Is there any difference between the antipsychotics?

Introduction

Antipsychotics have been the treatment of choice for schizophrenia for more than 40 years. During this time new antipsychotics have been extensively marketed and new indications have been investigated. But do the new generation of antipsychotics provide better treatment? Do they improve the quality of life for suffers of this severe and enduring mental illness? Should we now avoid the older generation antipsychotics? This article will explore the differences between the antipsychotics and discuss factors that health care professionals should consider when choosing an antipsychotic for an individual.

Antipsychotics have revolutionised psychiatry. Before their discovery there was no true pharmacological treatment for schizophrenia (see Table 1 for symptomatic criteria for schizophrenia, ICD-10). Treatments included electroconvulsive therapy (ECT), insulin shock therapy and a variety of sedating drugs such as paraldehyde and barbituates.[1] ECT is still occasionally used in resistant cases but other therapies were deemed unsafe and not effective, and they have long since been discontinued. The discovery of chlorpromazine in the 1950s heralded a new age in the treatment of schizophrenia. Chlorpromazine was the first drug to reduce symptoms of psychosis even without causing excessive sedation. From chlorpromazine the other typical antipsychotics were synthesised.[1] At that time producing extrapyramidal side-effects (EPSE) was thought to be a requirement for antipsychotic action. The discovery of clozapine in the 1960s brought about a change in this belief[1] because it was shown to be an effective antipsychotic without causing EPSEs. Clozapine's use increased slowly into the 1970s until reports of severe blood disorders and consequently a number of fatalities saw its sudden withdrawal from the market. A few countries, however, continued to use clozapine on a named patient basis and interest grew again particularly for treating those who had failed to respond to previous antipsychotics. In 1988 Kane and colleagues published a pivotal paper, which showed clozapine's superior efficacy to other antipsychotics.[2] This was the first time anyone had shown a difference in efficacy among the antipsychotics and enabled clozapine to be re-launched with mandatory blood monitoring. Across the 1980s and 1990s there was great interest in developing an antipsychotic with a similar superior efficacy to clozapine but without the potentially serious blood disorders. This led to the development of the second generation antipsychotics, known as atypicals.

Comparative efficacy

Although the antipsychotics are broadly divided into the two groups — typical and atypical antipsychotics — this broad classification is somewhat confusing. The antipsychotics vary considerably and are not homogenous groups. For example, many so-called atypical drugs have typical-like side-effects even within the normal therapeutic range. Because all antipsychotics block or partially block dopamine (DA; particularly at dopamine D2 receptors) it may be more accurate to classify antipsychotics on a continuum of potency of DA blockade (see Table 2). The more potent an antipsychotic is at blocking DA the more likely are movement disorder side-effects, such as EPSE. Although DA blockade is the core principle of the antipsychotic action this may be an over simplification and many other neurotransmitters such as serotonin, glutamine and gamma-aminobutyric acid may also be involved.[1]

To add to the debate there have been a number of meta-analyses and naturalistic studies to examine efficacy differences between the typical and atypical antipsychotics. Their conclusions are very similar. Excluding clozapine there is little difference in any efficacy marker between the typical and atypical antipsychotics.[4,5,6] The most recent meta-analysis by Leucht and colleagues[6] included 150 double-blind studies with more than 21,000 participants. Only amisulpride, clozapine, olanzapine and risperidone were more efficacious than typical antipsychotics. When industry-sponsored studies were excluded from this analysis only clozapine and olanzapine proved more effective. Leucht and colleagues also looked at quality of life markers, an area atypical antipsychotics would be expected to excel in. In the limited number of studies only amisulpride, clozapine and sertindole improved quality of life above the typical antipsychotics. These rather disappointing results dispute the hypothesis that all atypical antipsychotics are superior and confirm that the typical antipsychotics still have a place to play in schizophrenia therapy.

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Table 1. Symptomatic criteria for schizophrenia ICD-10, Chapter 5, F203

The normal requirement for a diagnosis of schizophrenia is that a minimum of one very clear symptom (or two if less clear) from a–d below or symptoms from at least two of the groups e–h should have been clearly present for most of the time for 1 month or longer.

a) Thought echo, thought insertion or withdrawal, and thought broadcasting
b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations: delusional perceptions
c) Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body
d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible
e) Persistent hallucinations in any modality, when accompanied by fleeting or half-formed delusions without clear mood content, or be persistent overvalued ideas, or when occurring every day for weeks or months on end
f) Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms
g) Catatonic behaviour, such as excitement, posturing, waxy flexibility, negativism and stupor
h) Negative symptoms such as marked apathy, paucity of speech and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or to antipsychotic medication
i) A significant and constant change in the overall quality of some aspects of personal behaviour manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude and social withdrawal.

Adverse reactions of the antipsychotics

The real difference between the antipsychotics lies in their pharmacological profile and adverse effect potential. The greater their DA receptor blocking potency the more likely are movement disorders and hyperprolactinaemia. There are four main types of EPSEs — akathesia, pseudoparkinsonism, dystonias and tardive dyskinesia. Akathesia presents as a compulsion to keep moving and motor restlessness. Sufferers are often seen repeating movements such as rocking from foot to foot, pacing or crossing and uncrossing their legs. Akathesia usually appears within a few days of beginning or increasing the dose of a high potency antipsychotic and may be linked with increased suicidal behaviour and violence. In an acute psychiatric emergency where antipsychotics are often used for their calming effects emerging akathesia can often worsen the situation. Pseudoparkinsonism symptoms are similar to those seen in Parkinson's disease such as bradykinesia, tremor and rigidity. Dystonias are sustained or repeated involuntary muscular contractions, which if they include the laryngeal muscles is a medical emergency requiring immediate intramuscular or intravenous procyclidine or benzatropine. Tardive dyskinesias (TDs) are late appearing, often irreversible, involuntary movements. Symptoms vary in severity and muscles affected but may include a constant protruding tongue, lip smacking or neck twisting. It usually takes months to years to develop TDs, which are usually related to long-term antipsychotic exposure. Movement disorders such as these were once commonly seen in patients treated with antipsychotics, but with the increasing use of the atypical antipsychotics they have become much rarer. They are treated either by reducing the antipsychotic dose or switching to a lower potency (usually atypical) antipsychotic. Clozapine, olanzapine, quetiapine and aripiprazole are associated with a very low incidence of movement disorders and are particularly recommended. In pseudoparkinsonism and dystonias an anticholinergic drug such as procyclidine is useful if the antipsychotic cannot be switched. Anticholinergics, however, should only be used if absolutely necessary because they are also associated with adverse effects, such as constipation, urinary retention, dry mouth, dizziness and confusion. Anticholinergics are not effective in akathesia and can worsen symptoms of tardive dyskinesia.

Another DA blocker adverse effect is hyperprolactinaemia. Prolactin is released from the anterior pituitary gland and comes under DA control in the tuberoinfundibular pathway. DA inhibits prolactin release and antipsychotics, through DA blockade, increase prolactin. All antipsychotics increase prolactin levels to some extent but some do not increase it above the normal range. These include clozapine, olanzapine, quetiapine and aripiprazole.[8] The more potent the antipsychotic is at blocking DA receptors the more significant is the increase in prolactin. All typical antipsychotics and the atypicals, risperidone, paliperidone and amisulpride cause a high incidence of prolactin elevation. Although hyperprolactinaemia can be asymptomatic, adverse effects such as gynaecomastia, galactorrhoea, menstral changes and sexual dysfunction are commonly reported. With long-term hyperprolactinaemia a decreased bone mineral density with accompanying osteoporosis and an increased risk of breast cancer have been reported.[9]

Neuroleptic malignant syndrome (NMS) is a rare (incidence: 0.01–0.02%)[10] but potentially fatal adverse reaction related to DA blockade. It is thought to be related to the sudden blockade of DA in the temperature regulatory centres found in the hypothalamus and corpus striatum.[1] It is characterised by fever, severe muscle rigidity and mental state changes. Immediate medical attention and cessation of the offending antipsychotic are essential in suspected NMS as fatalities are seen in 10% of cases.[10] Those who are newly prescribed a potent antipsychotic, are dehydrated or present with physical exhaustion are more likely to develop NMS.[10]

Although the atypical antipsychotics have reduced the incidence of the movement disorders and NMS as outlined above they are associated with other physical health effects. The most troublesome appear to be weight gain, dyslipidaemia and diabetes. Although these physical health effects can also be seen with the typical antipsychotics (see Table 2) they are most prevalent with olanzapine and clozapine — two widely used atypical antipsychotics.

Antipsychotics vary in their potential to cause weight gain — but this can be dramatic and have severe consequences to overall health and self-image. It is also difficult to

Table 2. Comparative adverse effects of the antipsychotics[8,11]

Antipsychotic	Dopamine D2 blocking potency	Adverse effects: EPSE	Raised prolactin	Weight gain	Diabetes	Raised lipids	QT*
Haloperidol	High affinity	+++	+++	+	+	-	+++
Zuclopenthixol		+++	+++	++	++	+	?
Flupenthixol		++	+++	++	++	+	+
Chlorpromazine		++	+++	++	++	+	++
Sulpiride		+	+++	+	-?	- ?	+
Amisulpiride		+	+++	+	-	-?	+
Risperidone		+	+++	++	++	+	+
Paliperidone		+	+++	++	++?	+	+?
Olanzapine		-	+	+++	+++	+++	-
Quetiapine		-	-	++	++	++	++
Aripiprazole	Moderate affinity	-	-	+	-	-	-
Clozapine		-	-	+++	+++	+++	+

Reducing

Key: EPSE=extrapyramidal side-effects; QT=QT prolongation; ?=unknown or limited data available; -=very low incidence; +=low; ++=moderate; +++=high*

predict — with some individuals gaining many kilograms while others gain only limited weight. Olanzapine and clozapine are probably associated with the greatest increases (average increase at 10 weeks is 3.5–4 kg).[11] Many hypotheses exist to explain why antipsychotics cause weight gain, such as histamine antagonism (which causes sedation) and 5-hydroxytryptamine antagonism.[1] Added to this are the symptoms of schizophrenia itself, such as social withdrawal and apathy, which interfere with the motivation needed to participate in regular physical exercise and healthy eating. Educating the patient about the potential weight gain with antipsychotics, increasing physical exercise combined with dietary and lifestyle interventions may help. Close monitoring of weight and body mass index should also be advised for all patients receiving antipsychotics (see Table 3).

Dyslipidiaemia is common in people prescribed an antipsychotic, but again the antipsychotics vary in their ability to raise lipids. Olanzapine and clozapine are associated with the greatest increase in both triglycerides and cholesterol but all patients taking any antipsychotic should have their lipid profile measured at baseline then regularly throughout treatment. Some antipsychotics also affect glucose homeostasis, which can lead to or worsen diabetes. Schizophrenia is also associated with a higher rate of diabetes mellitus than that of the general population even in the absence of antipsychotics.[1] Olanzapine and clozapine appear to be associated with the highest risk with up to one third of patients developing diabetes after five years of treatment with clozapine.[8] Fasting blood glucose monitoring is recommended at baseline then repeated at least after every six months (more frequently if prescribed olanzapine or clozapine).

Antipsychotics can also have a range of effects on the cardiovascular system. This includes postural hypotension (common with clozapine and chlorpromazine) tachycardia and QT prolongation (the time taken to complete the depolarization and repolarisation cycle of the ventricles). Haloperidol, pimozide and sertindole (a rarely used atypical antipsychotic) are associated with the greatest increases in QT interval and therefore a baseline ECG is recommended before prescribing and following a dose increase.[8]

In some patients with a severe and enduring illness clozapine probably represents the best hope for recovery.

Long-acting antipsychotic injections

Antipsychotics are available in a number of long-acting intramuscular (depot) injection formulations (see Table 4). The typical antipsychotic depots are all oil soluble compounds, which produce a predictable release of antipsychotic over two to five weeks. Risperidone is the only atypical antipsychotic currently available in a long-acting injection (LAI) formulation, but olanzapine LAI will be available from mid-2010. In the risperidone LAI, risperidone is coated in a polymer to form microspheres, which are then suspended in water. This rather unique formulation then takes 3–4 weeks to break down so there is a 3-week lag

Table 3. Monitoring required when prescribed an antipsychotic*

Parameter and frequency	Comment
Baseline	
Urea and electrolytes, liver function tests, full blood count, lipid profile, weight and BMI, plasma glucose, blood pressure and pulse, ECG (for haloperidol, pimozide, sertindole and clozapine only), prolactin.	A full blood count is mandatory for clozapine every week for 18 weeks, every 2 weeks for 1 year then every 4 weeks.
After 3 months (1st year only)	
Lipid profile, weight and BMI, plasma glucose.	Weight, BMI and plasma glucose more frequently with olanzapine and clozapine.
Blood pressure and pulse.	Blood pressure and pulse should be repeated frequently during the first few months.
Every 6 months or annually depending on clinical need	
Urea and electrolytes, liver function test, full blood count, lipid profile, weight and BMI, blood pressure and pulse, plasma glucose, prolactin (if symptomatic).	ECG if clinically indicated.

**This information, adapted from the Maudsley prescribing guidelines,[8] is intended as a guide only. Monitor more frequently if clinically indicated. Key: BMI=body mass index; ECG=electrocardiogram*

time after administration before risperidone is released. Patients taking risperidone LAI therefore require additional antipsychotic cover for the first 3–4 weeks of treatment, which is usually then tapered down and stopped over the subsequent two weeks.[12]

Olanzapine LAI has recently been granted a European medicine license but will not be launched in the UK until mid 2010. There are reports of an unpredictable post-injection syndrome (where symptoms similar to olanzapine overdose are seen) so it will be restricted to use in health care facilities only. After receiving olanzapine LAI patients will also need to remain in the facility for three hours for close monitoring of adverse effects.[13] This intensive monitoring is unfeasible in most community mental health teams so is likely to limit the usefulness of olanzapine LAI.

Long-acting injections may help improve compliance and reduce relapse rates but if adverse effects develop they are likely to be prolonged because doses cannot be quickly altered or stopped. For this reason a small test dose is needed to check for emerging adverse effects. With risperidone LAI and olanzapine LAI a test dose is not practicable so patients are recommended to try the oral preparations first.

Clozapine the unique antipsychotic

Clozapine has been conclusively shown to be more effective in treating resistant schizophrenia than other antipsychotics.[2,6,7] In some patients with a severe and enduring illness clozapine probably represents the best hope for recovery. It has, however, been associated with a wide range of adverse effects, which restrict its use to after two antipsychotic trials have failed.

Of particular concern is the association between life-threatening agranulocytosis and clozapine. Mandatory differential white cell counts are required with clozapine and it can only be dispensed following a satisfactory result. Other adverse effects such as constipation, tachycardia, hypersalivation and seizures are also reported with clozapine and these must be closely monitored for and appropriately treated.

Table 4. Long-acting antipsychotic injections[8,14]

Drug (trade name)	Test dose	Usual maintenance*	Comment
Flupenthixol decanoate (Depixol®)	20mg	50mg every 4 weeks to 300mg every 2 weeks	Caution: can be given at much higher equivalent antipsychotic doses and remain within *BNF* limits (monitor for ADRs).
Fluphenazine decanoate (Modecate®)	12.5mg	12.5–100mg every 2–5 weeks	Not available in the UK until mid 2010.
Haloperidol decanoate (Haldol®)	25mg	50–300mg every 4 weeks	
Olanzapine pamoate monohydrate (Zypadhrea®)	Oral olanzapine	210–300mg every 2 weeks (or 405mg every 4 weeks)	Restricted to use in health care facilities only and 3 hour post dose monitoring required.
Pipothiazine palmitate (Piportil®)	25mg	50–100mg every 4 weeks	
Risperidone (Risperdal Consta®)	Oral risperidone 100mg	25–50mg every 2 weeks	Initial 3 week lag time before release of risperidone.
Zuclopenthixol decanoate (Cloxipol®)		200–500mg every 1–4 weeks	

**maintenance = maintenance dose.*

Conclusion

The use of the terms atypical and typical antipsychotic can be both confusing and inaccurate. Recent evidence confirms that, excluding clozapine, there is little difference in efficacy between the two groups. It would be more accurate to view the antipsychotics as individual drugs with different adverse effects than two distinct groups. Antipsychotics should be chosen in collaboration with the patient, looking at medical co-morbidity, previous response, and adverse effect profile. Patients should be educated about potential adverse effects and an informed choice of the antipsychotic that would suit their lifestyle best should be made in conjunction with the health care professional. For those who are too unwell to choose their antipsychotic immediately they should be given the opportunity to write and plan, when stable, an advanced directive indicating their treatment choices. Pharmacists have an important role to play to engage and help patients make this choice and ensure antipsychotics are appropriately and safely managed. ✣

Declarations of interest

The author has no interests to declare.

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