Behavioural pharmacology of the new generation of antipsychotic agents

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Antipsychotic agents have been the mainstay in the management of schizophrenia for a number of years. Their therapeutic efficacy is primarily attributed to dopamine receptor antagonism (Creese *et al*, 1976), leading to a reduction in the positive symptoms of schizophrenia such as paranoia and hallucinations. Unfortunately, they have little effect on the negative symptoms (such as flattened affect, poverty of speech, anhedonia and social withdrawal) or cognitive deficits. The blockade of central dopamine receptors by classical antipsychotic agents also leads to the development of both acute and chronic motor disturbances (extrapyramidal side-effects) (EPS) (Meltzer, 1992).

One agent, clozapine, appears to differ from the classical agents. This compound possesses antipsychotic activity without producing extrapyramidal side-effects (Hippius, 1989), treats both positive and negative symptoms, and is effective in patients resistant to other treatment (Kane *et al*, 1989; Helmchen, 1989; Fitton & Heel, 1990), demonstrating that it is possible to develop agents which do not induce EPS. Preclinically, clozapine differs from other antipsychotic agents: for example, it fails to induce catalepsy in rodents (a test which predicts liability to EPS), and demonstrates mesolimbic selectivity (Coward *et al*, 1989; Coward, 1992, 1993). This unique profile led to it being referred to as an 'atypical' antipsychotic agent, to differentiate it from existing treatments (for review see Casey, 1992). Unfortunately, the incidence of agranulocytosis associated with clozapine precluded its use as first-line therapy, so that it was necessary to develop newer agents that are safe, and effective against both positive and negative symptoms, while producing no EPS.

The search for a safe clozapine-like compound has proved difficult because of the multifaceted pharmacological profile required. Clozapine has affinity for a wide range of receptors, including dopamine D_1, D_2 and D_4 receptors, 5-HT_{2a}, 5-HT_{2b} and 5-HT_{2c} receptors, histamine H_1 receptors, α_1 and α_2 adrenergic receptors and muscarinic cholinergic receptors (Fitton & Heel, 1990; Coward, 1992, 1993; Meltzer, 1994; Bymaster *et al*, 1996). Evidence to date suggests that the 'atypical' profile of clozapine cannot be attributed to a single action but is due to its non-specificity and relative interaction at a number of different receptors (for review see Kinon & Lieberman, 1996). Until we elucidate the mechanisms by which clozapine produces its 'atypical' actions, one approach to the development of agents with improved efficacy and safety will be to identify compounds that have a behavioural profile similar to that of clozapine.

The complex nature of clozapine's pharmacology has led a number of research groups to develop agents that encompass some aspects of its unique profile. For example, some have developed agents that possess mesolimbic/mesocortical selectivity, such as sertindole (for review see Dunn & Fitton, 1996). However, not all agents possessing such a profile have been shown to exhibit a robust antipsychotic effect (e.g. 5-HT_3 antagonists). Other groups have developed agents with affinity for a subset of clozapine binding sites, such as risperidone, which has affinity for both dopamine and 5-HT_2 receptors (Janssen *et al*, 1988; Leysen *et al*, 1994); recently, ziprasidone has been shown to have a similar profile, with additional affinity for 5-HT_{1a} and 5-HT_{1d} receptors (Seeger *et al*, 1995). Quetiapine has high affinity for α_1 and histamine H_1 receptors and relatively weak dopamine and muscarinic receptor affinity (for review see Goldstein & Arvanitis, 1995). A third approach involved the development of agents with a broad pharmacological profile similar to that of clozapine: for example, olanzapine, which has somewhat higher affinity for dopamine receptors than clozapine, but has a similar profile at 5-HT, α_1, histamine H_1 and muscarinic sites (Bymaster *et al*, 1996; for review see Fulton & Goa, 1997).

This article will review the key behavioural actions of these newer agents and compare these to the typical agent, haloperidol, and the 'atypical' antipsychotic, clozapine.

ANIMAL MODELS OF SCHIZOPHRENIA

One of the major issues in the development of new antipsychotic agents is the lack of an animal model of schizophrenia. Over the years various behavioural assays have been labelled 'models of schizophrenia'. However, at best these 'models' demonstrate predictive validity or construct validity, mirroring only some aspects of the symptoms of schizophrenia (Ellenbroek, 1993). Early behavioural tests focused on the 'dopamine hypothesis', leading to the development of a large number of 'me too' dopamine antagonists (Minchin & Csernansky, 1996).

Behavioural actions of dopamine antagonists

Typical antipsychotic agents which possess predominantly dopamine antagonist activity produce a broad range of effects on behaviour (Table 1) (for reviews see Ellenbroek, 1993; Ogren, 1996). Such compounds prevent the hyperactivity induced by dopamine agonists or indirect releasers of dopamine. The hyperactivity produced by excessive stimulation of the dopamine system is

Table 1 Behavioural assays to detect new antipsychotic agents

Apomorphine-induced climbing behaviour	Dopaminergic function (efficacy)
Stimulant-induced hyperactivity	
Conditioned avoidance	
Induction of catalepsy	Dopaminergic function (side-effect potential)
Hindlimb/forelimb retraction time (paw test)	
Pre-pulse inhibition	Construct validity
Social withdrawal models	Negative symptoms?
Schedule-controlled behaviour	

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manifested as an increase in locomotor activity and stereotyped behaviour (consisting of repetitive sniffing and gnawing) in rats. The locomotor response is predominantly mesolimbically mediated, while the stereotypy is mediated by striatal dopaminergic overactivity (Ogren, 1996). Using this anatomical differentiation, a number of groups have developed agents that preferentially block the locomotor response at doses lower than those preventing the stereotyped behaviour (Ogren *et al*, 1984; Ogren, 1996). Dopamine antagonists also block the climbing response produced by apomorphine in mice, and this test has been utilised to assess the dopamine antagonist properties of the newer agents (Moore & Axton, 1988).

Dopamine antagonists also disrupt the conditioned component of an avoidance procedure, while having negligible effect on the escape response; this test is believed to predict the antipsychotic efficacy of a compound (Arnt, 1982; Ogren, 1996). Agents possessing dopamine antagonist activity produce a characteristic immobility in rodents, called catalepsy, which is believed to be due to dopamine receptor blockade in the striatum. This phenomenon was initially used to predict clinical efficacy, but is now believed to be the rodent correlate of EPS (Creese *et al*, 1976; Hippius, 1989). Recent studies have concentrated on developing agents that show activity in models believed to be indicative of antipsychotic efficacy while having a reduced propensity to induce catalepsy (Kinon & Lieberman, 1996).

Dopamine antagonist actions of the new antipsychotic agents

Apomorphine-induced climbing behaviour

All the recently developed agents produced dose-related reductions in apomorphine-induced climbing behaviour, indicating that *in vivo* the agents possess functional dopamine antagonist properties. The climbing response has previously been shown to require activation of both D_1 and D_2 receptors (Moore & Axton, 1988). However, the data suggest (Table 2) that the newer agents exert their effects on the climbing response via an interaction with D_2 receptors.

Table 2 The effect of clozapine, haloperidol and the newer antipsychotic agents on apomorphine-induced climbing behaviour in mice and their affinity for dopamine D_1- and D_2-like receptors

	In vitro D_1 binding Ki (nM)	*In vitro* D_2 binding Ki (nM)	Apomorphine-induced climbing (ED_{50} mg/kg)
Risperidone	75	3	0.3
Haloperidol	25	1	0.5
Olanzapine	31	11	5
Sertindole	210	7.4	7.5
Ziprasidone	330	9.7	10
Clozapine	85	125	10
Quetiapine	455	160	40

Bymaster *et al*, 1996; Moore *et al*, 1993; Moore, unpublished observations; Schotte *et al*, 1996.

Stimulant-induced hyperactivity

Antagonism of stimulant-induced locomotor activity and stereotyped behaviour has been extensively used in the search for novel antipsychotic agents. Recently, Arnt (1995) investigated the inhibitory actions of a number of established and newer compounds on the hyperactivity induced by amphetamine at two dose levels (0.5 mg/kg and 2.0 mg/kg). Typical agents such as haloperidol prevented the hyperactivity induced by both doses of amphetamine, whereas the newer agents – olanzapine, quetiapine, risperidone, sertindole and ziprasidone as well as clozapine – preferentially inhibit the response produced by low-dose amphetamine (Table 3). Similar results have also been reported when the hyperactivity produced by amphetamine is compared with that produced by cocaine. Olanzapine (2.5–10 mg/kg) produced a significant reduction in cocaine-induced hyperactivity. In contrast, olanzapine failed to antagonise hyperactivity induced by amphetamine; the lowest dose actually enhanced the response (Moore *et al*, 1994*a*). There are a number of possible explanations for the differential action of the newer agents on hyperactivity induced by amphetamine (low *v.* high dose) and cocaine. The response induced by high doses of amphetamine may be primarily stereotyped hyperactivity, and mediated by striatal structures, while cocaine- and low-dose amphetamine-induced hyperactivity may be mesolimbically mediated. It could be hypothesised that olanzapine and the other newer agents preferentially reduce mesolimbic activity and thus the cocaine or low-dose amphetamine response.

Table 3 The effect of clozapine, haloperidol and the newer antipsychotic agents on the hyperactivity induced by two doses of amphetamine

Compound	Amphetamine 0.5 mg/kg (ED_{50} mg/kg)	Amphetamine 2.0 mg/kg (ED_{50} mg/kg)	Ratio col. 3/col. 2
Clozapine	0.36	3.6	10
Haloperidol	0.03	0.06	2
Olanzapine	0.44	2.88	6.5
Quetiapine	0.92	>8	>8.7
Risperidone	0.08	0.85	11
Sertindole	0.06	1.0	12
Ziprasidone	0.11	1.4	12

Data from Arnt (1995).

Conditioned avoidance and catalepsy

Inhibition of a conditioned avoidance response is thought to predict antipsychotic efficacy, while the induction of catalepsy in rats is indicative of EPS in the clinic (Arnt, 1982; Worms *et al*, 1983; Ellenbroek, 1993). Thus by comparing the doses required to antagonise conditioned avoidance and induce catalepsy, it is possible to obtain some indication of the therapeutic index of the new agent. Table 4 shows the ED_{50} for inhibiting the avoidance response and inducing catalepsy in rats; haloperidol induced catalepsy at doses only slightly higher than those required to block the avoidance response, whereas clozapine blocked conditioned avoidance but failed

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Table 4 The effect of clozapine, haloperidol and the newer antipsychotic agents on conditioned avoidance responding (CAR) and the induction of catalepsy (CAT) in rats

Compound	CAR	CAT	CAT/CAR
Clozapine	21.3	>160	>8
Haloperidol	0.5	1.1	2.2
Olanzapine	4.7	39.4	8.4
Quetiapine	108	NT	–
Risperidone	0.9	6.3	7.0
Sertindole	3.0	>100	>33
Ziprasidone	2.6	12	4.6

The results are expressed as ED_{50} values (mg/kg). The ratio is the ED_{50} CAT/ED_{50} CAR. (Data from Moore *et al*, 1992; Seeger *et al*, 1995; Nielsen *et al*, 1996.)

to induce catalepsy at any dose tested. Although most of the newer agents did produce some catalepsy, this only occurred at doses higher than those required to block the avoidance response. For all the newer agents, the doses including catalepsy were at least four times as great as those blocking conditioned avoidance. Given the superior EPS profile observed in clinical studies, those data would seem to predict that agents with a CAT/CAR ratio greater than 4 (see Table 4) are less likely to produce EPS clinically; however, clinical experience with risperidone suggests that the therapeutic index of compounds with ratios less than 8 may be somewhat narrow.

Both olanzapine and quetiapine produced dose-related reductions in conditioned avoidance response in primates, with a minimum effective dose of 10 mg/kg by mouth (quetiapine) (Migler *et al*, 1993). The data for quetiapine suggest that this agent is more effective in avoidance tests in primates than in rodents.

Rat paw test

Another test used to differentiate the newer antipsychotics from existing agents is the rodent paw test. Here, typical agents affect both the forelimb retraction time and the hindlimb retraction time over a similar dose range, whereas clozapine is much more effective in increasing hindlimb retraction time at doses which have little effect on forelimb retraction time. In this test, olanzapine, sertindole, and risperidone produced an 'atypical' profile similar to that of clozapine, increasing hindlimb retraction time at doses much lower than those necessary to increase forelimb retraction time. Although quetiapine displayed some selectivity, this was less than observed with other newer agents (Table 5) (Cools *et al*, 1995).

These results show that all the newer agents possess some dopamine antagonist activity, and preferentially inhibit behaviour types thought to be predictive of antipsychotic activity at doses lower than those indicative of EPS. On the basis of these findings, all the newer agents are thought less likely to induce EPS than existing typical agents such as haloperidol.

Interactions with other neurotransmitter systems

5-HT_{2a}

In addition to their dopamine antagonist properties, the new agents also possess significant affinity for other neurotransmitter receptors. All the agents reviewed in this article have affinity for 5-HT_2-like receptors, reflected in the antagonism of various 5-HT_2-mediated behaviours. For example, olanzapine and risperidone antagonise the discriminative cue produced by the 5-HT_{2a} agonist DOI (2,5-dimethoxy-4-iodo-amphetamine) (Arnt, 1996). Olanzapine, risperidone and quetiapine have also been shown to antagonise the head twitch response produced by 5-HT_p in mice, with a rank order predicted from the *in vitro* 5-HT_{2a} binding (Moore *et al*, 1992, 1993; Bymaster *et al*, 1996). Sertindole and ziprasidone also antagonised the 5-HT_{2a}-mediated, quipazine-induced head twitch response in rats, in a dose-related manner (Sanchez *et al*, 1991; Seeger *et al*, 1995).

Table 5 The effect of clozapine, haloperidol and the newer antipsychotic agents on hindlimb (HRT) and forelimb retraction time (FRT) in the rat paw test

Compound	FRT (EDmin mg/kg)	HRT (EDmin mg/kg)	Ratio FRT/HRT
Clozapine	>100	10	>10
Haloperidol	0.25	0.25	1
Olanzapine	10	0.5	20
Quetiapine	100	25	4
Risperidone	5	0.5	10
Sertindole	0.06	1.0	18

Data from Cools *et al*, 1995; Ellenbroek *et al*, 1996.

Muscarinic receptors

Olanzapine is the only newer agent which, like clozapine, possesses significant affinity for muscarinic receptors *in vitro*. However, this high *in vitro* affinity does not translate into potent anticholinergic activity *in vivo*. Olanzapine (2.5–10 mg/kg by mouth) produced a reduction in oxotremorine-induced tremor in mice, albeit at higher doses than one would predict from the *in vitro* binding profile. Clozapine (ED_{50} 12 mg/kg by mouth) also antagonised the tremor-producing action of oxotremorine in mice (Moore *et al*, 1992).

Olanzapine (0.3–2.5 mg/kg i.p.) had very little effect on performance in a water maze swimming task. The rats took slightly longer to locate the platform at the highest dose tested (2.5 mg/kg), but there was no significant change in path length. Olanzapine (2.5 mg/kg) also reduced the speed of swimming significantly (Moore *et al*, 1997). This effect is similar to that reported for other compounds with dopamine antagonist properties (Scheel-Kruger, 1992). The anticholinergic, scopolamine, resulted in a marked increase in the time taken to escape, the path length and speed. These results demonstrate that although olanzapine possesses antimuscarinic activity *in vitro*, this does not lead to an anticholinergic-like deficit in a spatial memory task (Moore *et al*, 1997). Recently, Skarsfeldt (1996) also tested a number of the newer agents in a water maze. Sertindole and quetiapine had no effect over the dose range tested, whereas clozapine produced a deficit during the early trials. Risperidone and haloperidol also impaired performance,

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but, as in the earlier study, this only occurred at doses which also reduced the speed of swimming. Ziprasidone and olanzapine were also reported to produce deficits, independent of swim speed; however (particularly with olanzapine) this only occurred at the highest dose tested (2.5 mg/kg s.c.) (Skarsfeldt, 1996). Although the authors suggest that affinity for muscarinic receptors may contribute to the deficit, this is difficult to reconcile with the observation that ziprasidone, an agent without muscarinic affinity, also produced a similar deficit.

Table 6 Minimum effective dose (ED_{min} mg/kg) of olanzapine and various other agents for decreasing spontaneous activity or preventing PCP-induced (3 mg/kg) hyperactivity in mice

Compound	Spontaneous activity (ED_{min} mg/kg)	PCP-induced activity (ED_{min} mg/kg)	Ratio of spontaneous to PCP-induced
Clozapine	3.0	0.3	10
Haloperidol	0.3	0.1	3
LY53857	>3.0	0.1	>30
MDL 100,907	0.3	0.003	100
Olanzapine	1.0	0.03	33
Ritanserin	>1.0	0.01	>100

Data from Gleason & Shannon (1997).

Table 7 The effect of a number of antipsychotic agents on PCP-induced (20 mg/kg) and amphetamine-induced (2.5 mg/kg) hyperactivity in rats

Compound	PCP-induced activity (ED_{50} mg/kg)	Amphetamine-induced activity (ED_{50} mg/kg)
Clozapine	0.04	8.8
Haloperidol	0.13	0.04
Olanzapine	0.003	1.2
Risperidone	0.002	0.2
Quetiapine	0.33	21.7

Data from Maurel-Remy *et al*, 1995*b*.

Interactions with glutamatergic systems

A great deal of interest has recently focused on the role of the glutamatergic system in schizophrenia and the action of antipsychotic agents (for review see Olney & Farber, 1995). This interest is partly based on findings which suggest that there is an interaction between glutamatergic and dopaminergic neurons and that non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonists are psychotomimetic in man, inducing certain symptoms that are indistinguishable from those observed in sufferers from schizophrenia.

Hyperactivity induced by NMDA receptor antagonists

A number of reports have shown that newer agents with significant affinity for 5-HT_{2a} receptors antagonise the hyperactivity produced by the non-competitive NMDA glutamate receptor antagonists, phencyclidine (PCP) and MK-801 (Maurel-Remy *et al*, 1995*a*,*b*; Gleason & Shannon, 1987). Olanzapine, clozapine, risperidone and quetiapine antagonised hyperactivity induced by phencyclidine (PCP) at doses significantly lower than those reducing spontaneous activity or antagonising amphetamine-induced hyperactivity; a similar effect was observed with other 5-HT_{2a} antagonists, whereas haloperidol only reduced the response at doses similar to those inhibiting spontaneous activity or antagonising amphetamine hyperactivity (Tables 6 and 7) (Gleason & Shannon, 1997; Maurel-Remy *et al*, 1995*b*).

In view of the observation that the NMDA antagonist-induced hyperactivity is mediated via 5-HT_{2a} receptor activation, while the amphetamine response requires dopaminergic stimulation, these data confirm other reports (see above) that clozapine, olanzapine, risperidone and quetiapine preferentially antagonise 5-HT_{2a} function at doses lower than those which inhibit dopamine-mediated behaviours.

Glutamate and pre-pulse inhibition

Some patients with schizophrenia have an inability to filter or 'gate' extraneous auditory stimuli. This deficit can be modelled in animals by the administration of a number of central nervous system (CNS) agents such as apomorphine, amphetamine and DOI, resulting in reductions in the pre-pulse inhibition of a startle response (Swerdlow *et al*, 1996*a*). Reversal of this deficit appears to be pharmacologically specific, i.e. dopamine antagonists prevent apomorphine-induced disruption, while 5-HT_{2a} antagonists reverse the DOI-induced deficit (Varty & Higgins, 1995*a*; Swerdlow *et al*, 1994). NMDA antagonists such as PCP and MK-801 have also been shown to produce a similar deficit (Swerdlow *et al*, 1996*a*; Varty & Higgins, 1995*a*,*b*). This deficit is reversed by clozapine and the newer agents olanzapine and quetiapine, while 'typical' agents have little effect until high sedative doses are used (Varty & Higgins, 1995*a*,*b*; Bakshi & Geyer, 1995; Swerdlow *et al*, 1996*b*). At the moment, the data on risperidone are equivocal: one study demonstrated a reversal of an MK-801 deficit (Varty & Higgins, 1995*b*), while a second study failed to demonstrate an effect (Swerdlow *et al*, 1995*b*).

PCP-induced social isolation

PCP has also been shown to selectively inhibit the amount of time which pairs of rats spend displaying social behaviours. It is suggested that this deficit models some aspects of the negative symptoms of schizophrenia (Corbett *et al*, 1995). Olanzapine, like clozapine, was shown to restore the social interaction of animals pre-treated with PCP. Haloperidol and risperidone had little effect on social isolation at doses which did not suppress exploratory behaviour (Corbett *et al*, 1995). In a second study, a number of the newer agents were assessed for their ability to modify PCP-induced stereotypy and social isolation. Risperidone, sertindole, olanzapine or quetiapine was administered daily for either three or 21 days, and PCP (2 mg/kg) was administered for the last three days and the animals assessed in a social interaction test. All the agents reduced the PCP-induced stereotypy

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but had distinct effects on social isolation (Sams-Dodd, 1997). Sertindole partially reversed the PCP-induced social isolation at doses reversing the stereotypy, whereas haloperidol, risperidone and olanzapine did not normalise the level of active social interaction. However, the author comments that olanzapine may need to be tested at higher doses (Sams-Dodd, 1997). Quetiapine had very little effect on the PCP-induced social interaction deficit, although it has previously been reported to prevent amphetamine-induced deficits observed in primates (Ellenbroek *et al*, 1996). Further studies investigating the effects of these newer agents on NMDA antagonist-induced deficits in social behaviour are necessary to assess the test's true predictive validity as a model of 'negative' symptoms.

Other behavioural actions of the new agents

Drug discrimination studies

Drug discrimination studies can be used to establish the pharmacological similarities between compounds. Although a number of CNS agents act as discriminative stimuli (Colpaert & Slangen, 1982), 'typical' antipsychotics fail to produce robust stimuli (Goas & Boston, 1978; Browne & Koe, 1982; Moore *et al*, 1992; Wiley *et al*, 1992; Hoenicke *et al*, 1993). In contrast, clozapine appears to act as a discriminative stimulus in rats, pigeons and monkeys (Goas & Boston, 1978). Clozapine (5 mg/kg i.p. produced a discriminative stimulus which the animals learnt in fewer than 40 sessions (Moore *et al*, 1992). Olanzapine (0.3–5 mg/kg i.p.) produced responses appropriate to clozapine, seven out of the eight animals selecting the clozapine lever after 1.25–mg/kg i.p. (Moore *et al*, 1992). Other studies have reported a partial substitution. For example, olanzapine in monkeys produced a partial generalisation; however, total substitution occurred in the presence of the D_2 agonist PHNO, (+)-4-propyl-9-hydroxynaphthoxazine, suggesting that olanzapine's clozapine-like interoceptive actions were masked by dopamine D_2 antagonist activity. Interestingly, quetiapine fully substituted for clozapine, while the structurally unrelated agents, risperidone and sertindole, failed to substitute for clozapine (Carey & Bergman, 1997). A recent report has shown that olanzapine can also act as a discriminative stimulus; rats were trained to discriminate 0.5 mg/kg olanzapine from the vehicle (Porter & Strong, 1997), and in this study, clozapine 0.625–5 mg/kg produced a dose-related substitution. These observations demonstrate that olanzapine has discriminative stimulus properties similar to those of clozapine.

Schedule-controlled behaviour: Models of 'anxiety'; 'Negative' symptoms

(1) Conflict procedures. A number of reports have shown that clozapine differs from 'typical' antipsychotics in its effects on schedule-controlled behaviour (for review see Bruhwyler *et al*, 1990). For example, clozapine increased the punished response in rats, squirrel monkeys and mice (Wiley & Porter, 1993). Olanzapine has also been reported to increase punished responding in rats and pigeons (Moore *et al*, 1994; Benvenga & Leander, 1995; Nanry *et al*, 1995). Olanzapine (0.3–1.25 mg/kg) and clozapine (1.25–5 mg/kg) decreased, or had no effect on, the high response rates produced in the reward component, while the rates in the conflict period of a three-component conflict schedule were increased (Moore *et al*, 1994*b*). This type of profile was not observed with haloperidol or risperidone, which decreased the response rates in all components. In pigeons, both olanzapine (0.03–1 mg/kg) and clozapine (0.01–1 mg/kg) produced increases in punished responding (Benvenga & Leander, 1995). The increased responding observed in rats and pigeons with olanzapine were qualitatively similar to changes produced by the anxiolytic agent chlordiazepoxide, although the magnitude of the response was smaller (Moore *et al*, 1994). It is tempting to speculate that the release of suppressed behaviour may predict a compound's efficacy in reducing the negative symptoms of schizophrenia. However, clinical evaluation of new agents with similar properties will be necessary to test this hypothesis.

(2) Other 'models' of anxiety. Sertindole is reported to be active in the mouse black and white two-compartment box, the rat social interaction test and the marmoset human threat test, while being inactive in a modified Vogel conflict test (Sanchez *et al*, 1995). Sertindole's potency in the black and white box and social interaction assays is somewhat surprising, being significantly more active than diazepam (Sanchez *et al*, 1995). This level of activity does not appear to be related to any known pharmacological actions of the agent. Clozapine and risperidone show activity affecting the social interaction between pairs of unfamiliar rats at doses of 10 mg/kg and 0.062 mg/kg, respectively, whereas haloperidol and chlorpromazine were inactive (Corbett *et al*, 1993). The significance of these observations will only be understood when the newer agents have received extensive clinical assessment.

SUMMARY

In conclusion, the newer agents all have behavioural profiles which can be clearly differentiated from those of the older, classical agents. Behavioural data indicate that to a greater or lesser extent, all the newer antipsychotics will produce fewer acute EPS than the older agents. However, the new 'atypical' agents all have distinct profiles.

Olanzapine has a profile similar to that of clozapine, albeit somewhat more potent. Olanzapine, like clozapine, displays a wide margin between the doses predictive of efficacy and those which induce EPS. The compound also substitutes for clozapine in drug discrimination assays and increases punished responding in a conflict paradigm.

Quetiapine also has a clozapine-like profile, although it lacks the cholinergic receptor affinity and is relatively weak in most behavioural assays. Quetiapine, like olanzapine, also reverses PCP-induced deficits, and substitutes for clozapine in drug discrimination assays. However, no data are currently available regarding quetiapine's action in anxiolytic tests.

Risperidone, sertindole and ziprasidone have profiles of activity different from those of older agents, predominantly due to their 5-HT_{2a} affinity. All these agents possess some properties similar to those of clozapine, but there are some differences: for example, risperidone and sertindole fail to substitute for clozapine in drug discrimination assays and are inactive in classical conflict models of anxiety. It is more difficult to make an accurate assessment of the behavioural profile of ziprasidone, due to a lack of published data.

Given the behavioural differences exhibited by animals receiving the new antipsychotic agents, one would predict that these drugs will have distinct clinical profiles. All the agents display activity indicative of agents with a reduced propensity to induce EPS. However, significant differences may be observed in their efficacy

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against negative and cognitive symptoms. It will be important to assess the clinical profiles of these agents carefully if the predictive value of the pre-clinical 'models' is to be improved.

DECLARATION OF INTEREST

Nick Moore is an employee of Eli Lilly.

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