Pharmacological approaches to the management of schizophrenia

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ABSTRACT

- Pharmacological treatment remains the mainstay of the management of schizophrenia.
- Older, "typical" antipsychotics carry a significant burden of side effects, notably extrapyramidal and neurocognitive side effects.
- Newer, "atypical" agents carry a lower risk of extrapyramidal side effects. They appear to have added benefit for treating negative and cognitive symptoms of schizophrenia, and hence can enhance the quality of life of some patients.
- The choice of particular agents for individual patients requires a balancing of efficacy and side effects.
- Medication is only one element of what should be an individualised comprehensive treatment plan for people with schizophrenia.

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THE INTRODUCTION OF CHLORPROMAZINE in 1952 heralded a new era of pharmacotherapy for people with schizophrenia.[1] Since then, numerous antipsychotic agents have become available. All block postsynaptic dopamine D2 receptors, and, more variably, a variety of other receptors. The propensity of these drugs to block D2 receptors in the mesolimbic projections is thought to underlie their therapeutic effects on positive symptoms. (For definitions of "positive" and "negative" symptoms, see Box 1.) Antipsychotic agents acting on D2 receptors in the basal ganglia and hypothalamus typically cause extrapyramidal side effects (EPS) (Box 2) and neurohormonal changes. As these side effects are an almost constant accompaniment to the therapeutic effects of these older agents, they are colloquially known as "typical" antipsychotics. As a group, these drugs have some major shortcomings:

- 30%–50% of patients with positive symptoms of schizophrenia are either not responsive or only partially responsive to typical antipsychotics;[3]
- Negative symptoms[4] and neurocognitive deficits (Box 1)[5] respond poorly to typical antipsychotics or are exacerbated by them[6] (see also Pantelis and Lambert *page S62*[7]);
- Typical antipsychotics can cause a plethora of common side effects, including sedation, cognitive impairment, weight gain, diabetes, hyperprolactinaemia (associated with sexual problems and possibly osteopenia), cardiac conduction problems (which may be fatal), seizures, postural hypotension, and antimuscarinic effects such as dry mouth, constipation and urinary retention.[8]

For these and other reasons, typical antipsychotics are increasingly being supplanted by the newer, "atypical" antipsychotics.

Atypical antipsychotic therapy

"Atypical" has had various meanings, which may be classified according to the effects that differentiate these drugs from "typical" agents (Box 3). It should be stressed that the atypicals are not a single class of drugs. Indeed, they differ from each other in terms of receptor binding, efficacy, and side-effect profile. Also, as they are relatively new agents, our clinical experience with them over long periods is not as extensive as for the typicals. However, the overall risk–benefit ratio is more favourable for the atypicals, making them the preferred treatment for most patients.[9,10]

The atypical agents currently marketed in Australia are clozapine, risperidone, olanzapine, quetiapine and amisulpride. Several other agents are in the final stages of development.

Clozapine

Clozapine is the prototypical atypical agent. It carries a negligible risk of acute EPS and tardive dyskinesia, and appears to have potential benefits for secondary negative symptoms[11] and certain domains of cognitive dysfunction[12] (E2) (see Box 4 for level-of-evidence codes). However, as the drug carries about a 1% risk of potentially fatal agranulocytosis, blood monitoring is part of the prescribing process (weekly full blood counts for the first 18 weeks, and monthly thereafter). Other side effects include sedation, weight gain, excessive saliva flow and convulsions. A rare but potentially fatal side effect is myocarditis.

Clozapine is introduced in a dose-incremental manner, with an average effective dose of about 350–420 mg/day in Australia (although some patients respond to lower doses, and some to much higher doses). Clozapine is generally considered for patients who have failed to respond to antipsychotics from at least two different antipsychotic classes, or who have experienced unmanageable EPS or tardive dyskinesia. There is also recent evidence (E2) for a specific anti-suicide effect with clozapine.[14]

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1: Symptom domains in schizophrenia

*Positive symptoms**

- Hallucinations and other false or abnormal perceptions.
- Delusions (fixed false beliefs held with incorrigible conviction).

Negative symptoms†

- Affective blunting (restricted emotional experience and expression).
- Anhedonia/asociality (loss of capacity for pleasure, impoverished social drive).
- Alogia (decreased amount of speech, loss of fluency of speech).
- Avolition/apathy (lack of motivation/drive).
- Attentional impairment (inability to focus/sustain attention.

Cognitive symptoms‡ (neurocognitive deficits)

- Impaired executive function (poor problem-solving, reduced ability to learn from mistakes or feedback, reduced capacity to form new concepts).
- Attentional deficit (see negative symptoms).
- Impaired memory (problems with encoding, consolidation, retrieval and recognition).
- Impaired language processing (associational errors).

* Symptoms (acquired through the illness process) that the patient does not normally have.
† Symptoms that reflect functions and behaviours that have been lost due to the illness.
‡ Deficits in thinking, present from the onset of the disorder.

Risperidone

Risperidone is now the most widely prescribed atypical antipsychotic agent in many countries, and, at recommended doses (< 6 mg/day), carries low rates of EPS (E1).[15] However, as the dose rises, so does the risk of EPS, and some patients are prone to EPS even at low doses. This reflects its enhanced propensity to occupy striatal D2 receptors at higher doses, as with typical agents.[16] Other potential side effects include hyperprolactinaemia and postural hypotension, the latter effect requiring a slow up-titration in 0.5–1 mg steps. Many patients respond to doses of around 2–4 mg/day. Doses over 6 mg/day should be used with careful scrutiny of the risk–benefit ratio for the patient, and are not routinely recommended.

2: Extrapyramidal side effects (EPS) of antipsychotic drugs and their clinical features*

Parkinsonism

- Mask-like facies; muscle rigidity ("cog-wheeling"); "pill-rolling" tremor; shuffling gait, festination, retropulsion; diminished arm-swing.

Dystonia

- Acute: involuntary sustained spasm of muscles, notably head and neck (eg, facial grimacing, protrusion of tongue, opisthotonos, oculogyric crisis).
- Chronic: sustained involuntary spasm of skeletal muscles, resulting in abnormal posture.

Akathisia

- Subjective feeling of "inner restlessness", with a drive to move. Frequent changes of posture, inability to sit still, constant walking.

Tardive dyskinesia

- Abnormal involuntary movements of face, tongue and lips, with chewing movements, tongue movement, puckering of lips, grimacing. May be associated with truncal movements and choreoathetoid movements of the extremities.

* Reproduced with permission from Castle et al,[2] page 2.

3: Advantages of atypical (second-generation) antipsychotic drugs compared with typical antipsychotics

- Improved therapeutic effect in some treatment-resistant patients.
- Improved therapeutic effect on negative symptoms and neurocognitive deficits.
- Reduced potential to cause acute extrapyramidal side effects (EPS) (eg, akathisia, dystonia, parkinsonism).
- Reduced potential to cause longer-term EPS (eg, tardive dystonia, tardive dyskinesia, tardive akathisia).
- Reduced potential to elevate prolactin levels (with the exception of risperidone and amisulpride, in some cases).

Olanzapine

Olanzapine is the most widely prescribed antipsychotic in Australia. It is generally well tolerated and does not usually cause EPS at therapeutic doses (E1).[15] The initial dosage is usually 5 mg/day or 10 mg/day. The recommended highest dosage is 20 mg/day, although some patients, especially in acute cases, benefit from higher doses without apparent adverse effects (E4).[17,18]

Olanzapine may have particular benefit for affective symptoms, including depression ($E3_1$),[19] and has proven efficacy in the treatment of acute mania (E2).[20] It is moderately sedating, but this can be beneficial in the acute phase of psychosis. The major problem side effect clinically is that of weight gain[21] and, in some patients, hyperlipidaemia as part of metabolic syndrome X.[22] In common with most antipsychotics, olanzapine may be associated with hyperglycaemia and diabetes mellitus type 2 (E4).[23] It should be noted that people with schizophrenia carry an elevated risk of diabetes, among other medical conditions, independent of antipsychotic therapy (see Lambert et al *page S67*[24]).

Quetiapine

Quetiapine is similar to clozapine in its very low propensity to produce EPS at any dose (E2).[25] Higher doses and rapid dose increments can be associated with postural hypotension, but otherwise are usually well tolerated. There remain some questions about the efficacy of quetiapine in treating negative symptoms.

Amisulpride

Amisulpride has a long history of use in France and only recent use in Australia. It has a favourable side-effect profile, although it can cause hyperprolactinaemia and EPS at higher doses. It appears to have particular benefits against negative symptoms at lower doses (50–300 mg/day) (E2),[26] while, at higher doses (400–1200 mg/day), it is more effective against positive symptoms (E1).[27]

4: Codes for levels of evidence based on those of the National Health and Medical Research Council[13]

E1 (Level I): Evidence obtained from a systematic review of all relevant randomised controlled trials.

E2 (Level II): Evidence obtained from at least one properly designed randomised controlled trial.

$E3_1$ (Level III-1): Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).

$E3_2$ (Level III-2): Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case–control studies, or interrupted time series with a control group.

$E3_3$ (Level III-3): Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.

E4 (Level IV): Evidence obtained from case series, either post-test or pre-test and post-test.

Use of antipsychotics in clinical practice

Atypical antipsychotics other than clozapine (which is usually reserved for "treatment-resistant" patients [see Pantelis and Lambert, *page S62*][7]) are advocated as first-line treatments for psychotic disorders, especially in patients experiencing their first psychotic episode. If one atypical is either insufficiently effective or produces worrisome side effects, another should be tried. Failure or intolerance of a second atypical should prompt a full review of the patient's status, including assessment of treatment compliance and potential aggravating factors such as illicit drug use (see Lubman and Sundram, *page S71*[28]). If such factors can be excluded or controlled, some clinicians would advocate the early introduction of clozapine. In its draft guidelines for the treatment of schizophrenia,[29] the Royal Australian and New Zealand College of Psychiatrists has advocated such an approach. Typical long-acting "depot" medication (given by slow-release injection) is considered an absolute last resort, owing to the burden of side effects and uncertainties about long-term risks and benefits. However, the use of typical depot antipsychotics in any individual patient should be examined in the light of the potential benefits and disadvantages outlined in Box 5.

After a first psychotic episode, most clinicians would advocate treatment for at least a year, after which a slow decrease in antipsychotic medication could be attempted with careful monitoring of symptoms.[30] It should be stressed that this represents an option for a minority of patients. For those who have experienced repeated psychotic episodes, long-term (even life-long) treatment is necessary, at the lowest effective therapeutic dose. A general principle, based on clinical experience, is to titrate the maintenance dose to a level of control of positive symptoms that is satisfactory to the patient, his or her family and the treating clinician, and then slowly lower the dose until optimal negative symptom control is achieved (E4). This process may take weeks to months. Whereas a "one size fits all" approach will work well for a majority of patients (ie, 4 ± 2 mg/day risperidone, 15 ± 7.5 mg/day olanzapine, 400 ± 200 mg/day amisulpride, or 600 ± 400 mg/day quetiapine), patients who receive optimised doses often report improvements in drug tolerance. An individualised treatment plan that includes multidisciplinary collaboration and input from all treating agencies (including general practitioners and non-government organisations providing community rehabilitation services) enhances the therapeutic alliance, leading to improvements in compliance and, ultimately, to improved quality of life. Small perturbations in positive symptom control can be best managed by temporarily increasing the dose of the atypical agent, with a firm commitment to reducing it again as soon as possible. The principle is to use the lowest dose possible to maintain control of the target symptoms (usually positive symptoms, but other domains are equally important). (See Pantelis and Lambert, *page S62*,[7] for further discussion.)

Switching

An important clinical decision is whether and when to switch patients from typical to atypical antipsychotics. Ideally, this should be a joint decision between the patient, the patient's family (if appropriate) and the clinician. Factors strengthening the case for switching medication are presented in Box 6. As switching does carry a small risk of relapse, patients should be fully informed and closely monitored during the changeover, which should follow an established switching protocol, if possible. A number of pitfalls may potentially impair the success of the switching process:[31]

- Patients may, in effect, be switching from high equivalent doses to much lower doses (often a consequence of the fact that there are acknowledged reference ranges suggested for the atypicals that were not in evidence with the typicals);

5: Advantages and disadvantages of using depot antipsychotics

Advantages

- Overcomes difficulties with oral medication compliance.
- Bypasses the pharmacokinetic hurdles of absorption and first-pass hepatic elimination.
- Delivers a fairly constant dose of antipsychotic throughout the injection cycle.
- Medications such as fluphenazine decanoate and haloperidol last for long periods between intramuscular injections (thus, infrequent injections required).

Disadvantages

- Understanding pharmacokinetics and dosing requires specialised knowledge.
- All current depot medications have the limitation of being first-generation antipsychotics.
- Many weeks or months of medication required to reach a steady state, with a corresponding long period of elimination should there be an adverse event (eg, extrapyramidal side effects).
- Medications such as fluphenazine decanoate last for long periods between intramuscular injections (thus, long "wash-out" time if problems arise).
- Patients dislike being "coerced" with needles.
- There is a tendency for polypharmacy with other (oral) neuroleptics.

6: Reasons for switching from typical to atypical antipsychotics

Typical antipsychotic medication may be withdrawn if:

- it has an inadequate effect on positive symptoms;
- it has little or no effect on negative symptoms;
- it has little effect on neurocognitive deficits, either primary or secondary;
- it produces extrapyramidal side effects;
- the patient experiences relapse, despite compliance;
- it causes other side effects with little accompanying benefit;
- it causes affective disorder within the context of schizophrenia;
- the patient or family requests it.

■ Published conversion references used to estimate equivalent doses can differ by as much as 500%, leading to erroneous assumptions about appropriate dosage of the new agent;

■ Salient pharmacodynamic and pharmacokinetic considerations (eg, very short plasma half-lives, long-acting depot formulations, antipsychotics that are loosely bound to dopamine receptors, anticholinergic and antihistaminergic blocking effects) may not be accounted for;

■ Withdrawal effects during switching are often neither recognised nor adequately treated. These include (i) supersensitivity psychosis, a "rebound" psychosis that appears some days or weeks after rapid lowering of previous antipsychotic levels, with subsequent overactivity of mesolimbic dopamine receptors; (ii) cholinergic rebound syndrome, a potentially severe, flu-like syndrome resulting from the rapid unblocking of central cholinergic muscarinic receptors; and (iii) withdrawal EPS, which can mimic any of the acute or persistent extrapyramidal syndromes, especially dyskinesia. (The latter is not a manifestation of "new" EPS caused by the new antipsychotic, but rather an effect similar to supersensitivity psychosis, in which striatal supersensitive dopamine receptors are too rapidly unblocked.)

Switching should usually be performed slowly, with cross-titration of agents (E4).[32] In the switching phase, anticholinergic agents such as benztropine mesylate should be used if they were used before, or if the prior antipsychotic was of an anticholinergic type (eg, chlorpromazine, thioridazine, clozapine). This is to avoid the cholinergic rebound syndrome. When switching from a sedating agent to a less-sedating one (eg, chlorpromazine to risperidone), short-term benzodiazepines and/or hypnotics such as zopiclone or zolpidem are commonly prescribed to manage any rebound insomnia. It is important to remember that the ultimate goal of switching is to have the patient receive the smallest effective dose possible of a single antipsychotic.

Managing acute relapse

In patients experiencing a relapse of psychosis, it is important to ascertain whether the medication itself is ineffective or the patient is not complying with the treatment regimen. Physical and social triggers may further contribute to relapse (substance abuse, family expressed emotion [ie, criticism/dissatisfaction and emotional overinvolvement expressed by the family towards the patient], comorbid physical or psychiatric illness, and "stress"). Reasons for non-compliance may include lack of insight, forgetfulness, or intolerance of side effects. Such factors need to be understood and acknowledged, and focused interventions should be offered.[2]

If the problem appears to be one of drug efficacy, it may be appropriate to increase the dose, while carefully monitoring side effects, or switch to an atypical agent. If the patient is already taking an atypical antipsychotic, switching to a new class may help. If the patient has already had trials of at least two types of antipsychotics, with at least eight weeks' treatment with each drug and adequate compliance, the patient may be considered "treatment resistant". Patients with a more chronic course may require longer medication exposure before it is decided that the treatment is ineffective. However, to our knowledge, there is currently no clear empirical trial evidence to support this notion (see Pantelis and Lambert, *page S62*[7]).

In the immediate acute phase, behavioural symptoms (including aggression) are often the ones that bring the patient to a doctor's attention. These situations require careful assessment, including an estimation of risk to self or others. The interventions required are multifaceted, but in terms of medication, symptoms may be best managed by adjunctive benzodiazepines (in Australia, diazepam 5–10 mg/day is commonly prescribed). For patients who are unresponsive to benzodiazepines, oral atypical agents have been successfully used (eg, olanzapine wafers [10–20 mg/day] or risperidone liquid [1–2 mg/day]). The use of an atypical antipsychotic in acute psychotic episodes allows patients to receive a single drug (rather than multiple agents), effectively targets behavioural disturbance and starts the process of treating the psychotic illness itself. The risk–benefit ratio with this strategy is better than poorly controlled polypharmacy for most patients.[33]

Parenteral control of acute behavioural disturbance should be a last resort. Preferred options include the use of benzodiazepines in the short term: intramuscular (IM) lorazepam 1–2 mg (maximum 8 mg/day) is recommended, although it is not always available in Australia and may need to be specially requested; IM clonazepam 1–2 mg (maximum 6–8 mg/day) is in fairly common use; IM diazepam is used to a lesser extent, but, as it has a poor risk–benefit ratio in this form, its parenteral use is not recommended. Intramuscular olanzapine 10 mg (maximum 20 mg/day in this form; to be available soon in Australia) offers good efficacy with few unwanted side effects (E2).[34] If such agents are unavailable or have failed, consideration can be given to IM administration of typical antipsychotics such as zuclopenthixol acetate (50–100 mg IM per 48 hours) or low-dose droperidol (5–20 mg; maximum 20 mg/day).

Despite the common belief that intramuscular typical agents are ultimately effective in controlling acute behavioural disturbances, the evidence suggests that these agents may not demonstrate any particular benefit in terms of sedation and behavioural control over standard treatments.[35] Furthermore, special caution should be exerted in using these agents, owing to their propensity to produce postural hypotension, EPS, and cardiotoxicity (especially

droperidol in larger doses). Intramuscular haloperidol has limited application nowadays in Australia because of the significant adverse behavioural effects (eg, akathisia and other EPS, dysphoria, cognitive problems, decreased sense of wellbeing) associated with its use. Finally, as patients often dislike receiving typical antipsychotics parenterally, their use may adversely affect the therapeutic alliance between clinicians and patients.

Enhancing adherence — the role of depot antipsychotics

For patients who do not reliably or consistently take oral medications, long-acting depot antipsychotics should be considered. Depot injections are widely used in Australia[36] and New Zealand.[37] While there are advantages and disadvantages of using depot injections (Box 5), one of the major problems with the depot antipsychotics currently available in Australia is that they are all "typical" agents, with the usual burden of side effects. A long-acting depot preparation of the atypical agent risperidone has recently been formulated and appears to be effective and well tolerated (E2).[38] It is expected to be released in Australia soon. A long-acting form of olanzapine is also expected within the next two years.

Conclusions

The atypical antipsychotic agents allow clinicians to offer their patients with schizophrenia potentially better and broader symptom control (notably for negative, cognitive, and affective symptoms), with fewer side effects such as EPS and tardive dyskinesia. However, these newer agents have their own side effects and are, unfortunately, not effective for all patients. Antipsychotic prescribing guidelines in countries such as the United States, the United Kingdom and Australia now suggest these agents should be given consideration as first-line treatments for psychosis — a view we share. Yet, medication should be seen as only one part of what should be a holistic and comprehensive biopsychosocial treatment plan for each individual patient.

Competing interests

TJRL has been on advisory boards for Janssen-Cilag, Eli Lilly, Pfizer, Lundbeck, Sanofi, Novartis and Faulding; has received funding for unrestricted research from Eli Lilly, Novartis, Janssen-Cilag, Bristol-Myers Squibb, Pfizer and AstraZeneca; and has received travel assistance to attend meetings from Eli Lilly, Novartis, Janssen-Cilag and Bristol-Myers Squibb. DJC has been on an advisory board for Eli Lilly; has received funding for investigator-initiated research from Eli Lilly and Janssen-Cilag; and has received speaker fees from Eli Lilly and travel assistance to attend meetings from Eli Lilly, Janssen-Cilag and Pfizer.

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