Atypical antipsychotics in schizophrenia

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Pharmacotherapy is the core of management for schizophrenia, and provides an essential foundation upon which psychosocial strategies for recovery can be built.

When antipsychotic treatment is initiated in a patient with schizophrenia, two points need to be considered:

- Which medication will work best for this patient?
- What are the associated risks of using the medicine in this patient?

This article focuses on the use of atypical antipsychotics, which are now the mainstay of treatment for patients with schizophrenia.

What are atypical antipsychotics?

Atypical antipsychotics, which are also known as novel or second-generation antipsychotics, have been successively introduced in Australia since the early 1990s. They are 'atypical' because they reduce the propensity for the unpleasant extrapyramidal side effects associated with the earlier 'typical' antipsychotics, which range from Parkinson's-like disorders, through akathisia (subjective and motor restlessness) and acute dystonia, to tardive dyskinesia (an involuntary movement disorder that usually heralds a more malign effect on the brain).

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Since their introduction, the atypical antipsychotics have been found to differ from typical antipsychotics in other ways. They have modest but clinically significant effects in a number of important domains related to patient outcome and, ultimately, quality of life;[1,2] these are described in the box on page 56.[3-10] Of particular importance to patients living in the community are the improvements in negative symptoms,[11] cognitive symptoms,[12] quality of life and psychosocial function,[13] as well as the reduction in relapse rates.[14]

In general terms, the most 'powerful' atypical antipsychotic agent available is clozapine (Clopine, CloSyn, Clozaril), but it is indicated for use only in patients who have treatment resistant schizophrenia. Most of the other atypical antipsychotics offer the range of class benefits, but there are differences in their short and long term side effect profiles. The choice of agent often depends on prescriber experience and patient feedback, which is driven by issues of tolerability and subjective wellbeing.[15]

When are they used?

According to RANZCP clinical practice guidelines, atypical antipsychotics should be first line treatment for schizophrenia and related psychotic conditions, especially in younger individuals.[16] For a patient who has experienced a first episode of psychosis, it is acceptable to use maintenance antipsychotics for at least 12 months and then, after discussion with the patient and family, attempt a negotiated withdrawal and monitor for signs of relapse for some time afterwards. For a patient who has experienced multiple episodes of psychosis, long-term continuous treatment is the rule of thumb.

How are they used?

The dosage of atypical antipsychotics is guided by the following principles:

- management should be tailored to the unique requirements of each patient, taking into account risks and benefits as they pertain to the patient
- whenever possible, the lowest possible dose should be used during the maintenance phase of the illness
- there is currently little support for combining antipsychotic agents.[17]

The Table lists suggested near-maximal effective adult doses for atypical antipsychotics.[18] Additional improvement is significantly less likely to be seen when more than the near-maximal doses are used, although it may be necessary to exceed these in certain individuals. Young and elderly patients, and those of Chinese or other Asian backgrounds, often require considerably smaller doses – in these groups, it is generally helpful to start at 50% of the target adult dose and to adjust carefully the prescription based on response and side effects.

Some of the minimal doses that have been shown to be effective in meta analysis[18] cannot actually be prescribed because the relevant formulations are not currently marketed in Australia. The lowest strength formulation of aripiprazole (Abilify) that is available is a 5 mg tablet. Olanzapine (Zyprexa) is available in tablets of 10 mg, which provide an effective low daily dose. The lowest strength formulation of injectable risperidone (Risperdal Consta) is 25 mg, requiring a special kit for delivery; for many patients 25 mg would be an adequate starting dose in a two-weekly regimen. Note that the dose of amisulpride (Solian) of 200 mg/day shown in the Table may reflect its role in controlling negative

Advantages of atypical antipsychotics in schizophrenia*

Positive symptoms

Atypical antipsychotics are at least as effective as typical antipsychotics.
Compared with other antipsychotic agents, clozapine has superior efficacy in patients with incomplete recovery.[3]

Negative symptoms

Atypical antipsychotics are more effective than typical antipsychotics.
Note that few studies specifically examine negative symptoms as the primary outcome measure (studies of amisulpride are the exception).[4]
It is unclear whether primary or secondary negative symptoms are affected.
Modest differences between agents exist.

Cognitive symptoms

Atypical antipsychotics are more effective than typical antipsychotics.
Different atypical antipsychotics may have different effects on cognition.[5-7]

Affective symptoms (mood stability)

Atypical antipsychotics are more effective than typical antipsychotics.

Suicidality

Clozapine is more effective than olanzapine;[8] there is no evidence available for other antipsychotics.

Behavioural symptoms[9]

Limited research is available to assess drug effects in managing behavioural symptoms.

Social and role functioning, and quality of life

More research is required, but there is some suggestion that atypical antipsychotics are more effective than typical antipsychotics.[10]

* Adapted from reference 1.

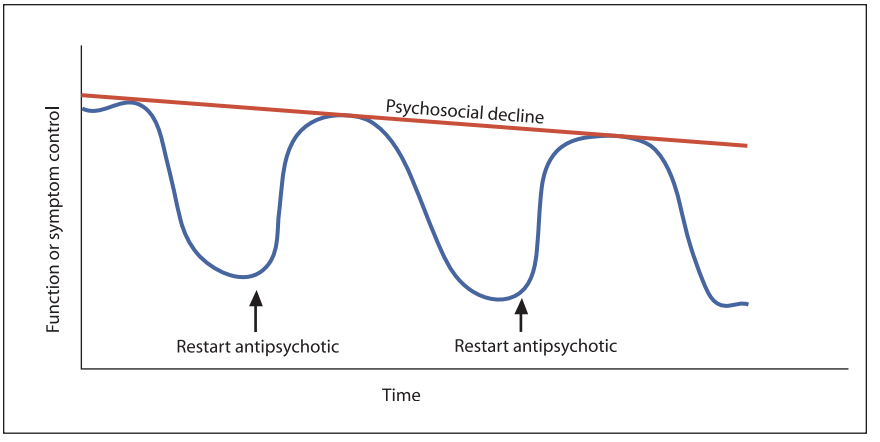

Figure. The square wave relapse signature in cyclical nonadherence.

symptoms; at least 200 mg (and more often 400 mg/day) would be more clinically feasible for controlling positive symptoms.

What needs monitoring?

The most important problem that faces physicians caring for patients with schizophrenia is nonadherence to medication: approximately 33% of patients are fully adherent, 33% are partially adherent, and 33% are fully nonadherent with prescribed maintenance treatment.[19] For patients with schizophrenia who are receiving treatment, approximately 55% of readmissions to hospital are directly attributable to nonadherence.[20]

Poor adherence, leading to a decline in function or symptom control, may be suspected after observing the pattern of the clinical response over time (see Figure). In this situation, consideration should be given to the use of a depot or long acting medication, although only one of the atypical antipsychotics (risperidone) is currently available in such a form. This type of treatment, which our research group first dubbed 'LANA' (Long Acting Novel Antipsychotic) combines the benefits of an atypical antipsychotic with high likelihood of adherence.

The second most important area of monitoring concerns physical health status. It is a damning fact that patients with schizophrenia die prematurely from preventable medical illnesses more often than should be expected.[21] Over 45% of patients with schizophrenia meet criteria for the metabolic syndrome, and this is therefore a serious public health issue. Antipsychotic medication contributes to the underlying propensity towards cardiovascular risk that seems to be inherent in patients with psychoses. For this reason, an Australian consensus statement concerning diabetes and antipsychotic medications has recently been developed that outlines a screening protocol for ensuring patients with schizophrenia do not 'fall between the cracks'.[22] (The full consensus statement and related documents that contain

Table. Using atypical antipsychotic therapy in schizophrenia

Agent	Near-maximal effective dose*	Comments on initiating therapy
Oral		
Amisulpride (Solian Tablets and Solution)	200 mg/day	Low dose may activate a patient; addition of a benzodiazepine may be helpful in the first two weeks
Aripiprazole (Abilify)	10 mg/day	Activation and other initiation side effects suggest that addition of a benzodiazepine may be useful in the first five to 10 days
Clozapine (Clopine, CloSyn, Clozaril)	>400 mg/day†	Requires slow titration (in approved centres only)
Olanzapine (Zyprexa)	>16 mg/day†	Can cause sedation May be increased to full dose quickly in the management of acute relapse
Quetiapine (Seroquel)	150 to 600 mg/day	Causes sedation, but can be initiated to maximal doses reasonably quickly in acute relapse
Risperidone (Risperdal)	4 mg/day	Can cause initial hypotension, which suggests dose should be built up over 3+ days in some patients
Injectable		
Risperidone, long acting (Risperdal Consta)	50 mg/two weekly	Requires antipsychotic cover (oral or previous depot) for three to six weeks until a steady state is reached

* Based on reference 18. The near-maximal effective dose is the threshold dose necessary to produce all or almost all the clinical responses for each drug. These values are not inconsistent with maintenance doses for patients with multiepisode schizophrenia.
† Upper limit not yet clearly defined.

practical advice for professionals and for consumers and carers can be downloaded from www.psychiatry.unimelb.edu.au/open/ diabetes_consensus.) The principles outlined in the consensus statement are consonant with those proposed by the RACGP.[23]

What about side effects?

It is important to enquire about common side effects of antipsychotics because these have an impact on quality of life and daily function and, subsequently, adherence to treatment. Sedation, weight gain, akathisia, and sexual side effects often cause much distress. Patients may experience long-term extrapyramidal side effects, such as tardive dyskinesia, but they might not complain of these spontaneously.

Many GPs have limited time to investigate side effects in depth. Self-report schedules that a patient can fill out in the waiting room may provide an efficient method of identifying issues that are of immediate importance to the patient. An example is the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS), which can be completed in about three minutes.[24-25] However, many side effects are not simply attributable to antipsychotics: psychotropic polypharmacy is common in mental health settings and contributes substantially to side effects such as weight gain and sedation. Polypharmacy should be avoided whenever clinically possible.

Conclusion

GPs care for a substantial proportion of patients with schizophrenia, and many atypical antipsychotics are now available for treating this illness. Selecting medications and maintaining patients on these medications requires careful monitoring of adherence, outcomes, mental state, and physical health status so that the risks and benefits are balanced. For most patients with schizophrenia, treatment is long term, and forming an enduring relationship with a GP will enhance the possibility of recovery by maximising the potential of treatment. MT

A list of references is available on request to the editorial office.

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