

NEWER ATYPICAL ANTIPSYCHOTICS

- Schizophrenia affects approximately 1% of the population worldwide.
- The newer atypical antipsychotics are as effective as the older ones but have a lower propensity to cause extrapyramidal side effects, have superior efficacy against negative and cognitive symptoms, and are of benefit in patients refractory to conventional agents.^{1,2}
- Clozapine represents the prototype of atypicality however its use is restricted because of side-effects. ³
- Atypical antipsychotics are more expensive than conventional agents.

History of antipsychotic development

The clinical picture of schizophrenia is varied but is recognised by two syndromes: (1) an acute syndrome with delusions, hallucinations, and disordered thinking- positive symptoms, and (2) a chronic syndrome with apathy, slowness, and social withdrawal- negative symptoms. An overview of the antipsychotics will be presented over two bulletins. This issue will look at the newer antipsychotics which have received renewed interest since thioridazine was restricted to second line treatment in adult schizophrenia only. The next bulletin will focus on prescribing in special population groups, (the elderly, children and adolescence, in pregnancy and lactation) and switching guidelines. The review will not discuss other treatments for psychosis which include cognitive therapy, social skills training, compliance therapy and family interventions.⁴

Chlorpromazine, introduced in 1952, was the first drug to reduce core psychiatric symptoms to such an extent that patients were discharged after years of hospitalisation. Other antipsychotics were subsequently introduced, including haloperidol, thioridazine and trifluoperazine. Two years after chlorpromazine was launched, movement disorders were recognised as an important side effect. These extrapyramidal symptoms (EPS) were manifest as dystonic reactions (involuntary muscle contractions especially of the face and jaw), akathisia (continual pacing or motor restlessness), parkinsonism (rigidity, bradykinesia, tremor), tardive dyskinesia (choreoathetoid movements of the tongue, lips and jaw) or rarely neuroleptic malignant syndrome (fever, muscle rigidity, coma and rarely death).

The traditional antipsychotics ranged widely in their basic chemistry, however they had one feature in common; they all blocked dopamine (DA) receptors.⁵ While it appears that the affinity of antipsychotic drugs for mesolimbic D2 receptors determines their efficacy, these agents also blocked dopamine receptors in the nigrostriatal system, explaining the EPS effects, and also in the tuberoinfundibular system thus explaining effects on prolactin levels, sexual function and weight.

The atypical antipsychotics were developed in response to the problems with the traditional antipsychotics, notably their troublesome side-effects especially EPS and tardive dyskinesia, their lack of efficacy in some patients and lack of improvement or

even worsening of negative symptoms. Although the precise definition of atypicality has never been established, a drug is said to have atypical properties if, unlike the traditional, it has a low propensity to induce EPS, is effective in treating both positive and negative symptoms of schizophrenia, improves cognitive function (impairment in executive functioning, attention, global and spatial working memory) and has a lower incidence of hyperprolactinaemia. **1,6,7** These “atypical” agents have less affinity for nigrostriatal D2 receptors, and have relatively high serotonin (5HT2A) to dopamine D2 receptor binding ratios. These properties appear to be responsible for the advantages these drugs have over the older agents with respect to side effects and efficacy.

Clozapine, introduced in the mid-1960's, was the first atypical antipsychotic, however following reports of agranulocytosis, a potentially life-threatening adverse effect, the product was not registered and marketed until 1990. It became evident from controlled trials that clozapine was effective against the positive symptoms of schizophrenia in patients who were resistant to, or intolerant of conventional neuroleptics, in addition to being beneficial against the negative symptoms of schizophrenia. **8,9,10,11** This was followed by the development and launch of other novel antipsychotic drugs. Unfortunately there are few head to head trials comparing the antipsychotics. Currently in Ireland there are 5 atypical antipsychotics licensed for the use in schizophrenia.

CLOZAPINE

Overview: Clozapine, a tricyclic dibenzodiazepine, represents the prototype of atypicality, however because of the risk of agranulocytosis, it is only indicated in the management of treatment resistant schizophrenic patients. Studies have demonstrated its effectiveness in schizophrenic patients with depression and suicidal ideation, schizoaffective or bipolar disorders and also in reducing violence and aggression in psychiatric patients. **12,13,14,15**

Trials: The position of clozapine was established in a number of landmark trials published in the 1980's, which unequivocally demonstrated its efficacy in patients with treatment resistant schizophrenia. **8,9,10** Recent studies have confirmed its place as the gold standard for treatment resistant schizophrenia. **16** In a meta-analysis of 30 trials, clozapine was more effective than conventional agents such as haloperidol and chlorpromazine in treating both the positive and negative symptoms of schizophrenia. **17**

Dose: Clozapine treatment must be initiated in hospital and patients are required to be registered with the Clozaril Patient Monitoring Service, ensuring mandatory monitoring of white blood cell counts. In adults the initial dose is 12.5mg once or twice daily followed by gradual titration to achieve a dose range between 200-450mg/day in most patients, (maximum dose of 900mg/day). **18** Cautious titration and a divided dosing schedule are necessary to minimise the risk of hypotension, seizures and sedation. **19,20**

Side-effects: Despite the low incidence of EPS and TD, **19** clozapine is associated with other significant side-effects, the most serious with potential life-threatening consequences is agranulocytosis, estimated to be 1-2%. **21** More recent post-marketing experience has indicated an overall frequency of agranulocytosis of 0.38%,

which peaks in the first 6 months of treatment, increases with age and is higher in women than in men.^{22,23,24} Clozapine is also associated with a significant dose-dependent risk of seizure. Less serious and more common side-effects of clozapine include sedation, hypersalivation, tachycardia, hypotension, hypertension, weight gain, constipation, urinary incontinence and fever which are generally tolerated by the patient.¹⁹ While it appears that all antipsychotics cause weight gain to some extent, clozapine appears particularly implicated. ^{25,26,27}

Interactions: Clozapine should not be used concurrently with drugs associated with the potential to depress bone marrow function. As with all antipsychotics, clozapine may enhance the central effects of alcohol, MAO inhibitors, and other CNS depressants. The cytochrome P-450 isoenzymes CYP1A2 and CYP3A4 are principally involved in the metabolism of clozapine, therefore drugs co-administered that are metabolised, inhibited or induced by these isoenzymes may effect the plasma concentration of clozapine. Refer to the Summary of Product Characteristics for more details. ¹⁸

RISPERIDONE

Overview: Risperidone, a benzisoxazole, is indicated for the treatment of acute and chronic schizophrenic psychosis, and other psychotic conditions in which positive symptoms and/or negative symptoms are prominent. Risperidone also alleviates affective symptoms associated with schizophrenia, and is indicated for the treatment of behavioural disturbances in patients with dementia where symptoms of aggressiveness, activity disturbances and psychotic symptoms may be prominent.²⁸ Risperidone is also licensed for bipolar-disorder.

Trials: Although all the newer antipsychotic agents have been promoted as “clozapine without the adverse effects”, most of the controlled studies have compared risperidone with clozapine. In the management of treatment-resistant chronic schizophrenia, both drugs significantly reduced symptom severity²⁹ and risperidone was determined to be at least as effective as clozapine.³⁰ In a double blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia, clozapine showed superior efficacy over risperidone in the patient population and while both treatments were equally well tolerated, clozapine was associated with a lower risk of EPS than risperidone.³¹ Risperidone has also been compared to olanzapine in the treatment of schizophrenia.^{32,33,34} A randomised double-blind study of risperidone (2-6mg/day) and olanzapine (5-20mg/day) concluded that while both treatments were well tolerated and efficacious, there were greater reductions in severity of positive and affective symptoms in the risperidone group and greater weight gain associated with olanzapine.³² In a double-blind comparison study with olanzapine (10-20mg/day), the authors acknowledged that the fewer adverse effects in the olanzapine group may be explained by possibly higher doses of risperidone (4-12mg/day) and rapid dose titration³³. A Cochrane review of risperidone versus other atypical antipsychotic medication for schizophrenia, concluded that there was little to choose between risperidone, olanzapine or amisulpride, and recommended longer-term studies measuring the comparative value of the various atypicals.³⁵

Dose: In adults, risperidone may be given once or twice daily with the usual starting dose of 2mg daily, increasing to 4mg/day on the second day. Most patients will

benefit from daily doses of between 4 and 6mg/day, although an optimal response may be obtained at lower doses. Maximum dose 16mg/day.²⁸ Risperidone is available in tablet and liquid formulations.

Side-effects: Risperidone is generally well tolerated and in many instances it may be difficult to differentiate adverse events from the symptoms of the underlying disease.²⁸ Risperidone is associated with relatively few motor side-effects compared to the traditional antipsychotics, and weight gain is less likely with risperidone than with either clozapine or olanzapine.³⁶ The most common side-effects associated with risperidone are insomnia, agitation, anxiety and headache.²⁸ Relative to the other atypical antipsychotics, risperidone has been associated with change in serum prolactin levels which is dose-dependent.^{37, 38} The actual clinical significance of elevated prolactin concentration is unclear. Elevated serum prolactin levels may be asymptomatic, but may lead to galactorrhea, sexual dysfunction, breast swelling, anovulation and osteoporosis. In men it may cause impotence and azoospermia.^{37,39,40} Risperidone also appears to be associated with dose-related risks for EPS, although the rate is similar to placebo at doses of ≤ 6 mg/day.^{37,41,42}

Drug interactions: Risperidone has a low potential for metabolic drug interactions. Drugs that inhibit or induce cytochrome P450 2D6 or CYP 3A4 may alter risperidone concentrations.⁴³ Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally acting drugs.²⁸

OLANZAPINE

Overview: Olanzapine a thienobenzodiazepine, is effective for the treatment of both positive and negative symptoms of schizophrenia, is safer than conventional antipsychotics and is comparable to the other atypical antipsychotics.⁴⁴ Olanzapine is also licensed for the treatment of depressive symptoms in schizophrenia. In clinical trials, olanzapine was effective in treating psychotic symptoms and mood instability in bipolar disorder,⁴⁵ and as an augmenting agent with fluoxetine in the treatment of non-psychotic treatment-resistant major depression.⁴⁶ These are as yet unlicensed indications.

Trials: Olanzapine has similar or improved efficacy compared to haloperidol,⁴⁸ and was demonstrated to be non-inferior to clozapine and better tolerated among resistant patients eligible for treatment with clozapine.⁶⁹ Overall, both olanzapine and risperidone have been found to be comparable for the treatment of positive and negative symptoms of schizophrenia.³³ In a trial to evaluate the cognitive changes in early phase schizophrenia, olanzapine had superior cognitive benefits relative to haloperidol and risperidone.⁴⁹ There were no significant differences between olanzapine and chlorpromazine when they were compared in treatment-resistant schizophrenia.^{50,51}

Dose: Olanzapine is available as a conventional tablet and a bioequivalent rapidly dispersible tablet. The recommended starting oral dose for olanzapine is 10mg/day, administered as a single dose. Daily doses may subsequently be adjusted to within the range 5-20mg daily with a routine therapeutic dose of 10mg/day. In clinical trials, the effective dosage of olanzapine is in the range of 10-20mg/day for most patients.

Side-effects: Olanzapine is not associated with the risk of agranulocytosis as seen with clozapine, is associated with fewer EPS than haloperidol and risperidone, and significantly less hyperprolactinaemia than with risperidone. **52** Olanzapine has transient dose related increases in prolactin at week 2 which falls to levels comparable to placebo at weeks 4 and 6.**70** Very common (>10%) undesirable effects associated with the use of olanzapine in clinical trials include sedation and weight gain. Weight gain was related to a lower pre-treatment body mass index (BMI) and initial starting dose of 15mg or greater.**53** Weight gain may exacerbate subclinical diabetes or promote glucose metabolic abnormalities.**54** Appropriate clinical monitoring is therefore advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus. Other less common adverse effects (1-10%) include dizziness, increased appetite, oedema, orthostatic hypotension and mild transient anticholinergic effects including constipation and dry mouth and transient asymptomatic elevation of hepatic transaminases, ALT and AST. **53,55**

Interactions: As with all antipsychotics, caution should be used when olanzapine is prescribed in combination with other agents that act on the central nervous system. Medications that induce or inhibit CYP 450 1A2 may affect olanzapine pharmacokinetics. Smoking may reduce olanzapine levels to a small extent, although there is no data to recommend dosage modifications in smokers.**55**

AMISULPRIDE

Overview: Amisulpride is a substituted benzamide that is indicated for the treatment of acute and chronic schizophrenic disorders in which positive and/or negative symptoms are prominent. It is also indicated in patients characterised by predominant negative symptoms.

Trials: A 4-week trial in schizophrenic patients showed that 400-800mg/day was effective for the positive symptoms, but with less EPS than haloperidol 16mg/day.**56** Overall, in a 4-month study, amisulpride was superior to haloperidol in the treatment of acute exacerbations of schizophrenia and significantly improved patients' quality of life and social adjustments.**57** In a one-year efficacy study, patients with chronic schizophrenia received either amisulpride or haloperidol. Positive symptoms improved similarly in both groups, but amisulpride caused a significantly better improvement in negative symptoms, social functioning and quality of life. Adverse effects were similar in both groups although EPS were more frequent for haloperidol.**58** In comparison to other antipsychotics, amisulpride was equally effective to risperidone but the latter group experienced a greater increase in body weight.**59**

Dose: Initiation of treatment with amisulpride does not require dose titration and for acute psychotic episodes, oral doses between 400-800mg/day are recommended. . When negative symptoms predominate, doses between 50 and 300mg/day are recommended.**60**

Side-effects: In controlled clinical trials, the most common adverse effects reported (5-10%) include insomnia, anxiety and agitation. Less common adverse effects include somnolence, gastrointestinal disorders such as constipation and nausea, and dry mouth. In studies of chronic schizophrenia, endocrine effects, including hyperprolactinemia, were similar in amisulpride, haloperidol and risperidone

groups.⁶¹ Studies have also suggested that amisulpride is associated with dose-dependent EPS.³⁹

Interactions: Amisulpride has few known drug interactions and appears not to inhibit cytochrome P450 enzymes. ⁶⁰

QUETIAPINE

Overview: Quetiapine, a dibenzothiazepine, is an atypical agent structurally similar to clozapine. In contrast to clozapine, agranulocytosis has not been noted to date and therefore does not require haematological monitoring.

Trials: Being a relatively new antipsychotic, there are fewer comparative published trials with quetiapine but it is at least effective as older antipsychotics, (chlorpromazine and haloperidol), and has similar response rates compared to other atypical antipsychotics.^{62,63,64,65}

Dose: The total daily dose on initiation as recommended by the manufacturer is 50mg, (day1), 100mg, (day2), 200mg, (day3), 300mg, (day4). Thereafter the dose should be titrated to within the usual effective dose of between 300-450mg/day. Depending on the clinical response, the dose may be further adjusted to within the dosage range 150-750mg/day.⁶⁶

Side-effects: Quetiapine is generally well tolerated. Initial assessments of clinical trials have suggested a good safety profile with regard to EPS, which may be advantageous when considering treatment in the elderly, and in patients with pre-existing dopaminergic pathology such as Alzheimer's disease and Parkinson's disease.⁶⁷ Quetiapine has also been shown to have negligible effects on prolactin level and is associated with less weight gain than clozapine or olanzapine.^{63,68} Other reported adverse effects include somnolence, dry mouth, dizziness, LFT and TFT changes.⁵⁵

Drug interactions: As with other atypicals, quetiapine should be administered with caution with other CNS acting drugs. The cytochrome 3A4 isoenzyme is primarily responsible for the metabolism of quetiapine.

Drug	Routine Therapeutic Dose/Range (As per SmPC)	Cost (€)
Clozapine Clozaril®	200 – 450mg	5.43 – 12.22
Risperidone Risperdal®	4 – 6mg	3.49 – 6.04
Olanzapine Zyprexa®	10mg	5.94
Amisulpride Solian®	Acute episodes 400 – 800mg	2.88 – 5.75
	Predominant negative symptoms 50 – 300mg	0.39 – 4.31
Quetiapine Seroquel®	300 – 450mg	4.53 – 4.83

Cost based on GMS data (September 2001)

Antipsychotic Relative Adverse Effects: (Ref: Partly reproduced from Maudsley 2001)

Drug	Sedation	EPS	Anti-cholinergic	Hypotension	Cardiac Toxicity	Prolactin Elevation	Weight gain
Clozapine	+++	-	+++	+++	+	-	+++
Risperidone	+	+	+	++	-	+++	++
Olanzapine	++	+/-	+	+	-	+	+++
Amisulpride	-	+	-	-	-	+++	+
Quetiapine	++	-	+	++	-	-	+

Key:

+++	High incidence/severity	+	Low
++	Moderate	-	Very low

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