Advances in psychopharmacology – schizophrenia

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Every so often in the history of medicine, events occur which in retrospect seem to mark a defining moment. For psychiatry, the decade of the 1950s uses one such ‘moment’. On 28 December 1951, J. Sigwald started solo chlorpromazine treatment of a 57-year-old psychotic lady and, thereby, it might be argued, began the modern era of psychopharmacology.

The impact of antipsychotic drugs on the management and also the conceptualization of schizophrenia has been enormous, but the unbridled enthusiasm with which their use was first greeted has had to be tempered. Most of the standard compounds are essentially derivative and none offers any clear advantage. As a group, they perform the tasks required of them inadequately in relation to the ‘positive’ features of the illness¹,² and marginally or not at all on ‘negative’ features³,⁴, while a substantial cost may be exacted in adverse effects, especially those indicative of disruption to extrapyramidal motor function.

Despite an acknowledged need for new drugs, the field of antipsychotics has not until recently been productive. This does not relate to the number of compounds available, but to the breadth of vision applied to possible mechanisms of action. It is only in the past decade that developments have allowed us to break free from the strictures of the classical dopamine hypothesis into which antipsychotic pharmacology had to some extent become confined.

The highly selective approach

The ready acceptance of the name by which antipsychotic drugs have become most widely known is revealing, for while alternatives were proposed that spoke more of their effects on mental state, ‘neuroleptics’ emphasised their neurological actions. This was in keeping with the widely held view at the time that extrapyramidal signs were a necessary herald of therapeutic efficacy, a view that by the mid-1960s had fallen into disrepute⁵. Nonetheless, the discovery by Carlsson and Lindquist
that these drugs blocked dopamine receptors\(^6\) focused research on this as their possible—or indeed probable—mode of action. Throughout the 1970s, a substantial body of evidence, both laboratory and clinical in nature, built up in support of this general view. Following Kebabian and Calne's dichotomous classification of dopamine receptors\(^7\), attention was firmly directed towards blockade of the D\(_2\) subtype as the explanatory hypothesis for their mode of action.

Major problems remained, however, not least in the fact that while dopamine blockade, as inferred from a rise in serum prolactin, seemed to occur early in exposure, therapeutic efficacy was delayed. This raised the possibility that dopamine blockade might be an important or essential precursor to other more fundamental changes elsewhere\(^8\). And, of course, there was the issue of the neurological profile. How could generalised dopamine (D\(_2\)) blockade be reconciled with the changed perception of extrapyramidal symptomatology from necessary to adverse effect? The proposal of an 'anatomy' of schizophrenia offered a solution—a pathophysiology of the disorder (and hence the target of its treatment) rooted in mesolimbic systems: the organisation of motor function (and hence the site of side effects) in the striatum\(^9\). Thus a credible theory could be formulated to support the view that the ideal antipsychotic drug should be a highly selective dopamine (D\(_2\)) antagonist with preferential action at limb sites.

Pimozide fulfilled at least one of these criteria, but did not appear to offer advantages in neurological tolerability. Sulpiride was likewise highly D\(_2\), and on animal models apparently limbic, selective and, furthermore, was claimed in low dose to exert predominantly presynaptic, autoreceptor actions, thereby suggesting efficacy in 'negative' states\(^10\). Inability to establish such an effect in controlled trial settings\(^3\) and continuing doubt about whether, at dose equivalence, it does indeed have reduced extrapyramidal side effect (EPS) liability overall, combined with poor pharmacokinetic properties, have meant a limited role for sulpiride, especially in the UK.

From the late 1970s, the search began for new antipsychotic benzamides that appeared more limbic selective by animal models and, although only one achieved a wide, if brief, launch (remoxipride), others may still be in the offing.

**Substituted benzamides**

These are substituted amides of benzoic acid, developed originally from procainamide via the antiemetic metaclopramide.
Remoxipride is a highly selective if relatively weak D₂ antagonist with low affinity for and no apparent activity at D₁ sites. It has no appreciable affinity for other receptors, with the exception of sigma sites to which it binds strongly. Although chronic exposure results in upregulation of D₂ receptors, this does not appear to be associated with functional supersensitivity. Remoxipride is an effective antipsychotic agent against acute schizophrenic symptomatology, though with no clear advantage over standard drugs. A single relapse prevention study and long-term extension of treatment of patients in acute trials suggest a maintenance effect. No adequate data on treatment resistance are available. The evidence in support of an effect on primary ‘negative’ states is slight, and comes from samples selected on the basis of having ‘positive’ features in whom ‘negative’ ratings would be expected to be low.

The general tolerability (excepting haematological, see below) profile is compatible with the drug’s binding profile and is very favourable. It is well tolerated and non-sedative, with little effect on cardiovascular function, though long-term use is associated with some weight gain. It does not alter the EEG. Despite the preclinical data, however, clinical studies do not point clearly to a reduced EPS liability. Unfortunately most studies addressing this question used the high potency/high liability comparator haloperidol, often in high dose, which precludes an unbiased evaluation. Nonetheless, those studies which used lower haloperidol doses (mean 15 mg/day or less) do show a consensus in favour of remoxipride, with EPS less prominent and, in all but one study, requirements for ‘rescue’ anticholinergic significantly reduced. However, none of the three studies which used a low potency comparator (chlorpromazine or thioridazine) was able to bestow any clear advantage on remoxipride.

In November 1993, after only 2 years, remoxipride was withdrawn from general use in the light of a major safety issue—namely a reported cluster of 8 cases of aplastic anaemia, two of which were fatal, associated with its use. It is currently only available under conditions of strict haematological monitoring.

Amisulpride has been available in France for some time, and is under consideration for a wider launch at present. The English language literature on it is sparse, and claims of specific benefits on negative symptomatology must await replication.

Raclopride, unlike remoxipride, binds with high affinity to D₂ receptors and insignificantly to other sites, including sigma. In a blind comparison with haloperidol, raclopride did demonstrate antipsychotic efficacy. The therapeutic advantages were, however, in favour of haloperidol, though extrapyramidal tolerability was clearly better with raclopride. These data need cautious interpretation, as there may have been a problem with dose equivalence in this study.
The ‘highly selective’ approach to antipsychotic drug development, as exemplified by the benzamides, is unlikely to be abandoned completely, but until the theory of a discrete separation of functions between limbic and striatal dopamine systems, and laboratory tests of these, can be validated (see below) this would seem to remain a high risk strategy.

**The multiple receptor interaction approach**

The previous insistence that the ideal antipsychotic must be a drug of ‘clean’ pharmacological habits, has been supplanted by the active pursuit of ‘dirty’ pharmaceuticals. Historians of psychopharmacology may not quite come to see the rehabilitation of clozapine as one of psychiatry’s ‘defining moments’, but it will surely be viewed as a catalyst that rekindled broader perceptions about possible modes of antipsychotic action. By the same token, the drug’s rich pharmacology poses a challenge for the understanding of its clinical effects. The new compounds, arrived or in late development, have (to varying degrees) sought to reproduce this pharmacological ‘richness’, though with a consistent emphasis—namely potent serotonin, and specifically 5HT₂, antagonism. This represents the revivification of a theory of schizophrenic pathophysiology which antedated the dopamine hypothesis and which, although displaced, was never disproved²³,²⁴.

**Clozapine**

Clozapine is also a child of the explosive era of the 1950s but was originally synthesised as an antidepressant. It is a dibenzodiazepine, closely related to imipramine. Although unimpressive as an antidepressant, its antipsychotic properties were evident, but unfortunately its development was curtailed in many countries in 1975, following reports from Finland of a cluster of agranulocytosis, 8 cases of which were fatal. Its rehabilitation has been dramatic.

The pharmacology is complex²⁵. In vitro, it interacts moderately with D₁, D₂, D₃ and D₅ dopamine receptor subtypes and powerfully with the D₄ subtype. In vivo, it produces relatively low levels of D₂ receptor occupancy compared with standard drugs, while that attained at D₁ sites is comparable to that at D₂²⁶. In addition, clozapine exerts powerful antiserotonergic (especially anti-5HT₂) and anti-adrenergic (especially anti-alpha₁) effects, and is a potent H₁ and muscarinic cholinergic antagonist²⁵. In contrast to standard drugs, chronic use does not result in supersensitivity of striatal D₂ receptors, though upregulation does appear
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to occur at D₁ sites. A further striking difference is that clozapine causes only a mild and ill-sustained rise in prolactin secretion.

Only a few controlled trials addressed the question of clozapine's efficacy in unselected acute schizophrenic patients and these were mainly done at a time when trial methodology was perhaps less rigorous than it is today. Nonetheless, these do show clozapine to be an effective antipsychotic agent in this situation, though interestingly there is no more than a hint of better efficacy than a standard drug. The same conclusion of essentially comparable efficacy in acute situations can be drawn from a more recent comparison with risperidone.

Much has been made of clozapine's value in long-term maintenance, though on the basis of open follow-ups, as no blind, randomised relapse prevention studies have yet been reported. Long-term use of clozapine (over years) is not associated with the development of tolerance to the antipsychotic effect. The particular claims stem from striking improvements in quality of life parameters at up to 12 months in previously treatment-resistant patients. In view of the unique circumstances in which clozapine requires to be monitored, however, such reports, although impressive, are no substitute for controlled and blind evaluation. Of special interest might be an assessment of the drug's impact on the 'expressed emotion' of carers.

Clozapine is the first antipsychotic to which enhanced efficacy has been attributed, albeit in a specific clinical context. In what has become a highly influential study, Kane et al. recruited schizophrenic patients who had failed to respond to at least three different antipsychotics in adequate dose and entered them in a 6-week single blind treatment period with haloperidol. Those who remained unimproved then entered a 6-week double blind phase (n=268), where they received either clozapine up to 900 mg/day or chlorpromazine up to 1800 mg/day, combined with the anticholinergic benztropine. The clozapine-treated group showed clear advantage in terms of Brief Psychiatric Rating Scale (BPRS) total scores, constituent items, global impression of improvement and nurse ratings. By a priori criteria, 30% of those on clozapine were assessed as having improved, compared to only 4% in the chlorpromazine/benztropine group.

There is some degree of consensus that clozapine use is associated with a reduction in ratings of 'negative' symptomatology. Interpretation of this finding is, however, bound up in the well described conceptual and methodological problems surrounding the evaluation of 'negative' states. While the US multicentre study did find clozapine superior to chlorpromazine/benztropine 'in the treatment of negative signs and symptoms', this occurred in the context of improvements in EPS ratings. Considering the temporal relationships between the mental state and neurological changes, it is likely that clozapine's benefits were in
Table 1 Clozapine: general adverse effects reported by at least 10% of patients

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<tr>
<th>Effect</th>
<th>Acute phase treatment</th>
<th>Continuation phase treatment</th>
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<tr>
<td>Anergia</td>
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<td>15.7</td>
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<tr>
<td>Drowsiness</td>
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<td>Weight gain</td>
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<tr>
<td>Blurred vision</td>
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<td>Excitement</td>
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<td>1.7</td>
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<td>Weight loss</td>
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<td>Nausea</td>
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<td>5.2</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>8.3</td>
<td>10.5</td>
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</table>

After Lieberman et al.33

terms of so-called secondary 'negative' symptomatology. The majority view would support this interpretation at present33,34, though a direct action on the pathophysiological substrate underlying primary negative features has been argued35.

There are three requisites for establishing the unique general adverse effect profile of any psychotropic agent: comprehensive assessment; standardised recording; and a placebo group. The latter is necessary to accommodate hangover effects from previous medication, symptomatology emanating from the mental state disorder, and the random prevalence of non-specific complaints in the population at large. Deficiencies in these requirements, especially the lack of placebo groups, make it difficult to place clozapine's profile in context. Table 1 lists side effects recorded by Lieberman et al. at least once in 10% or more of patients during short and long term treatment33. Hypersalivation is the exception in being the opposite from what would be anticipated by the drug's binding profile. The reasons for its prominence are unknown. This is also the only one of the frequently reported side effects to increase in prevalence with continued exposure (though urinary frequency tends to remain constant in around 10%). The cardiovascular signs of hypotension and compensatory tachycardia are also compatible with known antiadrenergic actions, and tend to settle with continued exposure. The major concern with clozapine is its tendency to damage the granulocyte cell line. Neutropenia, reversible on discontinuation, has a cumulative risk of 2.33% at 12 months and approximately 3% at 24 months, with a small (0.74% and 0.45%) but continuing risk thereafter (Clozaril Patient Monitoring Service, Sandoz Pharmaceuticals: submitted for publication). Data from America show a cumulative risk for agranulocytosis of 0.8% at 1 year and 0.91% at 18 months37, while British figures from a smaller sample but extended over a longer period are 0.73% at 1 year and 0.8%
at 2 years, a figure that translates into a rate of approximately 1:1400 exposures. The peak risk for agranulocytosis is in the third month, and no cases have yet been reported after 2 years. Surprisingly, comparable reliable data for other antipsychotics do not exist. One study many years ago suggests that the risk of agranulocytosis with psychotropics in general to be in the range of 1:2000 exposures, though a prospective study confined to phenothiazines calculated a figure of approximately 1:1200. There is clearly a need for further research of a question that for standard drugs has traditionally been considered peripheral, but perhaps ought not to remain so.

The mechanism of this potentially fatal development is unknown, though its characteristics strongly suggest an allergic reaction. Similar problems with other antipsychotics is not a contra-indication to the subsequent use of clozapine, though the development of agranulocytosis with clozapine is a proscription on its further use. In the small number of typical cases in whom re-exposure has been tried, recurrence has been swift. Although trophic factors, such as granulocyte colony stimulating factor (G-CSF), have been tried, their use remains experimental and treatment continues to be supportive.

Clozapine produces a higher prevalence of EEG abnormalities (23–34%) than standard drugs, and the overall fit frequency at 4% is 4 times greater. Fit frequency is, however, dose dependent—14% on >600 mg/day, <1% on doses below 300 mg/day, which is comparable to the risk of standard drugs. Neuroleptic malignant syndrome has been reported, though with cumulative incidence figures of 0.08% in the UK since 1990 (Sandoz Pharmaceuticals: data on file) the risk would seem to be at the lower end of that reported in the literature in general. Furthermore, the majority of reports concerned patients receiving other psychotropics in addition.

The fact that clozapine possesses a reduced liability to promote extrapyramidal side effects is beyond debate. Only one clinically recognisable (and at that not entirely typical) case of acute dystonia has been reported in a world-wide pool now extending to over three-quarters of a million exposures—an astonishing fact for a side effect that afflicts up to one-third of those on standard drugs. The prevalence of Parkinsonism is approximately half that found with standard drugs (33% versus 60%) while striking reductions in akathisia occur over a 12 week period following transfer. Likewise, impressive and clinically significant reductions in tardive dyskinesia ratings have been reported. Lieberman et al. noted 43% of their samples showed a 50% or greater reduction in severity ratings over an average follow-up of 27.8 months, though with considerable individual variation. Whether such data reflect a direct anti-dyskinetic action is unclear, although the protracted time scale over which improvements occur might suggest that the drug is
acting indirectly by holding mental state stable for a sufficient period to allow resolution of the pathophysiology underlying the movement disorder.

There can be no doubt that clozapine represents an important advance in the psychopharmacology of schizophrenia, even although the evidence to date would not support its use beyond its current restricted licence—namely, in treatment-resistant schizophrenia and neurological intolerance. It may be that ultimately, however, its value will be judged as much in terms of what it has done for the direction of psychopharmacology research as for its still limited clinical applications.

Risperidone

This is the first of the new generation of what might be called ‘designer’ antipsychotics—drugs whose development represents a conscious break with the constricting inferences of the classical dopamine hypothesis.

Risperidone is a dibenzisoxazole derivative which represents a new class of psychotropics. It binds to D₂ receptors with about 50 times greater affinity than clozapine and only 2–3 times lesser affinity than haloperidol. It also has powerful affinity for D₃ and especially D₄ subtypes but low affinity for D₁. It binds powerfully to alpha₁ adrenoreceptors and to a lesser extent to alpha₂ sites, and also occupies H₁ receptors, but has no significant muscarinic cholinergic interactions. It is however a powerful 5HT₂ₐ antagonist, binding to these sites with about 100-fold greater affinity than to other 5HT subtypes and about 20-fold greater affinity than to D₂ receptors. Antagonism of 5HT₂ₐ sites occurs early, followed by later, more gradual and partial D₂ occupancy. Its use is associated with a dose-dependent increase in prolactin secretion.

The Phase III data available on risperidone at launch in June 1993 constitute one of the largest bodies of information on any single antipsychotic agent. The two major fixed dose studies—a North American one published separately as Canadian and US arms, and a multinational one conducted in 15 countries worldwide—together comprised almost 2,000 patients. Both used doses in the range 2–16 mg/day that to some extent dovetailed, and in both the active comparator was haloperidol in a dose of 20 mg/day and 10 mg/day, respectively. The North American study was placebo controlled, while in the multinational study a small dose of risperidone (1 mg/day), presumed to be subtherapeutic, was used as ‘placebo’ in order to address potential ethical concerns.

These studies show risperidone to be an effective antipsychotic agent against acute symptomatology with optimal benefit in the 4–8 mg/day
dose range. However, the clear dose-response relationships evident in the multinational study were not seen in the North American sample. This important discrepancy may reflect differences in patient and physician acceptance of trial conditions in the US, where drop out/removal was greater\textsuperscript{14}. This general conclusion of efficacy is, however, supported by results from smaller, single site trials using different comparators\textsuperscript{56-58}. There is as yet no evidence of enhanced efficacy attributable to risperidone.

Results from randomised, relapse prevention studies have not been reported, though open long-term follow ups would indicate a comparable maintenance effect to that of standard drugs (Janssen Pharmaceutica, data on file). Likewise, the question of treatment resistance has not yet been addressed. To some extent risperidone's performance in this context will be an important test of one of the planks of the 5HT theory, particularly as it relates to clozapine's enhanced efficacy.

Much has been made of risperidone's putative efficacy in 'negative' states\textsuperscript{59}, though support for such an action comes just from the North American study, and is weak. In the Canadian arm, 'negative' ratings were significantly improved over placebo only in the group on 6 mg/day, which in turn showed only a trend ($p < 0.08$) to superiority over haloperidol 20 mg/day\textsuperscript{53}. In the US arm, risperidone fared better than placebo at both 6 and 16 mg/day dose ranges, but neither of these were significantly better than haloperidol\textsuperscript{54}. No benefits attributable to the drug could be discerned in the multinational study\textsuperscript{55}. Thus, at this stage, it would seem prudent to treat with caution claims of a specific effect on 'negative'—especially primary 'negative'—features, particularly so in the light of risperidone's neurological tolerability (see below).

Data from the Phase III risperidone studies fulfil the criteria to permit construction of a detailed general side effect profile—in this case relative to two dose schedules of haloperidol\textsuperscript{14}.

Complaints reported spontaneously by patients were trivial. Only insomnia, agitation, constipation, nausea and dizziness were reported with 5% or greater frequency than with placebo, and rhinitis was the sole complaint that, by the same criterion, was more common than with haloperidol. Comparing these data with those from the other large placebo controlled, flexible dose study\textsuperscript{60}, only insomnia and constipation were, by the 5% criterion, common to both\textsuperscript{14}. These figures suggest good patient acceptability.

The two fixed dose studies mentioned above, recorded general side effects elicited from the patients on the UKU Side Effect Scale. These show a side effect profile compatible with the drug's binding profile (Table 2). It is clear that 1 mg of risperidone, although perhaps subtherapeutic, is not inactive. The drug produces dose-dependent increases in asthenia/lassitude, sedation, accommodation disturbances,
Table 2  The general side effect profile of risperidone relative to placebo and haloperidol

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*Average figures from 2 dose regimes

orthostatic dizziness, palpitations/tachycardia and (especially male) sexual dysfunction. Increased sleep duration, dream activity and frequency of diarrhoea, polyuria/polydipsia, weight gain and impaired libido less clearly related to dose or present only at the highest doses are also evident. In comparison with haloperidol, risperidone has slight advantages in terms of less asthenia/lassitude, sedation, accommodation disturbances, reduced salivation and micturition disturbances, but is more often associated with palpitations/tachycardia, weight gain and ejaculatory dysfunction.

Subjective cardiovascular symptoms occur in the context of a transient, dose-dependent increase in heart rate (average 6–7 beats/min at 6 mg/day) and fall in supine blood pressure (average systolic/diastolic fall 1.8/7.4 mm Hg, respectively), which are not clinically significant and which tend to resolve within the first week. No specific ECG or laboratory changes have been found.

Thus, within the recommended dose range of >10 mg/day and adopting slow incremental dosing in the first week, risperidone appears to be safe and well tolerated.

Neurologically, it does not cause significant EEG changes and has not been associated with enhanced seizure liability. Neuroleptic malignant
syndrome has been reported, though in only one case was documentation adequate.62

There is no doubt that risperidone can induce extrapyramidal side effects (as rated in the Phase III studies on the Extrapyramidal Symptom Rating Scale or ESRS). While the North American study showed no enhanced liability with 6 mg/day or less over placebo in any of the major categories (subjective symptoms, total scores, Parkinsonism, Parkinsonism hypokinetic and hyperkinetic subscores and dyskinesias), the likelihood is again of a dose dependent relationship, as clearly emerged in the multinational study. In general, risperidone 16 mg/day appears to have comparable EPS liability to haloperidol 10 mg/day but less than 20 mg/day, while in the recommended dose range of 8–10 mg/day or less, it has a clearly reduced liability compared to both doses of haloperidol14. The particular interest of risperidone lies in the ESRS Parkinsonism hyperkinesia subscore which in both studies was significantly lower than with haloperidol and in the recommended dose range no greater than with placebo/1 mg/day61. This subscore comprises tremor and akathisia, and a similar finding holds true when akathisia ratings are considered alone61. Thus, the particular benefit of risperidone may lie in its strikingly diminished liability to promote akathisia. In view of the distressing nature of this side effect and its major impact on compliance, confirmation of this finding in other data sets, and especially against other comparitors, would endow risperidone with a very particular advantage. The suggestion of an antidyskinetic effect63 must, at present, be viewed with circumspection.

Risperidone is in the vanguard of the new generation of antipsychotic drugs. The evidence to date does not support the view that it is in effect clozapine mark II, but would justify its place as a safe, well-tolerated and effective treatment of acute schizophrenia with potential advantage over standard drugs. Its role in other treatment situations remains to be established. Its costs are, however, more compatible with those of clozapine than standard ‘first line’ compounds and with successors that will no doubt be in similar price bands, research into the comparative economics of antipsychotic use must become an increasingly important field of study.

Compounds in late development

The reviewer in this field is immediately confronted with a problem—namely a hitherto uncharacteristic coyness on the part of the pharmaceutical industry. This no doubt reflects a perhaps understandable need to protect substantial commercial investments, but the result is that
Table 3 Receptor binding affinities of new antipsychotic drugs (Ki values (nM)* IC$_{50}$s)

<table>
<thead>
<tr>
<th>Drug</th>
<th>D$_1$</th>
<th>D$_2$</th>
<th>5HT$_{2A}$</th>
<th>5HT$_{1A}$</th>
<th>1</th>
<th>2</th>
<th>H$_1$</th>
<th>M$_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertindole (Sanchez et al.)</td>
<td>28</td>
<td>4.1</td>
<td>0.39</td>
<td>2600</td>
<td>3.4</td>
<td>350</td>
<td>600</td>
<td>2500</td>
</tr>
<tr>
<td>Olanzapine (Moore et al.)</td>
<td>31</td>
<td>11</td>
<td>4</td>
<td>-</td>
<td>19</td>
<td>228</td>
<td>7</td>
<td>1.9</td>
</tr>
<tr>
<td>Seroquel* (Salter &amp; Szamata)</td>
<td>1243</td>
<td>329</td>
<td>148</td>
<td>720</td>
<td>90</td>
<td>270</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone (Howard et al.)</td>
<td>1243</td>
<td>329</td>
<td>148</td>
<td>720</td>
<td>90</td>
<td>270</td>
<td>30</td>
<td>-</td>
</tr>
</tbody>
</table>

prior to regulatory approval one has often only minimal data presented in minimalistic style on which to form objective judgements.

One of the first of the new batch of drugs to achieve regulatory approval is likely to be sertindole. *In vitro*, it has high affinity for 5HT$_{2A}$, D$_2$ and alpha$_1$ receptors, but no affinity for 5HT$_{1A}$ and muscarinic cholinergic receptors$^{64}$ (Table 3). *In vivo*, its pharmacology is unusual in that it appears ineffective in acute tests of dopamine antagonism$^{65}$. Sertindole appears to exhibit very potent and protracted anti-anxiety effects in animal models$^{66}$.

Olanzapine is a thienobenzodiazepine analogue of clozapine$^{67,68}$, with a very similar pattern of receptor binding, including a high affinity for the D$_4$ dopamine sub-type (Table 3). Its activity is, however, greater at all sites, except alpha$_2$.$^{65}$

In a unique manoeuvre (which it is hoped will not be repeated), ICI-204,636 has been universally referred to from the start by its registered trade name Seroquel, which is now uncomfortably ensconced in the professional subconscious. It is novel dibenzothiazepine which also shares structural similarities to clozapine$^{69,70}$. Seroquel exhibits only modest *in vitro* affinity for a wide range of receptors, including D$_2$ (Table 3). Unlike clozapine, it lacks appreciable *in vivo* activity at D$_1$ sites and has no antimuscarinic effects. As with clozapine, however, chronic use appears to result in down-regulation of 5HT receptors in frontal cortex but no up-regulation of striatal D$_2$ receptors$^{71}$.

Ziprasidone is a benzisothiozoyl piperazine which binds with high affinity to D$_2$ and especially 5HT$_{2A}$ sites$^{72,73}$. Unlike risperidone, however, it also shows high affinity for 5HT$_{1A}$ receptors but is inactive at alpha$_2$ sites (Table 3).

Also in the wings are zotepine, ORG-5222, mazapertine and even the far from youthful melperone, along with possibly amperozide and savoxepine.

A full review of those of the above that make it past the final hurdle to clinical launch must await the availability to wider scrutiny of Phase III data which will, in its turn, now probably post-date regulatory approval.

All of the above new generation compounds have deliberately sought 'atypicality'. Just what those properties are that make an antipsychotic 'atypical' are however unclear, as the concept is capable of definition on a
number of axes, especially pharmacologically. At a clinical level, the criterion would be satisfied if a drug's effective use were associated with an absent or even clearly diminished liability to promote extrapyramidal side effects, especially those of acute/intermediate type (acute dystonias/Parkinsonism/akathisia), with a reduced risk of tardive dyskinesia remaining a long-term expectation. The question must be posed as to whether these new drugs can fulfil this basic clinical requirement. Risperidone has one of the highest 5HT₂/D₂ affinity ratios and does have a more favourable EPS profile than haloperidol. Ignoring the fact that this is a standard drug of high propensity, risperidone's advantage on present evidence seems focused, particularly on akathisia. Furthermore, there is reason to question the simplistic view of the functions of mesolimbic versus striatal dopamine systems, and very real reason to question the assumption that laboratory tests of 'limbic selectivity' actually do predict a reduced liability to EPS in patients. Of those drugs that interact at multiple receptor sites, only clozapine does not produce dystonia in haloperidol sensitised rats, although the ability of Seroquel in this regard is weak. Detailed data on clinical performance will be necessary to allow a firm judgement on clinical atypicality, but it is important to bear in mind that what in the laboratory appears to be 'atypical' may operate in the clinic as merely 'less standard'.

Other developments

The focus of clinical neuroscience on the D₂ dopamine receptor left the D₁ receptor as somewhat of an entity seeking a function, a situation of neglect encouraged by the absence of selective D₁ ligands. The first selective D₁ antagonist, SCH-23390, had major safety problems and did not reach clinical evaluation, though a more selective and potent successor, SCH-39166, has been developed. There is evidence that D₁ antagonists may have antipsychotic potential and possibly, though more controversially, less liability to produce EPS. This strategy remains at an early stage, though offers an alternative explanation of clozapine's advantages. There is, however, no evidence to support the view that standard drugs with a relatively greater affinity for D₁ receptors, such as zuclopenthixol, are either more effective or better tolerated than those with lesser or no affinity.

Molecular biological techniques have now identified two 'families', rather than single types, of dopamine receptor—the D₁-like (D₁/D₅) and the D₂-like (D₂/D₃/D₄). Particular interest was shown in the D₄ isomorph in view of the relatively high affinity clozapine exhibited for these sites, though it seems unlikely this alone explains its therapeutic
and tolerability effects. Nonetheless, exploration of the balance of dopamine interactions of new drugs is likely to be an important aspect of future research.

A sophisticated alternative to the reduction of dopaminergic transmission by postsynaptic antagonism is the development of dopamine agonists. These compounds bind to dopamine sites, but have variable ability to elicit a response (i.e. variable intrinsic activity). Full agonists have high intrinsic activity, while in drugs acting as antagonists, intrinsic activity is extremely low. Most dopamine agonists that are of interest as potential antipsychotics combine high affinity for the dopamine site with varying degrees of intermediate intrinsic activity, and hence function as partial agonists. The theoretical attraction of a partial agonist is that by occupying a receptor, its full stimulation by the endogenous neurotransmitter is prevented, yet some response is still produced, thereby attenuating, as opposed to blocking, activity at that site. Such drugs may act at postsynaptic sites but interest has particularly focused on their effects at presynaptic or autoreceptor sites. Presynaptic receptors are located at two main sites, cell bodies and dendrites, and nerve terminals. Somatodendritic receptors may regulate action potentials and protein synthesis and, thereby, suppress firing rates, while preterminal receptors seem to control transmitter release through a negative feedback mechanism. The net effect is a ‘dampening’ of the system.

Since the pharmacology of the first dopamine agonist (−3PPP) was elucidated, a number of such compounds have been developed, such as roxindole, talipexole, pramipexole and terguride, but the question of their antipsychotic efficacy must remain open. Furthermore, their purported benefits in negative states may be complicated by other aspects of their pharmacology. For example,roxindole, in addition to its dopamine agonist actions, exerts similar effects at 5HT_{1A} sites and inhibits serotonin re-uptake. Thus, it may have some antidepressant properties which could explain reported improvements in ‘negative’ symptomatology. It is perhaps revealing that these compounds are still often referred to by their development codes and this approach, while intriguing, remains in its infancy.

Other even more radical approaches are being explored that are not predicated on variations of the dopamine hypothesis or are only indirectly so. The most active takes its inspiration from the psychotogenic effects of the dissociative anaesthetic phencyclidine (PCP), advocated by some as the best drug-induced model of schizophrenia, as it can be associated with deficit as well as productive symptomatology. Phencyclidine interferes with receptor gated calcium ion conductance through the N-methyl-D-aspartate (NMDA) subclass of the glutamate receptor complex. This theory infers a deficiency of glutaminergic transmission underlying schizophrenia, especially from NMDA receptors.
thought to stimulate dopaminergic transmission in the ventral tegmental (A10) dopamine system\textsuperscript{87}. Attempts to modify the NMDA complex using exogenous glycine have not produced impressive results, nor have efforts to improve brain penetrance by using an acylated ‘pro-drug’ of glycine, melacemide\textsuperscript{88}. Adequate clinical testing of this hypothesis will have to await pharmacological probes as sophisticated as the theory.

The same might be concluded about attempts to modify actions at sigma sites, as currently available antagonists either lack specificity (e.g. tiospirone, gevetroline) or are of only low affinity (e.g. rimcazole)\textsuperscript{89}. The partial benzodiazepine receptor agonist bretazenil has been reported to be effective and well tolerated, but support for such effects being due to other than indirect benefits remains to be justified\textsuperscript{90}. Modulation of neurotransmission via the use of peptides is another strategy of theoretical sophistication, but as yet a lack of empirical promise.

These are exciting times in antipsychotic pharmacology in which clinicians should soon be able to share with the launch of the ‘new generation’ drugs. The ultimate levels to which such excitement rises, however, will depend not on the pharmacologists’ data or clinicians’ interpretation of them, but on patient acceptability, a tough constituency to master. It is unlikely that with the rapid advances in the neurosciences we will shall have to endure another 30 year hiatus before further clinical benefits percolate through. To help ensure this, it is perhaps important to encourage basic scientists not to substitute one obsession about the putative mode of action of antipsychotics with another. There is perhaps by now enough material on line by which the 5HT\textsubscript{2}/D\textsubscript{2} hypothesis may in the next few years be judged. If clozapine is indeed our model, there are other actions it possesses that may with value be explored, especially those involving noradrenergic mechanisms. There once was a noradrenergic theory of schizophrenia too!

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