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Developments in the pharmacological treatment of schizophrenia

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Schizophrenia is, at once, a biological disease, a neuropsychological disorder and a dysfunction of social interactions. This presents clinicians with a series of problems with regards to therapy. In the first section of this article, some of the clinical challenges that face those attempting to develop new drugs, are summarised. Several potential pharmacological therapeutic targets that have been, and are continuing to be used, in the development of new antipsychotic drugs, are then considered. This is followed by an outline of the pharmacological and clinical profiles of some of the newer generation antipsychotics, as well as investigational drugs in the pipeline for schizophrenia. Finally, the implications of the introduction of these new drugs for the management of schizophrenia, are discussed.

Keywords: 5-HT_{2A} receptor, amisulpride, antipsychotic, aripiprazole, atypical, clozapine, D1 receptor, D3 receptor, D4 receptor, dopamine, glutamate receptor, iloperidone, olanzapine, pharmacotherapy, quetiapine, risperidone, schizophrenia, ziprasidone

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1. Clinical challenges

Since the introduction of chlorpromazine [1], numerous antipsychotic drugs have been developed and numerous double-blind clinical trials have established their advantages over placebo in alleviating the positive symptoms of schizophrenia – the delusions, hallucinations and thought disorder that cut off the schizophrenic patient from reality, and can lead to inappropriate or dangerous behaviour. There is probably little hope of further improving these positive symptoms with new pharmacotherapies except in patients who are 'treatment resistant' (see discussion of clozapine in section 3). The focus for the development of new 'atypical' antipsychotic drugs has therefore been on overcoming:

- disabling side effects typically associated with traditional antipsychotic drugs
- negative symptoms
- neurocognitive dysfunction.

The main side effects associated with traditional antipsychotic drugs are extrapyramidal side effects (EPS). EPS arise mainly as a result of blockade of the D2 dopamine receptor in the basal ganglia (see Section 2). They range from pseudoparkinsonism and akathisia to tardive dyskinesias, and are both functionally disabling and socially stigmatising [2]. Moreover, their presence is a strong predictor of medication noncompliance [3].

Negative symptoms – affective flattening, avolition, apathy and anhedonia – have long been considered to be at the core of schizophrenia [4]. Yet, the potential role of medication in treating this so-called 'deficit syndrome' [5] has largely been ignored. Indeed, most of the existent clinical rating scales that are used to determine drug efficacy, place a much larger emphasis on positive than negative symptoms. Over the

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past few years, this situation has been challenged and there has been considerable interest in the development of drugs targeting negative symptoms. This development, however, poses a real challenge as it is difficult to distinguish 'core' negative symptoms from the so-called 'secondary' negative symptoms that result from EPS, depression or even positive symptoms [6].

Overcoming neuropsychological deficits is a third important target for pharmacological therapies. Cognitive deficits are thought to underlie the development of positive and negative symptoms and to impede the schizophrenic patient's ability to interact with his or her environment. Patients with schizophrenia show deficits in a variety of cognitive domains including executive function, attention, memory and language. Recent evidence suggests that cognitive dysfunction is intrinsic to schizophrenia rather than the result of chronic illness, institutionalisation or medication: cognitive deficits are present in adolescents at risk for schizophrenia [7], in those who will later develop schizophrenia [8], and in untreated schizophrenic patients at their first episode of psychosis [9]. Moreover, cognitive performance does not deteriorate over the first few years of illness when patients are treated [10]. Psychotropic medication can, in theory, impair or improve the cognitive skills of patients with schizophrenia. As discussed in section 3, there have been claims that some of the newer psychotropic medications may have selective beneficial effects on aspects of cognitive function in schizophrenia [11].

2. Therapeutic targets

The relationships between positive symptoms, negative symptoms, neurocognitive dysfunction and specific therapeutic targets, remain obscure. Nonetheless, it has long been known that all antipsychotic drugs with any clinical utility inevitably have some action at dopamine receptors [12]. The best known of these receptors is the D2 receptor. It is, however, the blockade of the D2 receptor in the basal ganglia that leads to the disabling EPS described above [12]. There has therefore been a long-standing desire to find novel therapeutic targets that are either completely non-dopaminergic or, at least, that act via novel dopamine receptors. These strategies are discussed briefly below. Although each therapeutic target is considered in isolation, most investigators believe that balanced actions of oligoselective drugs are likely to be more useful than monoselectively acting drugs.

2.1 The D3 receptor

There are several reasons to suppose that the D3 receptor may be an important novel target [13]. It is related to the D2 receptor, but has a selective limbic distribution [13,14]. There is some evidence of an increased frequency of genetic variants of the D3 receptor in patients with schizophrenia compared with controls, and more robust evidence that such variants can influence drug response [15,16]. D3 receptors are also presynaptic on dopamine terminals and antagonism of these receptors enhances dopamine release – an important therapeutic aim in schizophrenia [17].

There are a number of D3 receptor antagonists under very early development for use in schizophrenia, but none of them are yet in the public domain of clinical research. The drug, amisulpride, however, provides an interesting proof-of-concept for the role of D3 receptors. This drug preferentially blocks limbic D3 receptors to enhance dopaminergic neurotransmission and is a highly effective drug, particularly in treating the positive symptoms of schizophrenia [17,18].

2.2 The D4 receptor

The D4 receptor is another genetic relative of the D2 receptor with similar pharmacological characteristics. Interest in this receptor was stimulated by the observation that clozapine binds to it with a particularly high affinity [19]. Unfortunately, however, pharmacogenetic association studies suggest that action at the D4 receptor is unlikely to contribute to the clinical response of patients [20], as the receptor and its mRNA are present at negligible levels in the human brain [21]. Moreover, a clinical trial of a D4 antagonist (L-745870) failed to show benefits in the treatment of schizophrenia [22].

2.3 The D1 receptor

Imaging studies have demonstrated decrements in D1 receptors in the prefrontal cortex in patients with schizophrenia [23]. Short-term D1 receptor stimulation may reverse anyipsychotic-induced working memory deficits in monkeys [24]. Recent evidence suggests that, in drug-naive patients with schizophrenia, D1 receptor availability may be increased, and that this increase is a strong predictor of poor performance on a working memory task [25].

Stepholidine is a drug derived from psychotropic herbs of the stephania family. It possesses dual D1 agonist activity and D2 antagonist activity. There is evidence from several behavioural and electrophysiological studies that it may also possess antipsychotic activity [26].

2.4 The 5-HT_{2A} receptor

The 5-HT_{2A} receptor site is a strong candidate for a site of action of novel antipsychotic drugs. As discussed in section 3, the clinical profile of the drug, clozapine, which possesses 5-HT_{2A} activity in addition to D2 activity, was probably the main impetus for this line of research. In addition, there are some reports of abnormalities in 5-HT_{2A} genes in schizophrenic patients [27]. There are also strong and replicable associations between drug responses and variations in this gene [28].

2.5 The glutamate receptor system

The glutamate receptor is the major excitatory neurotransmitter system in the CNS, having a multiplex system of receptors. There is evidence for abnormalities in this system in schizophrenia [29]. It is the NMDA (N-methyl D-aspartate) receptor subtype that has received most attention as a therapeutic target,

principally because of the psychotomimmetic action of agents acting at this receptor, such as phencyclidine and ketamine. In addition, postmortem studies have revealed alterations in pre- and postsynaptic markers for glutamatergic neurons in several brain regions in schizophrenia [30]. The development of drugs acting at this receptor site is difficult because of the potential proconvulsant actions of such drugs. Nevertheless, some attempts have been made at manipulating the glycinergic allosteric regulatory site of this receptor by treating patients with glycine or D-cycloserine. These studies, so far, appear to show a weak beneficial effect on negative symptoms [31,32].

The sigma receptor may also be a relevant target. This is part of the NMDA receptor complex, but can also occur in the brain as a free standing entity [33]. There are a number of drugs in early phase clinical development that act at the sigma receptor: these include rimcazole, BMY-14802 and SL-820715. Results based on small open studies are conflicting. However, there may be specific actions on negative symptoms [34].

3. Pharmacological and clinical profiles of specific drugs

Over the last few years, several atypical antipsychotic drugs have been developed that have begun to overcome some of challenges described in Section 1, and that act at some of the receptor sites described in Section 2. Much of the impetus for the development of many of these drugs came from the unique clinical and pharmacological profile of clozapine – a drug that was first developed in the 1960s. Because of the impact of clozapine, its pharmacological and clinical profile will be described in some detail. The various drugs that have already been introduced (risperidone, olanzapine, quetiapine, amisulpiride and ziprasidone), will then be described before turning to other drugs in the immediate pipeline and that are likely to become widely available within the next four years (aripiprazole and iloperidone).

3.1 Clozapine

The receptor binding profile of clozapine differs from conventional antipsychotic drugs both within and outside the dopamine system. Within the dopamine system, most antipsychotic drugs at therapeutic doses occupy at least 60% of D2 receptors in the striatum [35]. In contrast, the average occupation of D2 receptors by clozapine is only 20% [36-38]. Furthermore, *in vitro*, clozapine's affinity for the D4 receptor is approximately ten times greater than for the D2 receptor and it has also been shown to bind to the D1, D3 and D5 receptors [12]. However, the most significant impact of clozapine has been a recognition of its activity at a broad range of receptors outside the dopamine system. Of particular interest is its high affinity for serotonin (5-HT) receptors, including the 5-HT_2 [39], 5-HT_3 [40] and the more recently discovered 5-HT_6 and 5-HT_7 receptor subtypes [41]. The possibility that clozapine's novel effects might be explained by the ratio of 5-HT_2:D2 antagonism [39], led to the development of many of the atypical antipsychotic drugs discussed below: the 5-HT2:D2 antagonists.

The original studies that compared clozapine with a variety of typical antipsychotic drugs showed it to be either equivalent or superior in efficacy against positive symptoms. Although clozapine does have some side effects (sialorrhoea, sedation, reduction in seizure threshold, sinus tachycardia and hepatitis), in all cases, it was better tolerated than conventional antipsychotics [42]. This is because it is devoid of EPS. Indeed, it was the clinical profile of clozapine that disproved the idea that EPS are an inevitable commitant of antipsychotic efficacy. In 1974, however, clozapine was withdrawn from use because it leads to a potentially fatal agranulocyytosis in 1% of patients, and to neutropaenia in 10% of patients [43,44]. However, when clozapine was shown to be effective in alleviating symptoms resistant to treatment by other antipsychotics in the late 1980s (see below), it was reintroduced for such 'treatment resistant patients' on the unprecedented condition of a haematological monitoring system via a drug based registry. This monitoring system has been shown to substantially reduce the risks of agranulocytosis [45,46].

The multi-centre, double-blind trial by Kane and colleagues [47] that established clozapine's position as effective in alleviating symptoms resistant to treatment by other antipsychotics, used rigorously defined criteria for 'treatment resistance'. Patients were only eligible if they had failed to respond to at least two other antipsychotic drugs, had no period of good functioning within the previous five years and were experiencing at least two positive psychotic symptoms. Improvement on clozapine was demonstrated in one third of these patients [47,48]. Several other studies unanimously confirmed the efficacy of clozapine in treatment resistant schizophrenia [49] and a recent meta analysis strongly confirms this consistent superiority [50]. Clozapine has also been associated with improved cognitive function in schizophrenia, particularly in attentional, verbal fluency and learning tasks [51,52].

It is tempting to assume that, because many of the newer antipsychotic drugs share many of clozapine's pharmacological properties, they are also more efficacious than conventional neuroleptics. However, double-blind trials directly comparing some of these new drugs with clozapine suggest that none possess the advantages of clozapine in ameliorating positive symptoms in the most treatment-refractory patients (see citations under the following sections). Thus, clozapine remains the gold standard in the management of 'treatment resistant' patients. Further double-blind trials with strict entry criteria will determine the role of other atypical drugs in the management of such patients.

3.2 Risperidone

The first of the new 'atypical' antipsychotic drugs to be introduced was risperidone – a bensisoxazole derivative, with a higher affinity for the D2 receptor than clozapine, and an even higher affinity for the 5-HT_2 receptor [53,54]. Risperidone also has actions at a variety of other receptors [55].

EPS appear at relatively high doses of risperidone while improvements in both positive and negative symptoms are evident at lower doses [56,57]. Head-to-head studies with other antipsychotics have demonstrated an optimal dose of ≤ 6 mg/day [58]. However, during initiation of treatment, even lower doses may be effective without any side effects [59]. There have been numerous studies of risperidone in treatment resistant patients. These seem to show an intermediate effect, with improved efficacy over traditional antipsychotic drugs but with a magnitude of response that is inferior to clozapine [60,61]. Like clozapine, risperidone has also been associated with improved cognitive function in schizophrenia [51,62].

3.3 Olanzapine

Olanzapine evolved from a research programme designed specifically to find an analogue of clozapine with comparable pharmacological properties, but without its propensity to induce agranulocytoisis. It is a thienobenzodiazepine and is chemically and pharmacologically similar to clozapine [63].

The size and number of pivotal trials for olanzapine is impressive. Again, improvements are seen in both positive and negative symptoms. The effects on negative symptoms appear to be particularly marked. Studies carried out by the manufacturers of olanzapine claim to demonstrate, using path analyses, that olanzapine acts on the primary deficit state rather than on secondary negative symptoms [64]. There are also good data on the long-term effects of olanzapine which leads to lower long-term relapse rates than typical drugs such as haloperidol [65]. However, an impressive study by Conley *et al.* [66], that used the methodology of Kane *et al.* [47] in the pivotal clozapine trial (described above in Section 3.1), failed to show any effect of olanzapine in patients with treatment resistant schizophrenia. Again, as with studies of risperidone, many of these patients subsequently responded to clozapine.

3.4 Quetiapine

Quetiapine is another of the D2/5-HT2 blocking agents, with a multireceptor profile that is similar to that of clozapine, but with a lower overall potency [67]. Quetiapine is particularly noteworthy for its placebo level side effect profile and, in this respect, is more like clozapine than all the other atypical agents [68]. In addition, quetiapine has no effect on serum prolactin levels [69]. There have been a number of controlled trials showing efficacy of quetiapine in comparison with placebo and haloperidol. Although the drug has a broad dose range, efficacy, in most instances, may not be apparent until doses of 400 mg are reached. Indeed, an unusually large number of participants in some of the major trials have dropped out due to a lack of efficacy [68].

3.5 Amisulpride

Amisulpride is a substituted benzamide which acts as a highly selective blocker of D2 and D3 receptors [14]. As with the other atypical drugs, it is effective compared with placebo and haloperidol, with lower rates of EPS [14]. The strength of amisulpride is its effectiveness against negative and affective symptoms. There is evidence that it shows superior efficacy against negative symptoms in comparison with haloperidol [70]. In addition, its antidepressant effect may be superior, not only to haloperidol, but also to risperidone [71]. Amisulpride might also be useful as an adjunct to clozapine in patients who are particularly difficult to treat [72].

3.6 Ziprasidone

Ziprasidone has already received regulatory approval in the US and in much of Europe, and is likely to receive regulatory approval in the UK and other parts of Europe in the near future. Ziprasidone is broadly similar to other D2/5-HT_2 blocking drugs, but is noteworthy for its additional 5-HT_{1A} agonist effects and its action as a selective serotonin uptake blocker [73,74]. As with other atypicals, the drug is efficacious when compared to placebo and typical drugs against positive and negative symptoms [75], with lower rates of EPS. A most interesting aspect of this drug is its low propensity to produce weight gain and associated hyperglycaemia [76]. The drug extends the QTc interval on the electrocardiogram (ECG) marginally more than some other atypical drugs. Although the risk from cardiac arrhythmias is very small and is yet to be carefully quantified, the drug is likely to be licensed in the UK with a requirement for some form of ECG monitoring.

3.7 Aripiprazole

Aripiprazole is a phenylbutylpiperazine and is likely to receive regulatory approval in 2003. Aripiprazole stands out amongst the new antipsychotics as having a genuinely novel mechanism of action. The drug is a potent partial agonist at D2 receptors and is theoretically able to stabilise both hyper and hypoactive dopamine systems (both of which might be relevant to the neurochemical aetiology of schizophrenia) [77]. Currently there is relatively good evidence from short-term studies that suggest the drug is active against both positive and negative symptoms. In addition, early phase studies suggest that this drug is effective against mood and cognitive disturbances [78]. These studies also show that the drug may have an unusually rapid onset of action. It has a placebo level tolerability profile.

3.8 Iloperidone

The regulatory status of iloperidone is somewhat unclear at present. At first sight, the drug appears to be a standard D2/5-HT_2 blocker. However, it also has an interesting ability to block α–2C receptors in the brainstem. This action potentially has a stabilising effect on fluctuations in ascending dopaminergic systems [79].

4. Expert opinion and conclusions

We have discussed some of the current and future drugs for the treatment of schizophrenia. Although most of the drugs

currently available rely on classical dopamine and 5-HT mechanisms of action, novel mechanisms of action may lead to the development of radically alternative drugs within the next ten years.

The main clinical impact of the drugs that have thus far been introduced has been their reduced propensity to produce EPS. In addition, these drugs may have an increased efficacy against negative symptoms or, at least, a lesser propensity to exacerbate secondary negative symptoms. The effects of the newer drugs on cognitive dysfunction, and the impact that such effects may have on psychosocial function, are still being explored. Although the 'atypical' antipsychotic drugs are more expensive than conventional neuroleptics, it may be that, in the long run, this greater short-term expense is more than offset by reduced morbidity-associated costs and gains in the patients quality of life [80]. Indeed, there is emerging evidence that the greatest impact of these drugs may be at the first episode of a patient's illness [81,82].

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- **The management of patients with schizophrenia in the early stages of the illness is becoming an increasing focus of research. This review discusses some of the questions that are being addressed.**

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