Road testing the newer antipsychotic agents

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BACKGROUND
Increasing community treatment of patients with psychotic disorders over the past 20 years has led to the general practitioner being more intimately involved the monitoring and management of these patients. Second generation antipsychotics have been available for use in psychosis for nearly a decade. In Australia they are considered to be first line treatment for a number of psychotic disorders.

OBJECTIVE
This article aims to inform the GP on current thinking on the use of second generation antipsychotics and to reinforce the importance of the GP's role in the care of patients with psychosis.

DISCUSSION
Second generation antipsychotics give patients a greater relief from the symptoms of psychosis, with fewer side effects. A renewed focus on the physical health needs of these patients stresses the importance of primary health promotion.

Over the past 30 years, models of intervention in the psychiatric treatment of psychotic illnesses have been transformed. Focus has shifted from treatment in institutional settings to community care. Furthermore, evidence has been gathered that highlights the importance of the early recognition of psychosis so that it may be assertively managed. Secondary care teams are multidisciplinary and usually based within the local area mental health services in community clinics and in-patient hospital facilities.

General practitioners play a vital role in the care of patients with psychosis by:

- monitoring the treatment and progress of patients with established psychosis
- detecting early signs of psychosis
- liaising with agencies (eg. counselling, family support, psychiatric services), and
- maintaining the patient's physical health.

Antipsychotic medication forms the foundation of both acute and maintenance treatment of psychosis. Most of the evidence base has been gathered for psychoses due to underlying schizophrenia, but antipsychotics are also used in the treatment of mania, drug induced psychosis, schizoaffective disorder, delusional disorder, behavioural disturbance, and depression.

The novel antipsychotic medications, also known as 'atypical' or 'second generation antipsychotics' (SGAs) have helped to engender a more optimistic outlook in the treatment of schizophrenia in particular. This article aims to provide the GP with an update on the state of knowledge around these medications.

Antipsychotic medications

The first antipsychotic medication, chlorpromazine, became available for use in the 1950s. In the ensuing decades, other similar compounds followed (eg. thioridazine, fluphenazine and haloperidol). These drugs, now collectively referred to as the typical antipsychotics, treat positive symptoms of psychosis. They were also known as 'major tranquillisers' and 'neuroleptics' in reference to their troubling side effects. In particular extrapyramidal symptoms (EPS) are associated with nearly all the typical agents. The older drugs were often used in large doses,

with rapid increases leading to serious and sometimes fatal side effects.

Second generation antipsychotics

Second generation antipsychotics are internationally considered to be the first line drug of choice for psychosis.[1–3] They offer a number of advantages compared with the older 'typical' drugs – in particular in ameliorating the cognitive impairment that has been an under-recognised symptom cluster in people with schizophrenia (*Table 1*).

Neuropharmacology

Antipsychotic drugs act on many different receptors in the brain. This is thought to be the basis for both their therapeutic mode of action and their side effect profile.

Studies suggest that 60–80% occupancy of the dopamine D2 receptors is associated with antipsychotic efficacy and that higher occupation levels, as demonstrated by the typicals, are associated with EPS and hyperprolactinaemia.[4]

Other receptors that are activated include the adrenoceptors, histamine, acetylcholine and 5-HT receptors. These have been implicated in other effects of antipsychotics such as postural hypotension, sedation, anticholinergic effects, increased appetite, and antidepressant properties.[5]

The SGAs are heterogeneous in their receptor affinity profile, and therefore show differences in efficacy and side effects.

Efficacy

Meta-analyses[6] have demonstrated a greater efficacy for the SGAs versus the typicals for both the negative and neurocognitive symptoms of psychosis, but little difference for positive symptoms. There is discussion within some sections of the academic community regarding the validity of some of this data,[7] but nevertheless there is compelling evidence in particular for:

- risperidone – reduced relapse rate[8,9]
- olanzapine – improved treatment adherence,[10] and
- amisulpiride – reduction in negative symptoms.[11]

Clozapine has been shown to have a substantial superiority to other antipsychotics with regard to positive, negative and neurocognitive symptoms, and with lower rates of suicide, relapse rates and improved adherence.[12,13]

Tolerability/side effects

In general, the tolerability of antipsychotic medications is dose related. *Table 2* summarises the side effects of typical antipsychotic agents. *Table 3* summarises the efficacy benefits and major side effects of the SGAs.

Table 1. Positive, negative and neurocognitive symptoms of psychosis

Positive	Hallucinations, delusions, and thought disorder
Negative	Flat affect, lack of energy, poor motivation, poverty of thought, social withdrawal
Neurocognitive	Lack of concentration, poor memory, impaired higher conceptual thinking (test by asking to interpret a proverb, or comparing objects) Functional deficit – difficulty in learning, poor work, social performance

Neurological

The superiority of the SGAs over the typicals is most clearly seen with regard to EPS. In particular, the incidence of acute dystonia and later onset tardive dyskinesia is dramatically lower with the SGAs.[14–16]

Cardiovascular

Some antipsychotics are associated with QTc prolongation – this predisposes to ventricular arrthymias and sudden cardiac death. Risk is greater when multiple antipsychotics are used or when combined with other drugs that result in prolonged QT intervals.[17] There is debate regarding the possibility of an increased incidence of ischaemic stroke among elderly people receiving antipsychotic medication for the behavioural and psychological symptoms of dementia.[18]

Endocrine and metabolic

Clozapine and olanzapine are associated with weight gain.[19] Olanzapine is also associated with hyperlipidaemia and hyperglycaemia, sometimes with resultant type 2 diabetes mellitus.[10,20–22] Risperidone at higher doses can cause raised prolactin levels.[10]

Which antipsychotic?

The following factors should be considered in selecting which antipsychotic to treat a patient with[23]:

- past patient response or response of a family member
- side effect profile
- treatment adherence factors (*Table 3*).

The majority of patients that GPs treat will have had their medications started by the secondary care team. There are a number of important prescribing principles:

- It is important to develop a therapeutic relationship by relieving symptoms and educating the patient and their family on the medication and its side effects. All these factors promote longer term adherence to therapy – key to treating both the psychotic episode and to future relapse prevention
- Avoid prescribing multiple concurrent antipsychotics

– this leads to greater adverse effects with no improvement in efficacy (except in acute behavioural emergency, switching drugs and some cases of treatment resistance)

- Antidepressants, mood stabilisers and benzodiazepines are commonly used alongside antipsychotic agents to treat comorbid symptoms.

The form in which a medication may be prescribed needs to be taken into account. All are available in tablet form; risperidone and olanzapine are also as available as wafers; olanzapine as a rapid acting intramuscular injection (used for acute sedation/behavioural disturbance); and risperidone as a 2 weekly depot preparation. The use of a depot is reserved for patients who have demonstrated serious nonadherence to oral medication. Maintenance therapy needs to be continuous. Intermittent therapies are not recommended.[24]

In general, the number of relapses a patient has had guides how long a patient should continue to take an antipsychotic for relapse prevention. The Royal Australian and New Zealand College of Psychiatrists guidelines suggest they be taken for 1 year following a first episode psychosis, 2 years following a single relapse, and long term following any subsequent relapse.[1] It is common for GPs to be involved in the care and management of patients who fit any of these categories.

Using antipsychotics 'for life' is not a general rule. Medication may be gradually ceased after a prolonged period of stability in collaboration with patients and their carers.

In pregnancy, many clinicians attempt to discontinue their patient's antipsychotic medication. This leads to an increased risk of psychotic relapse at what is already an exciting yet stressful time for the expectant mother. Current evidence is limited surrounding the use of SGAs in pregnancy. To this end, we have recently set up an Australia wide register of pregnant women taking antipsychotics (National Register of Anti-psychotic Medications in Pregnancy). All clinicians managing a pregnant woman on any antipsychotic medication are urged to contact us (see *Resource*).

Table 2. Side effects of antipsychotic drugs

Extrapyramidal symptoms
- Dystonias
  - contractions of muscles resulting in abnormal movements or postures
  - laryngeal dystonia can be fatal
- Drug induced parkinsonism
  - resting tremor, rigidity, bradykinesia, flat affect, hypersalivation
- Akathisia
  - subjective feeling of restlessness (can be described as 'internal anxiety') and/or its objective manifestation (eg. inability to stand or sit still)
- Tardive dyskinesia
  - late appearing involuntary movements of the face, fingers, toes, trunk
  - very difficult to treat

Neuroleptic malignant syndrome

Sedation

Postural hypotension

Anticholinergic – dry mouth, constipation, urinary, retention

Hyperprolactinaemia – causes amenorrhoea, sexual dysfunction, galactorrhoea, gynaecomastia

Weight gain

Table 3. Summary of individual atypical antipsychotic drugs

Risperidone	Good evidence for greater efficacy
	Mild EPS and prolactin elevation at higher doses
Olanzapine	Good evidence for greater efficacy
	Mild sedation, weight gain, hyperglycaemia, hyperlipidaemia
Amisulpride	Evidence for good efficacy against negative symptoms in lower doses
	EPS common at higher doses
Quetiapine	Good efficacy when correct dose obtained
	Wide dose range
	Sedation
Aripiprazole	Novel action – partial agonist at D2 receptor
	Few side effects
	More clinical experience needed
Clozapine	Best efficacy for treatment resistant symptoms
	Sedation, weight gain, reduced seizure threshold
	Risk of agranulocytosis and myocarditis requires strict monitoring (blood tests, ECG and echocardiograms)

Changing antipsychotic

The main reasons a patient may be switched to an alternative SGA are if there is inadequate therapeutic response or poor tolerability to the first medication. It is important that when changing medication, the patient, their carers, and the treating team, are vigilant regarding the potential risks, ie. relapse of psychotic symptoms. Increased monitoring can pick up early warning signs of relapse quickly, and a crossover phase of 1–2 weeks can help reduce the risk of relapse.

In the initial period there may be an increase in side effects – the patient should be warned of this, but reassured that this usually subsides after a few weeks as the effects of the first medication wanes.

Particular education should be given to women changing from a medication which may give some contraceptive effect (eg. typicals via hyperprolactinaemia) to an SGA.

Drug interactions

Particular care is needed with concurrent medications that prolong the QTc interval.[17] Care is also needed with drugs that inhibit cytochrome enzymes (eg. ritonavir, azole antifugals, erythromycin) as they may increase the plasma concentration of antipsychotics.

Physical health

People with schizophrenia have a reduced life expectancy due to suicide and an increased incidence of medical illness, especially ischaemic heart disease.[25,26] They have higher rates of smoking and lower levels of exercise. General practitioners play a central role in primary health promotion. Physical check ups are necessary to monitor the side effects of antipsychotic medication. In particular, weight, body mass index, and blood pressure should be regularly assessed. Fasting plasma glucose (or HbA1c), lipid profile, and electrocardiogram should be regularly measured along with other investigations as indicated.[22]

Summary of important points

- SGAs are more effective and have fewer side effects than the 'typical' agents that preceded them.
- Attention to the physical health needs of psychiatric patients is essential. Focus should be high, particularly in regard to cardiovascular risk factors and metabolic side effects.
- A collaborative approach is important as the basis for continuing care. This helps to foster an effective therapeutic relationship between physician and patient.

Resource

National Register for Antipsychotic Medications in Pregnancy . C/-Professor J.Kulkarni, Alfred Psychiatry Research Centre, The Alfred, Commercial Rd, Prahran Vic 3181. Phone 03 92766564 Email j.kulkarni@alfred.org.au

Conflict of interest: there has been no specific funding for this article. Professor J Kulkarni has received honoraria for educational sessions and clinical drug trial research from Eli Lilly, Bristol Myers Squibb, Jansen-Cilaag, Astra Zeneca, and Novartis in the past 5 years.

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