# New therapies in SCHIZOPHRENIA

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*Schizophrenia is a serious, chronic illness of the brain that affects approximately 1% of the general population. In the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) schizophrenia is described as "a disturbance that lasts for at least 6 months and includes at least a month of active-phase symptoms (that is, two or more of the following: delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behavior, negative symptoms)".*

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**Summary**

In the previous century, treatment of schizophrenia focused mainly on reduction of positive symptoms and short-term outcome. Today we have more comprehensive assessment of outcome in schizophrenia, incorporating multiple outcome criteria such as level of occupational and social functioning, cognitive function, feeling of well-being, severity of side-effects, compliance, frequency of relapses and duration of hospitalization. Over the years, major progress has been made in the treatment of schizophrenia, and several new therapies have become available. The development of these new therapies was mainly as a result of research into second-generation antipsychotics, but also inquiry into the psychosocial factors affecting the disorder.

Clinical experience has shown that 20-30% of patients with schizophrenia do not respond to first-generation antipsychotic medications. Furthermore, these medications frequently cause severe, unwanted extrapyramidal side-effects (EPSE) such as parkinsonism, dystonia and akathisia. Of those first episode patients who do respond to treatment, approximately 60% will relapse within the first two years. It is therefore vital that the clinician understands the implications of treatment, the effect of the illness on the individual and the burden of side-effects as a reason for non-compliance.

Clozapine was the first of the "so-called" second-generation antipsychotic agents to become available. This unique medication is not only the most effective antipsychotic agent known to date, but also has the added advantage of very low risk of extrapyramidal side-effects. Unfortunately, clozapine may cause a number of other side-effects, some of which are only uncomfortable (sedation, hypersalivation, orthostatic hypotension) while others may be life-threatening (agranulocytosis, myocarditis and convulsions). This has limited its use to treatment-resistant cases and has stimulated the pharmaceutical industry to search for a safe alternative to clozapine.

## What is an atypical antipsychotic?

Typical antipsychotics (also known as first-generation, classical or conventional neuroleptics) have been available since the introduction of chlorpromazine in the 1950s and are well known to general practitioners. Other typical antipsychotics include haloperidol, trifluoperazine and thioridazine and depot preparations such as flupenthixol deaconate and fluphenazine deaconate. They have a high affinity for D2-receptors and are known for their propensity to cause extrapyramidal side-effects (EPS).

Atypical antipsychotics were defined by the re-discovery of clozapine (in 1988), with a relatively low affinity for D2-receptors and high affinity for 5HT2-receptors. These "atypical medications" are known for their low incidence of extrapyramidal and other neurological side-effects as well as superior efficacy in treatment of resistant or refractory schizophrenia and the negative symptoms of the illness.

Atypical antipsychotics are also referred to as second-generation neuroleptic medications. They include: risperidone, olanzapine, quetiapine, ziprasidone and amisulpride. In this review we focus mainly on these medications, their uses, side-effects and efficacy in the treatment of schizophrenia.

## Why have atypicals been developed?

Firstly, approximately 20% of first episode psychosis patients (newly diagnosed patients with schizophrenia) do not respond to conventional antipsychotics. Of those who do respond, many will relapse within the first two years. Conventional antipsychotics have little beneficial effects in the other symptom clusters of schizophrenia, such as negative symptoms, cognitive symptoms, mood symptoms and aggression. In fact, these first-generation medications, while effective in treating the positive symptoms (hallucinations, delusions and disorganised behaviour) in many patients, often exacerbate the other symptoms, e.g. negative symp-

toms and cognitive impairment). This is important, as reintegration into society, quality of life and ability to work seems to be largely dependent on effective management of negative and cognitive symptoms, rather than positive symptoms. Furthermore, EPS has been shown to be the principal cause of poor compliance with antipsychotic medication.

The atypical agents, on the other hand may improve positive symptoms in partial- and non-responders as well as the typical agents. Trials have shown lower relapse rates, fewer EPS and lower long-term risk of movement disorders such as tardive dyskinesia. Beneficial effects on negative symptoms have been demonstrated and patient acceptance is also better.

**How do the new therapies achieve their atypicality?**
Firstly, as already mentioned, they cause significantly greater blockade of serotonin (5HT2) receptors than dopamine (D2)-receptors.

Secondly, they selectively block dopamine-receptors in the mesolimbic regions of the brain compared to the nigro-striatal regions. Blockade of dopamine receptors in the nigrostriatal regions is responsible for the development of EPS.

Thirdly, they seem to bind "less tightly" to the D2-receptors, causing endogenous dopamine still to bind to these receptors as well, therefore causing a better balance in dopamine regulation.

**Advantages of new atypicals**
- They are as good as, and maybe even superior to, conventional medications in the treatment of positive symptoms.
- They may have a direct effect on the primary negative symptoms of schizophrenia.
- They also reduce the burden of secondary negative symptoms (i.e. side-effects caused by conventional antipsycotics).
- There is evidence that they may improve cognitive functioning.
- They may improve mood symptoms and decrease the incidence of depression.
- They have a decreased burden of neurological and anticholinergic side-effects.

**Disadvantages of new atypicals**
- Some of the atypicals can cause substantial weight gain. This may have secondary medical complications, such as decreased glucose tolerance with an increased risk of developing diabetes mellitus.
- They may also increase triglicerides and cholesterol levels. All of these side-effects may increase the risk of ischaemic heart disease.
- Some of the novel antipsychotic medications also prolong the QTc-interval on the ECG, increasing the risk of torsades de pointes and sudden death. This side-effect is specifically a problem with sertindole (not currently available in South Africa) and to a lesser degree with ziprazidone.
- Sedation can also be a major problem.
- High cost. (even in the private sector).
- In high dosages some may still cause hyperprolactinemia and EPS.

**What about tardive dyskinesia?**
Tardive dyskinesia is a disorder of involuntary, choreo-athetoid movements in voluntary muscles/muscle groups that may appear after chronic (>6 months) use of neuroleptics. The most common movements involve the orofacial region, followed by the fingers and toes. In seriously affected patients athetoid movements of the head, neck and hips occur, and in severe cases irregularities in breathing and swallowing can occur.

Up to 25% of patients treated with conventional neuroleptic medications over 4 years, develop TD. Risk factors for developing TD include: female sex, increasing age and the presence of a mood or cognitive disorder.

The new atypical medications have been shown to have a *significantly lower* incidence rate of TD. In some studies it has even been suggested that they improve, and therefore treat, TD.

**Serotonin-dopamine antagonists**

***Risperidone***
Risperidone is a benzisoxasole derivative, chemically unrelated to any other antipsychotic currently available. Like clozapine, it has a high affinity for of 5HT2, 5HT7, 1, 2-adrenergic and H1 histaminergic receptors. Although it is a potent antagonist of D2-receptors, it causes fewer extrapyramidal side-effects than haloperidol.

Optimum daily dosage of risperidone is estimated at 4-6 mg. No gains in efficacy have been demonstrated in doses above 8 mg per day. Additionally, EPS may become a problem in doses above 8 mg per day. Risperidone is also said to have possible advantages in the treatment of depressive symptoms and improvement of cognitive functioning in schizophrenia.

The initial dosage is usually 1 mg daily and can be titrated slowly to 2 mg twice daily over a 1-week period. Clinical response is expected after about 4 weeks of treatment. The dosage can be increased to 4 mg twice daily. Higher dosages are not recommended. It is safe for use as a first line treatment of schizophrenia. In the elderly dosages of 0.5-1 mg twice daily are recommended.

Common side-effects include somnolence, orthostatic hypotension, weight gain, constipation and erectile dysfunction. Risperidone-related seizures are seen in less than 1% of patients. Approximately 2% of patients may experience prolongation of the QTc interval to more than 450 ms. This may lead to cardiac arrhythmias or heart block.

***Olanzapine***
Olanzapine is a thienobenzodiazepine derivative. It is chemically related to clozapine and quetiapine. It has shown efficacy in the treatment of schizophrenia over placebo. It has a long half-life, therefore once-daily dosing is effective. It has a high affinity for 5HT2 receptors as well as dopamine 1 to 4, 1 adrenergic, muscarine 1 to 5 and H1-receptors.

It has a somewhat different side-effect profile to risperidone. Common side-effects include somnolence, weight gain and constipation. Less than 1% of patients develop signs and symptoms of orthostatic hypotension, such as dizziness, tachycardia and syncope. Limiting the starting dose to 5 mg/day, then increasing to a therapeutic range of 10-15 mg per day over a few weeks can minimise the risk of these effects. Olanzapine should be used with caution in patients with a history of myocardial

infarction or unstable angina. Problems regarding increased insulin tolerance and increased risk for developing diabetes are a major problem. In Japan it is contraindicated to prescribe olanzapine to diabetic patients.

Two per cent of patients taking olanzapine develop raised serum transaminases. This elevation is benign and reversible, but caution should be exercised in patients with a history of liver disease.

Olanzapine is safe for use as a first-line treatment of schizophrenia. The standard dosage is usually between 10-20 mg/day, but higher dosages are needed in some patients.

Olanzapine has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. Three large RCTs have compared olanzapine with haloperidol. In these studies olanzapine demonstrated several advantages over haloperidol.

Olanzapine has also demonstrated efficacy in the treatment of depressive symptoms as well as improving cognitive functioning. Currently it is also marketed as a mood stabiliser in the treatment of bipolar disorder.

### *Quetiapine*

Quetiapine is a benzothiazepine that is structurally related to clozapine and olanzapine. It has a high affinity for 5HT2 and 5HT6 as well as H1 and 1- and 2-adrenergic receptors. It has a low affinity for D2-receptors and is therefore not associated with EPS (a major advantage).

High dose quetiapine has been shown to be significantly superior to placebo in the treatment of schizophrenia. It may also reduce negative symptoms. There are also advantages in the treatment of depressive symptoms and improvement of cognitive functioning.

Most common side-effects are somnolence, postural hypotension and dizziness. Quetiapine causes a modest transient weight gain and transient rise in liver transaminases. Dosing should be twice daily. Effective dose range is estimated at 300-800 mg/day.

### *Amisulpride*

Amisulpiride is a substituted benzamide. It has strong affinity for dopamine 2 and 3 receptors. This affinity seems to be selective to the limbic areas. The t_ is 12 hours and the dose range from 50-1 200 mg/day.

At lower dosages (50-300 mg/day) it has been shown to be effective in the treatment of specifically the negative symptoms and in higher dosages (400-1 200 mg/day) it also addresses the positive symptoms. EPS are dose-related, but less than with the conventional antipsychotics. Although it causes no apparent weight gain, it may cause a rise in prolactin levels.

Amisulpride also has the advantage that it has no effect on the QTc-interval, and no EPS. The recommended dosage per day is 800 mg (400 mg bd). There is no need for titration. This dosage can be started immediately.

### *Ziprasidone*

Ziprazidone is one of the newest antipsychotics available on the international market, but has not yet been launched in South Africa.

Ziprasidone is a benzisothiazolyl piperazine. It causes antagonism of a wide variety of serotonin receptors, as well as dopamine and noradrenergic receptors. It also inhibits re-uptake of both serotonin and noradrenaline. These features suggest it may also treat anxiety and depression.

In a study conducted in 302 subjects, randomised to either ziprasidone 80 or 160 mg/day or placebo for 6 weeks, both doses of ziprasidone were significantly more effective than placebo in treating positive and negative symptoms. Ziprasidone 160 mg/day significantly improved depressive symptoms in subjects with a higher baseline depression compared to placebo.

In a one-year, double blind, placebo-controlled trial (2002), results demonstrated that ziprasidone was effective as maintenance treatment for patients with chronic schizophrenia.

In general it is a well-tolerated drug with no significant association with weight gain, EPS or cardiac disorders. Problems with QTc-prolongation are minimal and not statistically significant.

### When to prescribe atypical antipsychotics

- First line treatment in schizophrenia and schizophreniform disorder: Risperidone, olanzapine, quetiapine, amisulpride, ziprasidone.
- Patients who experience unwanted side-effects on conventional antipsychotic medications: Risperidone, olanzapine, quetiapine, ziprasidone.
- Patients resistant to treatment with conventional antipsychotic medications: Risperidone, olanzapine, Quetiapine, Amisulpride.
- Treatment of tardive dyskinesia: Quetiapine, olanzapine.
- Patients with known diabetes mellitus and cardiac disease: Risperidone,quetiapine, amisulpride.
- Patients where weight gain is a problem, or obese patients: Risperidone, amisulpride, ziprazadone.

### Conclusion

It is important for clinicians to be aware of the new therapies available in the treatment of schizophrenia. Every patient has the right to be treated with a medication that causes minimal side-effects and improves quality of life. Every patient with schizophrenia should be offered a trail on the new atypical medications, unless the use of a depot preparation is mandatory.

**See CPD Questionnaire p.49**

### REFERENCES

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**Note:**

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