Evidence-based management of schizophrenia

Marcelo Camprubi, Luiz Dratcu

Antipsychotic medication is the foundation of care for patients who suffer from schizophrenia and other psychotic conditions. Newly diagnosed patients should be treated with atypical antipsychotics, of which the National Institute for Clinical Excellence guidelines recommend five. The quality of clinical evidence will ultimately establish the differences between available treatments.

Schizophrenia is a common and impairing psychotic disorder associated with high rates of relapse and a chronic course (Kane, 1996; Mason et al, 1996), and which requires treatment in the long term. Some patients may experience acute relapses that may not always lead to long-term impairment, but many are likely to develop chronic symptoms and become severely disabled if left untreated (National Institute for Clinical Excellence (NICE), 2002).

Psychotic symptoms in this patient group have been clustered into two groups, namely 'positive' or 'negative' (*Table 1*), either or both of which can be present in an individual patient. Positive symptoms include delusions, hallucinations and thought disorder, while negative symptoms include affective flattening or blunting, poverty of speech, anhedonia and social withdrawal. Yet, psychotic symptoms may also occur in bipolar disorder, depression, substance abuse disorder, and medical illnesses such as Parkinson's disease or dementia.

CONVENTIONAL AND ATYPICAL ANTIPSYCHOTICS FOR SCHIZOPHRENIA

The clinical management of schizophrenia must address the full range of the patient's clinical, psychological and social needs (NICE, 2002). Ever since chlorpromazine was discovered in France in the 1950s, antipsychotic drugs have been the main treatment for schizophrenia. A favourable first experience of treatment using antipsychotics, ideally involving a clear therapeutic response and no adverse reactions, will influence the treatment outcome in the long term. Indeed, patients are more likely to adhere to treatment if the first antipsychotic they are prescribed effectively ameliorates their symptoms and is well tolerated (Naber and Karow, 2001), whereas the experience of extrapyramidal symptoms (EPS) and other unpleasant side effects from the beginning is likely to discourage compliance (Kane, 2001). EPS themselves have been associated with poor treatment outcome, failure to adhere to treatment, secondary negative symptoms, depression and an increased risk of developing tardive dyskinesia (Casey, 1995).

Early agents, such as phenothiazines and butyrophenones, effectively treated positive psychotic symptoms, but they proved disappointing in ameliorating negative symptoms of schizo-

Dr Marcelo Camprubi is Specialist Registrar in Liaison Psychiatry at Guy's Hospital, London and **Dr Luiz Dratcu** is Consultant Psychiatrist, Guy's Hospital, South London and Maudsley NHS Trust, and Senior Lecturer in Psychiatry, Guy's, King's and St Thomas' School of Medicine, London SE19 1SP

Correspondence to: Dr L Dratcu

TABLE 1.
Positive and negative symptoms of schizophrenia*

Positive symptoms	Delusions			
	Hallucinations			
	Thought disorder			
	Psychomotor agitation			
	Motor excitement			
Negative symptoms	Primary	Flat affect		
		Alogia		
		Avolition		
		Anhedonia		
	Secondary	Reaction to positive symptoms	Social withdrawal	
			Depression	
		Neuroleptic-induced deficit syndrome	Sedation	
			Extrapyramidal symptoms	Lack of facial expression
				Bradykinesia

* No psychotic symptom is pathognomonic of schizophrenia. Psychotic symptoms can also be associated with substance abuse (amphetamines, LSD (d-lysergic acid diethylamide), cocaine), withdrawal symptoms (alcohol, benzodiazepines), physical illness (brain injury, epilepsy, encephalitis) and other psychiatric disorders (mania, severe depression, some personality disorders).

phrenia (*Figure 1*). In addition to EPS, conventional antipsychotics could also cause a range of adverse effects (Kane, 1993; Hegerty et al, 1994; Casey, 1995; Dixon et al, 1995). The reintroduction of clozapine in the late 1980s heralded a new era for the treatment of schizophrenia: clozapine, the archetypal atypical antipsychotic, proved to be a highly effective drug, while largely devoid of the EPS induced by the other antipsychotics available. However, in addition to inducing a number of unpleasant side effects (e.g. weight gain, hypersalivation, hyperglycaemia), a major shortcoming of clozapine is the risk of agranulocytosis (up to 1.3%) associated with its use. This, and the costly blood monitoring that clozapine therapy requires, has restricted its prescription in everyday practice (Alvir et al, 1993). Soon, however, newer atypical antipsychotics were introduced: risperidone, which has been available in the UK since 1993, followed by olanzapine in 1997, sertindole, quetiapine and ziprasidone (not marketed in the UK). Some older drugs, such as zotepine and amisulpride, have been reconsidered and relaunched.

While conventional antipsychotics such as chlorpromazine and haloperidol may still be prescribed, the atypical antipsychotics – which offer similar therapeutic efficacy but a significantly better profile of safety and tolerability – had been increasingly used as first-line treatment for schizophrenia, even before the NICE guidelines were issued.

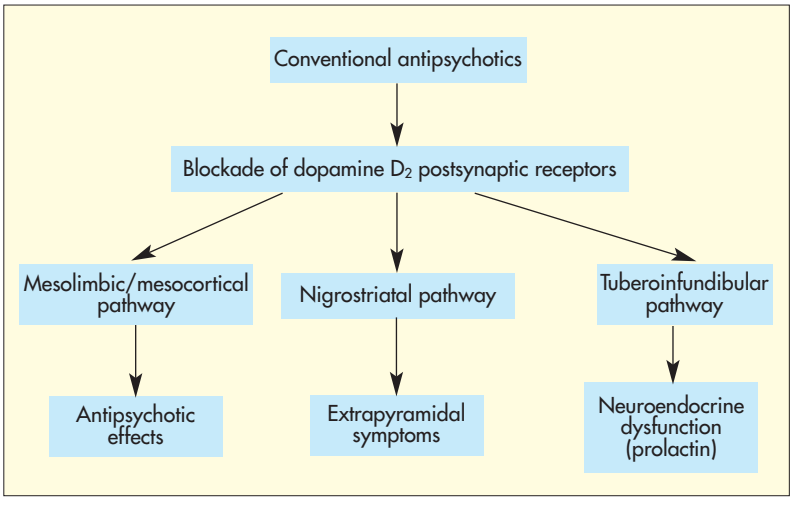
NICE GUIDELINES: QUALITY OF EVIDENCE

NICE recommends that newly diagnosed patients with schizophrenia, as well as those receiving conventional antipsychotics but whose symptoms are poorly controlled or who are experiencing unacceptable side effects, should be treated with one of the following five atypical antipsychotics: olanzapine, amisulpride, quetiapine, risperidone or zotepine. However, NICE does not offer guidelines to differentiate between individual atypical antipsychotics, nor does it make recommendations as to which treatment might suit individual patients. In principle, clozapine should be considered for patients suffering from treatment-resistant schizophrenia. Sertindole, which was voluntarily withdrawn by the manufacturer because of concerns related to cardiotoxicity but has been recently reinstated, should only be used in patients who have failed to respond to treatment using at least one of the other atypical antipsychotics.

NICE reviewed over 170 randomized controlled trials (RCTs), which included 29 head-to-head comparisons of atypical antipsychotics. Although 31 of the 170 studies monitored patients for more than 6 months, most studies were short term (4–8 weeks). The NICE guidelines were criticized not only because of the short duration of most studies that were reviewed, but also because of issues such as high attrition rates and the inadequacy of the methods used for collecting data on adverse events. Moreover, although efficacy and safety studies using a randomized controlled design can provide data on treatment outcomes under controlled conditions, these findings may not always translate directly into everyday clinical practice (Gilbody et al, 2002; Haro et al, 2003). Well-designed prospective observational studies can explore the outcome and course of treatments in the clinical setting, thereby providing enhanced external validity. A number of observational drug studies have been conducted in schizophrenia, but most have been retrospective and used small samples (Coley et al, 1999; Ho et al, 1999).

In the light of the limitations of the studies available, NICE has emphasized the need for more long-term, head-to-head RCTs of atypical antipsychotics as well as high quality observational studies of these drugs (NICE, 2002). Two such observational studies are currently in progress: the European Schizophrenia Outpatient Health Outcomes (SOHO) and the Schizophrenia Care and Assessment Programme (SCAP) (Haley et al, 1998; Edgell et al, 2003; Haro et al, 2003). After completion, these studies may hopefully provide comparative information on the outcomes and costs of using different antipsychotic treatments in the clinical setting.

Figure 1. Effects of conventional antipsychotics on dopaminergic pathways.



Meanwhile, the existing randomized long-term studies stand as the main guide for clinicians when deciding which atypical antipsychotic they should prescribe.

DIFFERENTIATING BETWEEN ATYPICAL ANTIPSYCHOTICS

Pharmacological profile

All antipsychotics, conventional and atypical, have affinity for the dopamine D_2 receptor, which remains one of the best predictors of therapeutic efficacy in pre-clinical testing (Kapur and Remington, 2001). However, the distinguishing feature of most atypical antipsychotics is a higher binding affinity for serotonin $5HT_2$ than for D_2 receptors (Goldstein, 2000; Kapur and Remington, 2001). Most atypical antipsychotics also interact with other receptor subtypes (e.g. D_3, D_4, D_5, $5HT_1$, $5HT_3$, and histamine H_1), which may account for differences in their side-effect profiles (*Table 2*). Claims that the atypical antipsychotics can be differentiated on the basis of their pharmacological characteristics are unlikely to abate, especially in view of the imminent advent of a newer drug of this class, aripiprazole. In addition to being a partial agonist at D_2 and $5HT_{1A}$ receptors, aripiprazole is an antagonist at $5HT_2$ receptors (McGavin and Goa, 2002). The clinical significance of D_2 partial agonism in the treatment of schizophrenia is yet to be fully demonstrated (McGavin and Goa, 2002).

Atypical antipsychotics may indeed be better than the older antipsychotics as they reduce the risk of EPS and drug-induced negative symptoms, which is a major benefit in its own right. However, although blockade of multiple receptor systems may be implicated in the therapeutic effects of atypical antipsychotics, it is also bound to induce side effects. Some, such as drowsiness, hypotension, and electrocardiogram (ECG), electroencephalogram (EEG) and laboratory abnormalities, had already been well recognized with the conventional antipsychotics. Others, including sexual dysfunction, weight gain and diabetes, although also known with the older drugs, are more prevalent with many newer antipsychotics. Postural hypotension and sexual dysfunction, for example, may be more prevalent with drugs with a strong alpha-1 adrenoceptor antagonism. Significant weight gain is observed in about two thirds of patients receiving clozapine.

Both clozapine and olanzapine have been associated with weight gain, in addition to sedation, dizziness and constipation. Risperidone, in turn, has been associated with sedation, EPS at higher doses and raised prolactin levels, which in the short term can cause sexual dysfunction and, in the long term, may contribute to the onset of osteopenia and osteoporosis. Quetiapine may induce sedation, fatigue, dizziness and orthostatic hypotension, while sertindole and ziprasidone may significantly prolong the QTc interval in the

TABLE 2.
Atypical antipsychotics: receptor affinity, doses and side effects

		Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Zotepine	Amisulpride	Aripiprazole
Receptor affinity	D_1	++	++	+++	+	+	++	...	
	D_2	++	++++	+++	++	+++	+++	++++	*
	$5HT_{1a}$	+	++	...	...	...			†
	$5HT_{2a}$	+++	+++++	++++	+	++++	+++		++
	α_1	+++	+++	+++	++++	++			
	α_2	+++	+++	...	+	...			
	H_1	++++	++	++++	++++	+			
	M_1	+++++	...	+++++	+++	...			
Dose range (mg/day)		200–900	4–8	5–20	300–750	80–160	75–300	400–1200	15–30
Main side effects		Agranulocytosis	Hyperprolactinaemia	Drowsiness	Hypotension	Sedation	Seizure	EPS at higher doses	Nausea
		Weight gain	Hypotension	Weight gain	Sedation	Dizziness	Hypotension/ tachycardia	GI effects	GI discomfort
		Hypotension/ tachycardia	Sedation	Nausea	Constipation	Hypotension	QT prolongation	Hyperprolactinaemia	Drowsiness
		Seizure	EPS at higher doses	Dry mouth		Nausea	GI disorders		
		Hypersalivation	Dry mouth						

* Partial D_2 agonist; † Partial $5HT_{1a}$ agonist. EPS = extrapyramidal symptoms; GI = gastrointestinal; ... = trace.

ECG, which may be a risk factor for arrhythmias in some patients. The association of several of these drugs with hyperglycaemia, new onset of type 2 diabetes and occasionally ketoacidosis (Henderson, 2002) has been uncovered by case reports and pharmacoepidemiological studies (Koro et al, 2002). Well-powered prospective studies are necessary to clarify whether or not one of these drugs is more likely than others to cause these metabolic abnormalities.

EFFICACY AND SAFETY IN RCTS *VS* COSTS

RCTs have shown that all atypical antipsychotics are superior to placebo in treating psychosis, and that they all seem to ameliorate both positive and negative symptoms of schizophrenia (Stahl, 1999). Most have also been shown to offer clear advantages over haloperidol, particularly in lowering the risk of EPS, with the proviso that the doses of haloperidol used across studies have usually been poorly controlled.

So far, only a few head-to-head studies of atypical psychotics have been conducted. The first such study to be reported (Tran et al, 1997) involved a 20-week comparison of treatment using risperidone or olanzapine in 339 patients who met *Diagnostic and Statistical Manual of Mental Disorders* fourth edition (DSM-IV) (American Psychiatric Association, 1994) criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder. The study found a significantly greater reduction of negative symptoms in patients receiving olanzapine compared with those receiving risperidone. Also, a higher proportion of patients in the olanzapine group responded to treatment (defined as a ≥40% decrease in the Positive and Negative Syndrome Scale (PANSS) total score) and maintained their treatment response. Finally, the incidence of EPS, hyperprolactinaemia and sexual dysfunction was significantly lower in patients receiving olanzapine.

Leucht et al (1999) subsequently conducted a meta-analysis of RCTs comparing risperidone (n=2215), olanzapine (n=2914), quetiapine (n=1414) and sertindole (n=702) with placebo or conventional antipsychotics in the treatment of schizophrenia. While sertindole and quetiapine were found to be as effective as haloperidol in terms of global efficacy, olanzapine and risperidone seemed slightly more effective than haloperidol, although this did not reach significance levels. Olanzapine seemed more effective in treating negative symptoms than all the other drugs, while sertindole was no different to, and quetiapine somewhat worse than, haloperidol. Relative to haloperidol, antiparkinsonian medication, although still required, was used less frequently during treatment with all the atypical antipsychotics. Compared with one-third of patients on haloperidol who required antiparkinsonian drugs, risperidone was the atypical associated with the highest rate of co-prescription (9%), followed by olanzapine (2%). In another meta-analysis of RCTs studies using atypical antipsychotics, Coleman et al (2003) concluded that the use of anticholinergic medication was significantly lower in patients receiving olanzapine compared with those receiving risperidone, quetiapine, amisulpride or ziprasidone. The analysis also associated olanzapine with higher indices of efficacy and safety compared with the other drugs, both in the short and long term.

Even though psychotropic drugs account for just 5% of the direct costs of schizophrenia in the UK (NICE, 2002), an over-zealous but probably misconstrued approach to drug treatment costing is the likeliest reason for some patients with psychotic disorders still being prescribed conventional antipsychotics. The older drugs are clearly much cheaper than the newer generation of atypical antipsychotics, but concerns about their safety and tolerability have been widely documented. Even though atypical antipsychotics are more expensive than the older drugs, therefore incurring higher prescribing costs, the use of atypical antipsychotics saves the NHS an estimated £1000 per patient year in hospital expenditure (NICE, 2002). Importantly, atypical antipsychotics are now available in different formulations which may encourage compliance with treatment. Many are available as oral tablets or liquid preparations and some, like olanzapine and risperidone, also as an oral fast-dissolving formulation. The recently introduced risperidone long-acting intramuscular injection may facilitate adherence to treatment in the long term.

CONCLUSIONS

2002 was the 50th anniversary of the launch of chlorpromazine, the first antipsychotic drug, a historical breakthrough in psychiatry. The advent of the atypical antipsychotics a few decades later represented a further major advance in this field. Patients can now count on treatments that are as effective as the older ones, if not more, but which are largely devoid of the sometimes severe EPS associated with the use of conventional antipsychotics. The newer drugs do have their own side effects, but the lower risk of EPS offers two crucial advantages. First, it facilitates adherence to treatment, which

becomes more acceptable in the absence of akathisia or chronic parkinsonism (Kane, 2001; Naber and Karow, 2001); this, in turn, is bound to enhance treatment outcomes, particularly in the long term. Second, it is likely to significantly reduce the risk of tardive dyskinesia, a potentially irreversible choreoathetoid syndrome which patients on conventional antipsychotics may develop as the years go by. However, atypical antipsychotics have not been available long enough to ascertain whether or not this will prove to be the case.

A much welcome development associated with the atypical antipsychotics is the number of systematic studies they have to undergo before reaching the market and the continued assessment of these drugs by post marketing surveillance. Comparative data on drug efficacy, tolerability and safety are increasingly available to help the clinician to reach a balanced decision in his/her prescribing choices. Whether or not one atypical antipsychotic is more therapeutically effective than another remains open to debate. Nonetheless, atypical antipsychotics do have different side-effect profiles, which should be considered before starting patients on any of the drugs recommended by NICE. Forthcoming head-to-head studies may help to further elucidate the therapeutic advantages as well as the relative cost effectiveness of the newer drugs. Ultimately, however, it will always be up to the clinician, in discussion with the patient, to decide which drugs best suit his/her clinical needs. A critical appraisal of the growing body of information on atypical antipsychotics is probably the best guide to the most appropriate choice. **HM**

Conflict of interest: none.

Alvir JM, Lieberman JA, Safferman AZ et al (1993) Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med* **329:** 162–7

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders.* 4th edn. American Psychiatric Association Press, Washington, DC

Casey DE (1995) Motor and mental aspects of extrapyramidal syndromes. *Int Clin Psychopharmacol* **10**(suppl 3): 105–14

Coleman C, Mudge M, Aldridge G et al (2003) A meta-analysis of randomised clinical trials comparing olanzapine with other antipsychotic agents used in the treatment of schizophrenia. Presented at the 2003 International Congress on Schizophrenia Research, Colorado Springs, Colorado, March 29–April 2

Coley KC, Carter CS, Dapos SV et al (1999) Effectiveness of antipsychotic therapy in a naturalistic setting: a comparison between risperidone, perphenazine, and haloperidol. *J Clin Psychiatry* **60:** 850–6

Dixon LB, Lehman AF, Levine J (1995) Conventional antipsychotic medications for schizophrenia. *Schizophr Bull* **21:** 567–78

Edgell ET, Haro JM, Novick D, SOHO Study Group (2003) Atypical antipsychotic treatment patterns over the first six months of treatment: Results from the Schizophrenia Outpatient Health Outcomes (SOHO) Study. Presented at Workshop On Costs And Assessment In Psychiatry – 2003, Venice, Italy

Gilbody S, Wahlbeck K, Adams C (2002) Randomized controlled trials in schizophrenia: a critical perspective on the literature. *Acta Psychiatr Scand* **105:** 243–51

Goldstein JM (2000) The new generation of antipsychotic drugs: how atypical are they? *Int J Neuropsychopharmacol* **3:** 339–49

Haley JC, Russo PA, Johnstone BM (1998) Prospective naturalistic outcomes measurement in schizophrenia: methodologies and results from the Schizophrenia Care and Assessment Program (SCAP). *Value Health* **1:** 89

Haro JM, Edgell ET, Jones PB et al (2003) The European Schizophrenia Outpatient Health Outcomes (SOHO) study: rationale, methods and recruitment. *Acta Psychiatr Scand* **107:** 222–32

Hegerty JD, Baldessarini RJ, Tohen M et al (1994) One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry* **151:** 1409–16

Henderson DC (2002) Atypical antipsychotic-induced diabetes mellitus; how strong is the evidence? *CNS Drugs* **16:** 77–89

Ho BC, Miller D, Nopoulos P et al (1999) A comparative effectiveness study of risperidone and olanzapine in the treatment of schizophrenia. *J Clin Psychiatry* **60:** 658–63

Kane JM (1993) Psychopharmacologic treatment of schizophrenia. *Schizophr Bull* **19:** 287–302

Kane JM (1996) Treatment-resistant schizophrenic patients. *J Clin Psychiatry* **57**(suppl 9): 35–40

Kane JM (2001) Extrapyramidal side effects are unacceptable. *Eur Neuropsychopharmacol* **11**(suppl 4): S397–403

Kapur S, Remington G (2001) Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia. *Ann Rev Med* **52:** 503–17

Koro CE, Fedder DO, L'Italien GJ et al (2002) Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *Br Med J* **325**: 243–45

Leucht S, Pitschel-Walz G, Abraham D et al (1999) Efficacy and extrapyramidal side effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res* **35**(1): 51–68

Mason P, Harrison G, Glazebrook C et al (1996) The course of schizophrenia over 13 years: a report from the International Study of Schizophrenia (ISoS) coordinated by the World Health Organization. *Br J Psychiatry* **169:** 580–6

McGavin JK, Goa KL (2002) Aripiprazole. *CNS Drugs* **16**: 779–86

Naber D, Karow A (2001) Good tolerability equals good results: the patient's perspective. *Eur Neuropsychopharmacol* **11**(suppl 4): S391–6

National Institute for Clinical Excellence (2002) *Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia.* National Institute for Clinical Excellence, London (www.nice.org.uk/pdf/ANTIPSYCHOTICfinalguidance.pdf)

Stahl SM (1999) Selecting an atypical antipsychotic by combining clinical experience with guidelines from clinical trials. *J Clin Psychiatry* **60**(suppl 10): 31–41

Tran PV, Hamilton SH, Kuntz AJ et al (1997) Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol* **17:** 407–18

KEY POINTS

- Antipsychotic medication is the foundation of care for patients with schizophrenia and other psychotic conditions.
- Atypical antipsychotics have replaced conventional neuroleptics in the management of psychosis; five atypical antipsychotics are currently recommended in the UK and several new agents are in development.
- When selecting an atypical antipsychotic, critical appraisal of the evidence is the best guide to the most appropriate choice.
- Only long-term, head-to-head studies, as well as extensive post-marketing surveillance and unique personal experiences, will help us to elucidate the therapeutic advantages of these new drugs.