SCHIZOPHRENIA

Review of antipsychotics

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The second part of the special feature on schizophrenia discusses the drugs in current use for the condition

In the 1940s and 1950s, treatment of schizophrenia, especially in North America and to a certain extent the UK, was heavily biased towards the view that psychoanalytic theory could explain not only the neuroses but also the major psychoses. This was in spite of the fact that the genetic basis of schizophrenia had been established. Schizophrenia was classified as a functional psychosis on the basis that no gross brain deficit had been demonstrated at that time. But the continued use of treatments such as insulin coma and prefrontal leucotomy, which at best were worthless and at worst barbaric did little to support biological research. Psychiatry was changed by three serendipitous discoveries:

1. Isoniazid, an antituberculous drug, with mood-elevating properties associated with amine oxidase inhibition was shown to be effective in some types of depression.
2. Chlorpromazine, an antihistamine derivative developed for use as a hypothermic agent to prevent shock in major surgery was found to have the new pharmacological property of a tranquilliser and was antipsychotic. In other words, the treated individual was not sedated, as was the case with the then traditional drugs of barbiturate and chloral hydrate, but was in a state where stress did not cause anxiety. Subsequently, it was noticed that chlorpromazine diminished hallucination and the associated delusions. The term antipsychotic was applied to to describe this property.
3. Lithium, a rare earth element, significantly reduced episodes of manic depressive illness.

All these discoveries had been accidental but they opened the way to a new pharmacology of psychiatric illness. This change in understanding was rather like the paradigm shift in 18th century medicine with the discovery of digitalis-sensitive dropsy of cardiac origin as opposed to digitalis-insensitive dropsy of renal origin.

Overnight, the drug treatment of schizophrenia with opiates, barbiturates, bromide, chloral and paraldehyde gave way to almost universal use of chlorpromazine. The red faces of patients with chlorpromazine photosensitivity in the summer months and the occasional retinopathy seemed of little consequence now that the florid positive symptoms of schizophrenia could be controlled. (At that time, the severe and crippling effects of tardive dyskinesia had not been recognised.) Locked wards were opened up and formal studies began comparing institutional with community care.

It seemed as though nothing would stop progress in the understanding of brain mechanisms underlying the illness and...
development of new drugs. But these serendipitous discoveries did not lead to the expected rapid understanding of schizophrenia and the parallel development of psychopharmacology. As Robert Kendall, then president of the Royal College of Psychiatrists pointed out in the plenary lecture to 3,000 psychiatrists and psychologists at the 1998 Glasgow lecture to 3,000 psychiatrists and psychologists pointed out in the plenary lecture to 3,000 psychiatrists and psychologists at the 1998 Glasgow CINP meeting, there has been no improvement in the efficacy of treatments for schizophrenia and depression for 40 years. Adverse effects of the new drugs may be less but their effects on symptoms are not much better than they were in the late 1950s.

Any review of treatment for schizophrenia should examine the social context of treatment and society's attitude to its management. This article will review current knowledge on the efficacy of typical and atypical neuroleptics and the extent and nature of their toxic effects, consider the impact of recent studies of the psychopharmacology of clozapine, and examine the state of research and development of new treatments based on the new understanding of dopamine signal transduction.

Atypical neuroleptics have become the first line preferred drugs in many hospitals and for many practitioners and sufferers. The acceptance of this increased cost in comparison with conventional neuroleptic drugs is justified by many providers of mental health services on the basis of reduced toxic effects and better compliance. In some areas, those responsible for local drug dispensing guidelines have reached a different view.

### CLINICAL EFFICACY

A number of questions may be asked, including: How do the atypicals compare with clozapine and the conventional neuroleptics in terms of clinical efficacy? Are the side effects of all atypicals less than those of the conventional neuroleptics? How effective are conventional and atypical drugs as regards overall system response?

**Atypicals versus clozapine** According to a Cochrane review, which used a global clinical index, new atypicals are broadly similar to clozapine, but this is based on only a small number of studies of short duration. Clozapine gives rise to more symptoms of fatigue, hypersalivation and orthostatic dizziness. The newer atypicals show more extrapyramidal side effects with the exception of olanzapine.

Weight gain remains a problem with all the conventional antipsychotic drugs and with the atypicals, including olanzapine and clozapine. Some patients are more affected by this but the prediction of who will show weight gain remains uncertain.

The Cochrane report emphasises that the impact on quality of life, service use and hospital admission and economics have not been reviewed. The overall conclusion is that equal effectiveness and tolerability in comparison with clozapine is not yet demonstrated.

### SIDE EFFECTS

It is well known that in the typical antipsychotic drugs, common side effects include anticholinergic effects, sedation, akathisia, dystonia, parkinsonism, tachycardia, hypotension, allergic phenomena and weight gain. Skin photosensitivity is confined largely to the phenothiazines.

In the atypicals, anticholinergic effects, sedation, tachycardia, hypotension and weight gain are found in clozapine and olanzapine. Clearly, the agranulocytosis is confined almost exclusively to clozapine. Weight gain is common, especially with olanzapine. It is reported in 6–29 per cent of patients, with an average weight gain of about 3kg in six weeks.

Sexual dysfunction can occur with the phenothiazines, pimozide and sulpiride.

A detailed comparison of the side effects of antipsychotic drugs is beyond the scope of this article, but can be found elsewhere.

### MODE OF ACTION

Figure 1 (p194) shows the presumed mode of therapeutic action on neurotransmitter receptors. It can be seen that a low ratio of 5-hydroxytryptamine/dopamine-D2 blockade combined with a1 adrenergic receptor antagonism, histamine-H1 antagonism and cholinergic-M1 antagonism is associated with parkinsonian symptoms in the case of phenothiazines.

Both clozapine and olanzapine have a high ratio of 5-HT2/D2 blockade which minimis-
es parkinsonian toxicity. It is of interest that sulpiride (classified here as an atypical) has a high ratio of D₂/5-HT blockade with low levels of extrapyramidal symptoms and the dyskinesias. The low-cost of sulpiride and its newer derivatives, combined with the low level of toxicity have undoubtedly increased the use of this class of neuroleptic.

Clozapine Many clinicians who use clozapine in treatment-resistant schizophrenic patients strongly believe that clozapine has a unique action which differentiates it from other atypical neuroleptics. We suggested, on the basis of improved levels of the arachidonic acid cell signalling in red cell membrane phospholipids following treatment with clozapine, that this unique effect was on phospholipid metabolism. In pharmacological studies, it can be shown that in an aqueous environment both the pheno- thiazines and clozapine have antioxidant properties. In a non-aqueous medium of the type present in biological membranes, clozapine has marked antioxidant action. Initial studies on rodents showed that, following chronic clozapine administration, there was a marked increase in the concentration of apolipoprotein D which has an important function in the metabolism of phospholipids. Clozapine increases apolipoprotein D which has an important function in the metabolism of phospholipids.

Figure 1: antipsychotic drugs classified according to their presumed mode of therapeutic action (adapted, with permission, from Shiloh, Nutt and Weizman, editors. Atlas of psychiatric pharmacotherapy. London: Martin Dunnitz; 1999)

<table>
<thead>
<tr>
<th>Presumed mode of therapeutic action</th>
<th>Other significant receptor antagonism capacity</th>
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<tr>
<td>High ratio D₂/5-HT blockade</td>
<td>D₁ adrenergic</td>
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<tr>
<td>Low ratio of D₂/5-HT blockade</td>
<td>H₁ histamine</td>
</tr>
<tr>
<td>Low ratio of 5-HT/D₂ blockade</td>
<td>M₁ cholinergic</td>
</tr>
<tr>
<td>High ratio of D₄ 5-HT/D₆ blockade</td>
<td>A₁ adrenergic</td>
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Phenothiazines
Haloperidol
Atypical drugs
Clozapine
Olanzapine
Quetiapine
Risperidone
Sertindole
Sulpiride
Ziprasidone

Key
- Main mode of action (related to therapeutic action)
- Minor mode of action (may be related to therapeutic action)
- Other clinically significant receptor antagonism capacities (mainly related to the side effect profile)

* Sulpiride is claimed by many to be an atypical agent because of its low propensity to cause extrapyramidal side effects or tardive dyskinesia

es depressive subjects and controls.9 There was a significant increase in serum samples from schizophrenic subjects compared to conventional antipsychotics and placebo. A meta-analysis of randomised control trials. Schizophrenia 1999;35:51–68.


ACKNOWLEDGEMENT I am grateful to my colleagues, Pauline Ward and Lois MacDonell for assistance and advice in preparation of this paper.

REFERENCES


