The newer, 'atypical' antipsychotic drugs — their development and current therapeutic use

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SUMMARY

General practitioners (GPs) need to become more aware of a new generation of antipsychotic drugs that are 'atypical' in that, unlike traditional neuroleptics, they do not cause extrapyramidal side-effects; they may also be more effective against both the positive and negative symptoms of schizophrenia by their actions on various neurotransmitter pathways in the brain. This is a non-systematic review of the development of these new drugs and outlines how they are currently being used. It includes information found from an electronic search of the databases MEDLINE (from 1966 to June 1998) and EMBASE (from 1980 to January 1998) using the combined search terms 'antipsychotic agents', 'atypical', and 'schizophrenia'.

Keywords: antipsychotic drugs; schizophrenia; neuroleptics; side-effects.

Introduction

THE first major advance in the treatment of schizophrenia was the introduction of chlorpromazine in 1952. Chlorpromazine (a phenothiazine), haloperidol (a butyrophenone), and other traditional antipsychotic drugs were found to be useful treatments for the positive symptoms of schizophrenia, including hallucinations and delusions. However, there were two main problems with these types of drugs. First, they seemed to be ineffective against the negative symptoms of schizophrenia — including apathy, withdrawal, and inactivity — that are often more disabling than the positive symptoms. Secondly, all the traditional antipsychotic drugs seemed to cause extrapyramidal side-effects, including dyskinesias and parkinsonian symptoms, giving them the description 'neuroleptic', which means slowing of the nervous system.

Early research suggested that neuroleptics exerted their effect by blocking dopamine receptors and reducing the production of dopamine in the brain. Studies of rat brains showed reductions in the firing rates of dopaminergic neurones after the application of antipsychotic drug compounds, and, over the course of a few weeks, blood and urine levels of homovanillic acid, a dopamine metabolite, dropped steadily in subjects taking antipsychotics.

Many dopaminergic neurones have their cell-bodies in the mid-brain. They project from the substantia nigra to the striatum (nigrostriatal system) and from other portions of the mid-brain to the limbic system in the temporal lobe (mesolimbic system). A separate dopaminergic system projects from cell bodies in the arcuate nucleus to the hypothalamus (tuberoinfundibular system). Dopaminergic neurones are also found in the cortex.

It is now known that all antipsychotics block dopamine receptors in the mesolimbic system through which, it is thought, they act to reduce the positive symptoms of schizophrenia.[1] The conventional antipsychotics, including chlorpromazine and haloperidol, also block dopamine receptors in the nigrostriatal system, which explains their extrapyramidal side-effects, and in the tuberoinfundibular pathway, which explains their effects on prolactin levels, sexual function, and body weight.

The observation that the effects and side-effects of traditional antipsychotic drugs seem to be mediated through dopamine blockade, coupled with the observation that dopamine agonist drugs sometimes caused psychotic symptoms, led to the development of the so-called 'dopamine hypothesis' that schizophrenia was caused by an abnormality of dopaminergic pathways.[2]

How clozapine challenged the dopamine hypothesis

Clozapine is a tricyclic dibenzodiazepine drug originally introduced in 1966. Clozapine was found to be effective against the positive symptoms of schizophrenia, but seemed to have advantages over the traditional neuroleptic drugs. Clozapine was 'atypical' in that it did not cause extrapyramidal side-effects and dyskinesia. This raised the possibility of treating the disorder without causing disabling movement disorders and presented a challenge to the dopamine hypothesis, which held that all antipsychotics would inevitably cause extrapyramidal side-effects by blocking dopamine receptors in the nigrostriatal system.[3]

Clozapine was withdrawn from use in the United States (US) and United Kingdom (UK) after reports of agranulocytosis among patients using the drug in Finland in 1975.[4] However, use of the drug continued in Europe and Scandinavia in the 1970s and 1980s, and a consistent finding was that clozapine seemed to be effective against the positive symptoms of schizophrenia in 30%–70% of patients who were either resistant to, or intolerant of, conventional neuroleptic drugs.[5,6] Carefully conducted controlled trials subsequently confirmed this advantage.[7,8] Clozapine also seemed beneficial against the negative symptoms of schizophrenia.[9]

The atypical properties of clozapine stimulated a search for other neurotransmitter systems that might be involved in the pathogenesis of schizophrenia. Advances in research on the brain have since uncovered a much more complicated picture than that suggested by the dopamine hypothesis. It is now known that there are at least two main classes of dopamine receptor, D_1 and D_2, of which five sub-types have been cloned through gene sequencing techniques.[10] At least seven sub-types of receptors for 5-hydroxytryptamine (5-HT, or serotonin) have also been identified.

In vivo radioligand studies, using single photon emission computerized tomography (SPECT) and positron emission tomography (PET) brain scans have shown that, while the conventional neuroleptic antipsychotics block 80%–90% of dopamine D_2 receptors in the mesolimbic and nigrostriatal systems, clozapine by contrast blocks only around 30% of D_2 receptors and shows greater occupancy of D_1 receptors.[11,12] Clozapine is also a potent blocker of 5-HT_2 (or S_2) receptors that are rich in the medial prefrontal cortex.[13] Clozapine also has high affinity for D_2 receptors in the cortex, the significance of which is not yet clear.

A new group of drugs — the 5HT2:D2 antagonists

Like the traditional neuroleptics, the atypical antipsychotics probably exert their effects on positive symptoms by blocking dopamine D_2 receptors in the mesolimbic system; however, they do not block dopamine receptors in the nigrostriatal system to

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anything resembling the same extent as the traditional drugs. The effects against negative symptoms may be mediated through the enhancement of dopamine activity in the pre-frontal cortex, either by selective binding to dopamine receptor sub-types or through antagonism at 5-HT_2 receptors.

Actions on other receptors, including alpha-adrenergic and muscarinic receptors, account for most of the side-effects of the antipsychotic drugs, although not all the mechanisms underlying their actions have been identified with certainty. Weight gain may be due, at least in part, to anti-serotonin activity leading to increased oxidation of carbohydrate instead of fat.

Table 1 shows the affinity of a range of drugs for various neurotransmitter receptors within the brain,[15] through which the corresponding side-effects are thought to result.

Individual drugs

Clozapine (Clozaril)

Figure 1 shows that clozapine is a relatively non-selective blocker of neurotransmitters. It does not bind to D_2 receptors in the nigrostriatal system, and this is probably why it does not cause extrapyramidal side-effects. Clozapine's actions on serotonergic, alpha-adrenergic, histaminergic, and muscarinic receptors may explain its side-effects of weight gain, postural hypotension, sedation, and anticholinergic effects.

Clinical experience so far indicates that clozapine can bring about a dramatic improvement in around one-third of patients with treatment-resistant schizophrenia, representing a significant advance in the treatment of this devastating condition. Another third will derive significant benefit, and one-third do not seem to respond at all, although clozapine should be continued for some months before non-response is accepted, as dramatic late improvement can sometimes occur. Around 10% of patients will develop neutropaenia, which, in most cases, is reversed on stopping treatment. Clozapine was reintroduced in the UK and the US in 1990, but only under conditions of strict monitoring of the blood count. In the UK this is carried out by the Clozaril Patient Monitoring Service, which is run by the manufacturer. Patients on clozapine require weekly blood counts for the first 18 weeks, fortnightly blood counts up to one year, and then monthly blood counts after that.

Clozapine may only be prescribed by a consultant psychiatrist in the UK, and then only for patients who have proved resistant to treatment with other antipsychotics. All other antipsychotic treatment must be withdrawn before clozapine is started. The drug must be withheld if neutropaenia develops, to a level below 1.5×10^9/l, or if the total white cell count drops below 3×10^9/l. This interference with white cell production can occur quite late in treatment, although the large majority of cases occur within the first three months. There is a dose-dependent risk of seizures with clozapine, which seems to be higher than other neuroleptics. Weight gain and anticholinergic side-effects may be significant and affect patient compliance, but clozapine is less likely to cause hyperprolactinaemia via dopamine blockade in the tuberoinfundibular system.

Risperidone (Risperdal)

Risperidone is a benzisoxales drug that was introduced in 1993. Table 1 shows that risperidone also has a strong affinity for 5-HT_2 receptors, although, unlike clozapine, it also has a strong affinity for D_2 receptors.[16,17] Treatment with risperidone follows a bell-shaped dose response curve, with maximum efficacy at around 6–10 mg per day. At this level there are no parkinsonian side-effects and few cases of dystonia or akathisia.[18] Above these doses, however, risperidone does cause movement disorder side-effects. Risperidone may be more effective in younger patients with a more recent onset of their illness and an affective component (disturbance of mood).[19] Risperidone is not suitable for very behaviourally-disturbed patients who need sedation, although it can work well in combination with a benzodiazepine for tranquilization. Anxiety may be a side-effect for some patients, and night-time insomnia may develop, leading to daytime drowsiness. Risperidone should be used with caution in elderly patients, or those with renal problems, as blood levels of the drug build up in the presence of poor renal function. Like clozapine, risperidone causes weight gain and seizures; however, this is rare. In common with the traditional neuroleptics, but unlike the other atypical drugs, risperidone can cause hyperprolactinaemia, leading to galactorrhea, amenorrhea, and reduced libido; however, anticholinergic side-effects are much less likely than with clozapine (Table 1).

Risperidone, unlike clozapine, is not restricted to treatment-resistant patients, and it is now being used first-line by a growing number of psychiatrists, in particular to avoid exposing treatment-naïve patients to the side-effects of the traditional antipsy-

Table.1 Relative receptor affinities and side-effects of antipsychotic drugs.

	Drug type					
	Dopaminergic		Serotonergic 5-HT_2	Adrenergic a_2	Histaminergic H_1	Muscarinic M_1
	D_1	D_2				
Side-effects	Extrapyramidal movement disorders. Elevated prolactin (poor libido, galactorrhea, amenorrhea) Weight gain		Weight gain	Postural hypotension (reflex tachycardia)	Sedation	Anticholinergenic (dry mouth, constipation, precipitation of glaucoma or urinary obstruction)
Drugs						
Haloperidol	+++	++++	+	++		
Clozapine	++	++	+++	+++	++++	+++++
Risperidone	++	++++	+++++	+++	++	
Olanzapine	+++	+++	++++		++++	+++++
Sertindole	+++	+++++	++++		+	+
Quetiapine	+	++	+	+	++++	+++
Ziprasidone	+	++++	++++		+	

chotics, thereby hopefully enhancing compliance.[20] However, this may not be as successful as is hoped, since one follow-up study showed that two-thirds of patients dropped out of treatment with risperidone over two years — a rate similar to traditional antipsychotics.[21] Depot preparations of traditional neuroleptics are possibly the best approach to reducing relapse rates where compliance is a problem, and they are cheap by comparison. The higher cost of risperidone has made some National Health Service (NHS) health authority purchasers wary of allowing provider hospital pharmacies to introduce the drug as first-line treatment (Table 2).

Olanzapine (Zyprexa)

Olanzapine, introduced in 1996, is a thienobenzodiazepine that was developed as the result of a specific search for a clozapine-like molecule that would not cause agranulocytosis. Three large randomized controlled trials have been carried out comparing olanzapine with haloperidol.[22] Olanzapine seems to be as effective as traditional neuroleptics against the positive symptoms of schizophrenia, does not cause extrapyramidal side-effects, and may be effective against the negative symptoms; however, experience in this area is limited so far.[23] Olanzapine is also being increasingly used as first-line treatment. The side-effects of olanzapine include sedation and weight gain, as well as dizziness and transient elevation of liver transaminases. Less commonly, seizures and sexual dysfunction can also occur (Table 1). Again, insomnia and daytime drowsiness may be a problem for some patients. No evidence of haematotoxicity was found among 2500 patients treated.[24]

Sertindole (Serdolect)

Sertindole, also introduced in 1996, is a phenylindole derivative that is more like risperidone, whereas olanzapine is more like clozapine; in other words, it binds with affinity to striatal D_2 receptors, so its decreased tendency to induce extrapyramidal side-effects must be due to some other effect[25] (Table 1). Sertindole is well tolerated and effective against positive symptoms while not causing extrapyramidal or anticholinergic side-effects. Early results suggest that it is also effective against negative symptoms.[26,27]

However, a particular problem with sertindole is that it causes a prolonged QT interval in around 1%–2% of patients, and therefore has the potential to precipitate cardiac arrythmias in certain circumstances. Electrocardiograms before and during treatment are mandatory, and patients must be warned that the drug may interact with antihistamines, including astemizole and terfenadine (which may be bought over the counter), as well as tricyclic antidepressants and antiarrhythmics. Sertindole is contraindicated in the presence of a low serum potassium, and so co-prescribing with a diuretic is potentially hazardous. The availability of sertindole was voluntarily suspended by the manufacturers in December 1998, following reports of cardiac arrhythmias and sudden cardiac death associated with its use, pending a full evaluation of its risks and benefits in collaboration with the UK Medicines Control Agency. Olanzapine and quetiapine may also increase the risk of arrhythmias, and concurrent use of drugs that prolong the Q-T interval must be avoided, especially in the elderly.

Table 2. Costs of 28 days' worth of typical doses of antipsychotic drugs.

Method of administering drug	Typical dose (mg)	Approximate cost (£)
Oral[a]		
Chlorpromazine[b]	300	1.28
Haloperidol[b]	10	9.75
Clozapine	300	150.15
Risperidone	6	109.20
Sertindole	16	102.55
Olanzapine	10	105.47
Quetiapine	300	169.65
Depot[c]		
Fluphenazine	25	2.46
Flupenthixol	40	2.60

[a]Typical daily dose; [b]generic preparations; [c]typical fortnightly dose.

Quetiapine (Seroquel)

Quetiapine, introduced in the UK in 1997, is more clozapine-like, with a lower affinity for D_2 receptors compared with 5-HT_2 receptors.[28] Early trials suggest that it is as effective as chlorpromazine against positive symptoms, is possibly effective against negative symptoms, has fewer extrapyramidal and anticholinergic side-effects in particular, and there is no evidence of hyperprolactinaemia.[29,30]

Amisulpride (Solian)

This is a substituted benzamide similar to the older drug sulpiride; a D_2 antagonist that is relatively selective for mesolimbic receptors, thereby working against the positive symptoms of schizophrenia. It is less active against the D_2 receptors in the nigrostriatal region, thereby causing fewer extrapyramidal side-effects.[31,32] Amisulpride was also introduced in the UK in 1997, and early experience suggests that it is effective against the negative symptoms of schizophrenia.[33]

Ziprasidone

Already in use in the US and likely to be introduced in the UK in the near future, ziprasidone is similar to risperidone in having strong affinity for both 5-HT_2 and D_2 receptors (Table 1).[34] Early clinical trials have shown ziprasidone to be effective against both the positive and negative symptoms of schizophrenia, and experience so far also suggests that, like risperidone, it is also more effective against depressive symptoms.[35] This may be because it also has affinity for other 5-HT receptor sub-types.[36] It has a low propensity to induce extrapyramidal side-effects at therapeutic doses.[35]

Possible future developments

Other neurotransmitter receptors may become more important in the future, both in the treatment and in the understanding of the pathogenesis of schizophrenia. These include the opioid sigma receptors, which may modulate dopamine receptors.[15] Remoxipride, another substituted benzamide similar to sulpiride, which was withdrawn in 1994 owing to the development of aplastic anaemia in a small number of patients, seems to bind to opioid sigma receptors, and this may have been one mechanism of its action. The other system that may become more important is the N-methyl-D-aspartate (NMDA) glutamate receptor.[37] Phencyclidine (PCP, 'angel dust'), which can cause hallucinations and delusions, binds to the NMDA glutamate receptor.

Current use of the atypical antipsychotics

The studies carried out so far have been very encouraging, suggesting that the newer antipsychotics are as effective as the older ones but with fewer side-effects and the possible added benefit of action against the negative symptoms of schizophrenia (Box 1). However, most of these drugs have not been studied for any great length of time, and it may be that serious side-effects will emerge, such as the agranulocytosis seen with clozapine. A sig-

- They do not cause extrapyramidal side-effects, which represents a major advance in the treament of schizophrenia.
- Clozapine is effective in 30% to 70% of patients resistant to traditional treatments; it remains to be seen whether the other atypical drugs also confer this benefit.
- Clozapine also seems to be beneficial for the negative symptoms of schizophrenia, including apathy and social withdrawal. Time will tell whether this is a true effect and whether it extends to other atypicals.
- Risperidone may be more effective among younger patients with a depressive component to their psychotic illness.
- The atypicals are expensive, but may be more cost-effective if they reduce specialist treatments and hospitalizations.

Box 1. Benefits of the atypical antipsychotics.

Side-effects common to most antipsychotics, including the atypicals:
- weight gain;
- postural hypotension;
- sedation, or anxiety and night-time insomnia;
- seizures; and
- sexual dysfunction.

Individual drug side-effects of note:
- rarely, agranulocytosis with clozapine, although reversible neutropaenia occurs in around 10% of patients treated and blood counts must be monitored;
- hypersalivation with clozapine;
- hyperprolactinaemia with risperidone, like the traditional antipsychotics but unlike the other atypicals; and
- prolonged QT interval with sertindole (currently unavailable), necessitating ECGs before and during treatment.

Box 2. Side-effects of the atypical antipsychotics.

- Clozapine is restricted to treatment-resistant patients; however, the other atypicals, especially risperidone and olanzapine, are increasingly being used as first-line agents, especially among treatment-naïve patients.
- All other psychotropic drugs must be withdrawn before clozapine may be commenced.
- Co-prescribing of traditional antipsychotics negates the benefits of the atypical drugs.
- Clozapine patients must have regular blood counts, initially weekly.
- ECGs before and during treatment are mandatory when prescribing sertindole (currently unavailable).
- Extreme caution is advised if prescribing atypicals for patients with heart disease.
- Avoid concurrent prescribing of antihistamines, diuretics, tricyclics, and antiarrythmics, especially in the elderly .
- Hypokalaemia must be corrected before prescribing an atypical.
- Patients should be warned to avoid concurrent use of over-the-counter antihistamines.

Box 3. Prescribing points.

nificant proportion of patients will be unable to tolerate even the newer antipsychotics, mainly because of side-effects such as weight gain, sedation or anxiety, or insomnia, depending on the particular drug used (Box 2).

At this time, most general practitioners (GPs) will not prescribe atypical antipsychotics themselves unless they have been recommended by a psychiatrist in the first instance, but as they gather experience in using these drugs there is no reason why they may not begin to initiate treatment in their patients. Clozapine may only be prescribed by specialists for patients who have proven to be resistant to, or intolerant of, traditional drug treatments. However, even clozapine may be managed by the primary health care team after one year's treatment, provided that effective shared care arrangements are in place. Box 3 lists important prescribing issues for the atypical antipsychotics.

Cost-effectiveness

For the time being, the costs of these drugs when compared with the traditional antipsychotics may limit the extent to which they are prescribed. Table 2 shows the cost of 28 days' treatment with typical doses of various traditional and atypical antipsychotics, according to the British National Formulary.[38]

However, it has been suggested that the newer drugs may be more cost-effective than the old ones, despite the initial greater expense of treatment. This is because they may prevent the hospitalization of people with schizophrenia, which is one of the major sources of cost in managing the condition.[39,40] Studies of clozapine have confirmed that it is more cost-effective than the traditional neuroleptic drugs,[41] but there is a need to establish the cost-effectiveness of the other atypical antipsychotics in controlled trials with follow-up over three to five years.[42] The NHS Research and Development Health Technology Assessment programme has recently commissioned such research in the UK.

A survey by Gary Hogman for the National Schizophrenia Fellowship in 1996 found that only 25% of psychiatrists had five or more patients receiving clozapine, while 35% had five or more patients on risperidone.[43] Others had been told by Trust managers or the pharmacy that these drugs were simply too expensive to prescribe. More recently, however, informal surveys suggest that prescribing has increased as health authority purchasers have begun to accept that increasing a Trust's prescribing budget may prevent more costly admissions.

One stumbling block preventing the wider use of the atypical antipsychotics outside hospitals in the UK is the current compartmentalization of budgets in the NHS, which means that if more expensive drugs are prescribed in general practice then they will have an adverse effect on the practice's budget, while any savings made in terms of hospital inpatient costs will benefit the health authority responsible for purchasing inpatient care and are not directly passed back to the practice (except for practices among the relatively small number of total purchasing pilots). If the newer antipsychotics are more cost-effective by reducing admissions, then some mechanism must be found within the health service for inpatient care savings to be passed on to practices if their true potential is to be realized — this may be possible in the new primary care groups (PCGs) in the future if PCGs develop to the stage where they hold the budgets for inpatient psychiatric care.

Conclusion

The drug treatment of schizophrenia continues to improve. It is now possible to help the large majority of patients, by not only reducing or removing their hallucinations and delusions, but also by ameliorating the socially disabling negative symptoms of schizophrenia, and this should be possible without causing parkinsonian or other movement disorders. The development of the newer atpyical antipsychotics is a fascinating story that illustrates the potential of modern psychopharmacology research.

There has also been significant progress in the non-drug treatment of schizophrenia, including the use of social skills training through which sufferers may learn to cope better with interpersonal difficulties;[44] these include cognitive-behaviour therapy,

which has been shown to help sufferers modify or cope with their delusional beliefs,[45] and psychosocial interventions, which can improve the home environment by reducing expressed emotion (such as excessive criticism or overprotection) by the family or other carers.[46] However, it is expensive and time-consuming for secondary care services to set up and maintain programmes of psychosocial interventions. It is much simpler and more commonplace for specialists to prescribe the latest drug treatments. It behoves GPs to be aware of the effects and side-effects of the new antipsychotics, as we are likely to find more of our patients taking these drugs on their return home from hospital to our care, and we are likely to find good reasons to start prescribing them ourselves for other patients in the future.

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Note: References 17, 19, 24, 27, and 32 are special supplements to journals, some of which may have resulted from drug company sponsored symposia, and it is not clear whether these were peer-reviewed before publication.

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