olanzapine, mean dose } 17.2 \text{ mg, } 47.3\% \text{ risperidone, mean dose } 7.2 \text{ mg}; P=0.059 \text{ for difference in completion rate)}\). The only significant differences in efficacy measures were that mean improvements in the PANSS depression item and SANS summary score were slightly, though statistically significantly, better in the olanzapine group \((\text{Table 3)}\).

In addition, significantly more patients in the olanzapine group achieved at least a 40% improvement in BPRS scores, though the absolute difference was modest \((\text{olanzapine } 36.9\% \text{ vs risperidone } 26.7\%, P=0.049)\). Using Kaplan-Meier survival curves, more olanzapine-treated patients maintained their response \((\text{time until } > =20\% \text{ worsening in BPRS total score and CGI-S } > =3)\). The estimated percentage of patients maintaining their acute response at 28 weeks was \(87.9\% \text{ for olanzapine and } 67.7\% \text{ for risperidone)}\).

The proportion of patients reporting any extrapyramidal event was significantly less for olanzapine \((18.6\% \text{ vs } 31.1\%, P=0.022)\). Results from the rating scales used are not presented but analysis of Simpson-Angus scores was

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Table 3 Key findings from olanzapine vs risperidone trial [27].

<table>
<thead>
<tr>
<th>Scale</th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS depression</td>
<td>Mean Baseline</td>
<td>−1.1</td>
<td>Mean Baseline</td>
</tr>
<tr>
<td>SANS summary score</td>
<td>12.2</td>
<td>−4.3</td>
<td>11.6</td>
</tr>
</tbody>
</table>

reported to show that fewer olanzapine patients experienced treatment-associated pseudoparkinsonism (12.5% vs 22.3%, \( P = 0.034 \)). Similarly, the proportion of patients who developed treatment-associated akathisia, based on the Barnes Akathisia Scale was lower in the olanzapine group (15.9% vs 27.3%, \( P = 0.023 \)). Finally, analysis of AIMS scores showed that the proportion of patients with dyskinetic symptoms was also lower for olanzapine (4.6% vs 10.7%, \( P = 0.049 \)). Amongst other adverse effects reported by patients, weight gain was more common with olanzapine (mean increase 4.1 kg vs 2.3 kg, \( P = 0.015 \)), while nausea, amblyopha, increased salivaion, suicide attempt, abnormal ejaculation, back pain, creatinine phosphokinase increases and urinary tract infection were all more common with risperidone.

Three smaller studies have also been published. There was no evidence of improvement in 10 patients who were resistant to clozapine treatment and who were switched to risperidone for 12 weeks [28]. In a randomised crossover study of 6 weeks treatment with clozapine and risperidone, there was no difference in efficacy as measured by PANSS, but sleepiness and lack of alertness were more frequent with clozapine while insomnia and restlessness were more frequent with risperidone [29]. In a similar but non-randomised small study, 13 patients were treated with risperidone for 3 months; five of the six who did not respond showed improvement after subsequent treatment with clozapine [30].

Other considerations

Atypical agents are currently available for oral administration in tablet form only except for risperidone which is also available as an oral liquid formulation. Conventional drugs are available in a wider variety of dose forms; for example, haloperidol is available for oral administration in tablet, low-dose capsule or liquid form, and for parenteral use as a conventional or depot injection. The absence of a depot form of atypical agents may be a significant practical drawback.

Treatment costs are up to 100 times greater than for conventional antipsychotics (Table 4). For example, the annual cost of treatment with clozapine at 150 mg day\(^{-1}\) is about £1000 but there are, in addition, hidden costs, including those of time spent for weekly monitoring by both patients and providers of care, and the costs of treatment of haematological toxicity.

In 1996, in England, there were 4.826 M primary care prescriptions dispensed for drugs used in psychosis and related disorders (BNF Section 4.2) at a total cost of £31.048 M, 1% and 0.8% respectively of total prescriptions and cost [31]. The most commonly prescribed agents were thioridazine, chlorpromazine and haloperidol, accounting for 64% of prescriptions for non-depot antipsychotics. Risperidone accounted for only 3.3% of prescriptions whereas it was the leading cost agent in 1996 (£10.8 M) accounting for 43% of the total cost of oral antipsychotics.

The number of patients receiving antipsychotic medication is difficult to estimate both because available data represents primary care prescribing only and because many drugs are used (often in lower doses) for conditions other than schizophrenia. In addition, because of local variations in practice, no single estimate can be placed on the number of patients who might be deemed appropriate for treatment with atypical antipsychotics and the additional costs which might consequently be incurred. The cost implications for the NHS of a wholesale change to atypical antipsychotics is substantial.

Given this large cost differential, robust evidence of cost-effectiveness would be of particular benefit in supporting prescribing decisions. Among the largest potential economic benefits are reductions in hospital...
### Table 4 Annual maintenance treatment costs of newer and selected conventional antipsychotics.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available presentations</th>
<th>Daily oral maintenance dose (mg day$^{-1}$)</th>
<th>Annual cost (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>oral</td>
<td>50–800</td>
<td>100–1460</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>oral, t.i.d., depot, rectal</td>
<td>75–300</td>
<td>8–13</td>
</tr>
<tr>
<td>Clozapine</td>
<td>oral</td>
<td>150–500</td>
<td>976–1957</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>oral, t.i.d., depot</td>
<td>5–10</td>
<td>47–98</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>oral</td>
<td>5–20</td>
<td>687–2531</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>oral</td>
<td>300–450</td>
<td>1376–1719</td>
</tr>
<tr>
<td>Risperidone</td>
<td>oral (including liquid formulation)</td>
<td>4–8</td>
<td>939–1859</td>
</tr>
<tr>
<td>Sertindole</td>
<td>oral</td>
<td>12–20</td>
<td>1336 (same cost for both doses)</td>
</tr>
</tbody>
</table>

### Conclusions

In terms of broad outcome measures, clozapine is as effective as, and may be more effective than, conventional antipsychotics. It is effective in some patients refractory to conventional antipsychotics and it has a substantially lower incidence of EPS. Sedation, which can be troublesome, and increased salivation are more common with clozapine. Clozapine is therefore a valuable option for patients who do not respond to treatment with conventional antipsychotics and/or those who experience, or cannot tolerate, extrapyramidal symptoms. However, patient selection is important in view both of the need...
for regular blood count monitoring and because of sedation.

Overall, risperidone is as effective as conventional antipsychotics such as haloperidol. Systematic review of available evidence concluded that the additional effect, if any, on negative symptoms was small. The incidence of extrapyramidal effects is significantly lower than with conventional agents (but rises at higher doses and may be higher than with other atypical antipsychotics).

Olanzapine is as effective as haloperidol. Olanzapine may be more effective than haloperidol for negative symptoms. The incidence of extrapyramidal effects is significantly lower than with haloperidol.

There is as yet insufficient published evidence to assess the place in treatment of sertindole, quetiapine and amisulpride. All appear to be as effective as conventional antipsychotics and to have a significantly lower incidence of extrapyramidal effects. Their effects on negative symptoms are yet further evaluation. Treatment with sertindole is complicated by the need for ECG monitoring.

Treatment with conventional antipsychotics, while effective in improving acute symptoms and for preventing relapse, has several limitations. The atypical antipsychotics represent an opportunity to address three of these—treatment resistance, extrapyramidal effects and negative symptoms, upon which conventional drugs have only a modest effect.

All atypical drugs are at least as effective as conventional antipsychotics and they have a significantly lower incidence of extrapyramidal effects. However, they may have other troublesome adverse effects. Some appear to result in more weight gain than older agents; clozapine causes drowsiness and increased salivation and requires specialist monitoring because of a higher incidence of blood dyscrasias; sertindole requires regular ECG monitoring.

There is no published evidence of their efficacy and safety during long-term treatment and there is only limited evidence from direct comparisons of their efficacy and safety. Thus, in one small study, clozapine and risperidone were similarly effective while in a larger trial, olanzapine appeared to be slightly more effective in improving negative symptoms than risperidone; to cause fewer extrapyramidal symptoms.

The use of atypical agents is therefore not straightforward. On current evidence, they should be reserved for patients resistant to, or unable to tolerate, optimum doses of conventional antipsychotics. Only clozapine has been proven to be more effective in treatment-resistant patients. For patients who suffer severe or intolerable extrapyramidal effects, there is no compelling direct evidence to favour one drug over another; most published evidence supports the use of clozapine. The choice of therapy for patients with predominantly negative symptoms is less clear. There is some evidence that risperidone and olanzapine may provide a small additional benefit, though whether this observed effect is the result of a specific action upon such symptoms or secondary to other effects is not clear. There is insufficient published evidence about sertindole, quetiapine or amisulpride to determine their place in treatment.

The lack of a depot injectable form of atypical drugs may be a serious practical disadvantage in practice.

There is little evidence to support the use of atypical agents for indications other than schizophrenia and schizotypal disorder but where conventional agents are commonly used such as behaviour disturbances in the elderly. This area is particularly complicated since doses are often considerably smaller than those used in younger patients with psychoses. Atypical agents are not currently licensed for these indications.

Finally, there would appear to be no rationale for the co-prescribing of atypical and conventional antipsychotics; any additional benefit would be likely to be lost. Co-prescribing of anticholinergics should not be necessary with the atypical agents; careful review of therapy may be needed to ensure that this has not been overlooked.

Other atypical antipsychotics are in development and studies are continuing with currently available atypical drugs. The management of schizophrenia seems likely to change further over the next decade with large clinical and financial implications for health services.

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References

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