

Behavioral Pharmacology of Olanzapine: A Novel Antipsychotic Drug

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Background: In this paper, we review the behavioral pharmacology of olanzapine and compare it to its in vitro profile and to clozapine and a number of other antipsychotic agents, and we estimate the likelihood that olanzapine will be an effective and safe antipsychotic with fewer side effects. **Method:** Since there is no model of schizophrenia, per se, a battery of behavioral assays was used. **Results:** Behavioral assays confirmed the in vitro results that olanzapine interacts with dopamine, serotonin, and muscarinic receptor subtypes. Moreover, olanzapine appears to have a clozapine-like atypical profile based on (1) mesolimbic selectivity, (2) blocking 5-HT receptors at a lower dose than dopamine receptors, and (3) inhibiting the conditioned avoidance response (indicative of antipsychotic efficacy) at doses that are lower than those required to induce catalepsy (indicative of extrapyramidal side effects). Not only is this profile similar to that of clozapine, but olanzapine has other similarities: olanzapine substitutes for clozapine in a drug discrimination assay; like clozapine and unlike "typical" antipsychotics, olanzapine increases responding in a conflict procedure; and olanzapine, like clozapine, reverses changes induced by antagonists of the NMDA receptor. **Conclusion:** On the basis of these findings, we predict that olanzapine will be an efficacious antipsychotic, active against both positive and negative symptoms, while producing fewer extrapyramidal symptoms than existing treatments.

(*J Clin Psychiatry* 1997;58[suppl 10]:37-44)

The report by Bymaster et al. (this issue) discusses the in vitro and in vivo biochemistry of olanzapine (LY170053; Figure 1), a novel, antipsychotic drug candidate. That report demonstrates that olanzapine's interactions with neuronal receptors are multifaceted as demonstrated in both in vitro receptor binding assays and in vivo functional studies. Olanzapine has high affinity for dopamine (D₁, D₂, D₃, D₄, D₅), serotonin (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}), norepinephrine (α_1 -adrenergic), acetylcholine (m₁, m₂, m₃, m₄, m₅), and histamine (H₁) receptors. It is atypical in that it (1) shows mesolimbic selectivity and (2) has a higher affinity for 5-HT₂ than D₂ receptors.

In the present article, we present the behavioral pharmacology of this novel antipsychotic agent, compare the behavioral and functional consequences to the receptor profile, compare olanzapine's in vivo pharmacologic properties

with those of clozapine, and assess whether the biochemical and behavioral data support the conclusion that olanzapine is likely to be an efficacious and safe antipsychotic agent with fewer side effects than existing treatments.

Since there is no animal model of schizophrenia per se, evaluation of the behavioral pharmacology of a new antipsychotic drug candidate involves using a range of different tests that have predictive validity for antipsychotic efficacy or for potential side effects than existing treatment.

METHOD

The ability of olanzapine to antagonize dopamine receptors was evaluated in two assays that are based on an increase in dopaminergic function in vivo. These were climbing behavior (of mice) induced by the dopamine agonist apomorphine¹—a response that requires both D₁ and D₂ activation,² and hyperactivity induced by a stimulant (cocaine, amphetamine, or other stimulants).^{3,4} Antipsychotic efficacy was also assessed using a conditioned avoidance response.^{1,5}

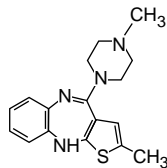
The potential for producing extrapyramidal side effects has also been assessed by induction of catalepsy^{1,6,7} and rat paw retraction test (hindlimb/forelimb retraction time).^{6,8}

The activity of olanzapine at serotonergic receptors was evaluated using head twitches induced by 5-HTP.¹ The consequences of olanzapine acting at muscarinic cholin-

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Presented at the closed symposium "Practical Issues in Using Olanzapine," held August 1-3, 1996, in Boston, Massachusetts, and made possible by an educational grant from Eli Lilly and Company.

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Figure 1. Structure of Olanzapine (LY170053)*

*2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine.

ergic receptors were evaluated using the Morris Water Maze Test, a spatial memory task.^{9,10}

Olanzapine has also been assessed in a prepulse inhibition test¹¹ based on PCP-induced deficits in "prepulse inhibition." This test is thought to mimic some of the symptoms of schizophrenia.¹¹

Olanzapine has also been evaluated in models that may relate to the negative symptoms of schizophrenia—social withdrawal models¹² based on PCP-induced social isolation and (conflict) behavior in a schedule-controlled setting.^{13,14}

Olanzapine's similarities to clozapine were evaluated in many of the above studies and also in a drug discrimination test^{5,15} and a PCP-induced hyperactivity test.^{16,17}

RESULTS AND DISCUSSION

Dopamine Receptors—Apomorphine-Induced Climbing

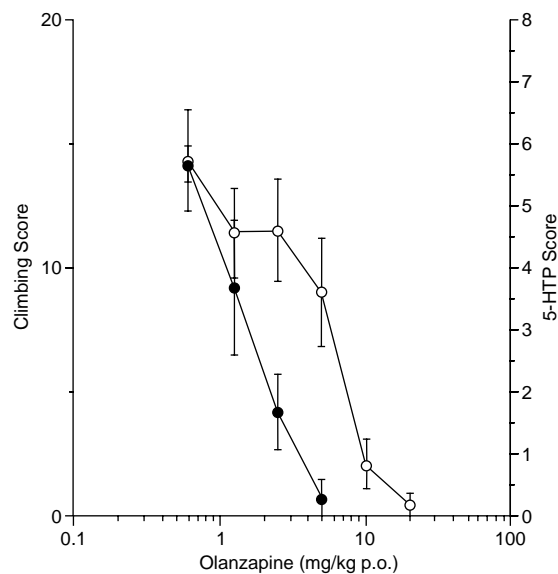
Figure 2 shows that olanzapine ($ED_{50} = 5$ mg/kg, p.o.) inhibits apomorphine-induced, climbing, in mice, in a dose-dependent manner. This demonstrates that olanzapine, in vivo, behaves as a dopamine antagonist.

Serotonin Receptors: Inhibition of 5-HTP-Induced Head Twitches

When mice are given the 5-HT precursor, 5-HTP, head twitches are induced, and this appears to be mediated by the 5-HT₂ receptor. Prior administration of olanzapine (1.25 to 10 mg/kg, p.o.; $ED_{50} = 2$ mg/kg) produced a dose-related reduction in this behavior (Figure 2), confirming the biochemical data that olanzapine preferentially antagonizes 5-HT₂ compared to dopamine receptors.

Muscarinic Cholinergic Receptors

According to the report by Bymaster et al. (this Supplement),²⁷ olanzapine is also a potent inhibitor of ligand binding to brain muscarinic cholinergic receptors in vitro. In vitro (1) olanzapine also blocks oxotremorine-induced release of arachidonic acid; (2) olanzapine ex vivo inhibits the binding of the muscarinic radioligand [³H]pirenzepine; (3) olanzapine lowers concentrations of striatal but not hippocampal acetylcholine levels; and (4) olanzapine inhibits oxotremorine-induced tremor,⁵ but only at higher doses. It therefore seemed possible that olanzapine functions in vivo as a muscarinic antagonist.

Figure 2. Effect of Olanzapine on Apomorphine-Induced Climbing Behavior (open symbols) or 5-HTP-Induced Head Twitch (closed symbols) in Mice*

*Reprinted from Moore et al, 1993.¹ Each point represents the mean \pm SE for groups of eight or nine mice.

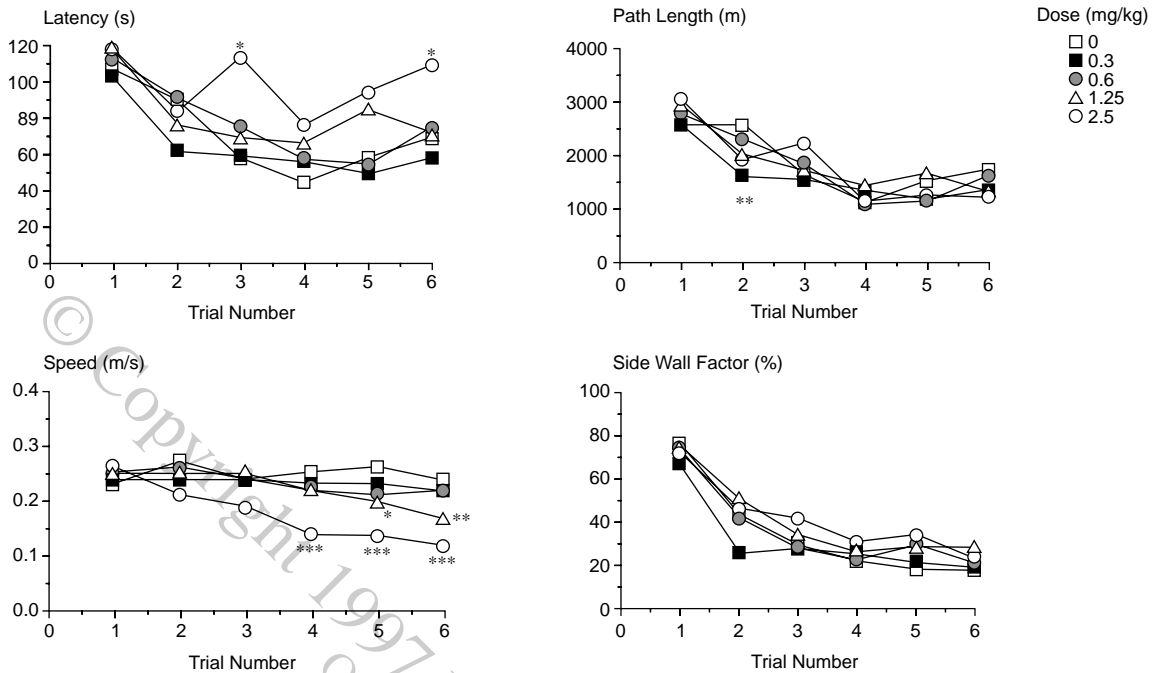
Accordingly, we evaluated the effects of olanzapine in an assay that can be disrupted by anticholinergic agents, namely, the Morris Water Maze Test in which acquisition of a spatial memory trace is necessary. In this task, rats are trained to locate a hidden (submerged) platform in a water-filled tank.¹⁰

Figure 3 shows that olanzapine had very little effect on performance. There was a slight increase in latency to locate the platform at the highest dose tested (2.5 mg/kg), without a significant change in path length. Olanzapine 2.5 mg/kg also produced a significant reduction in swim speed. This effect is similar to that reported for other compounds with dopamine antagonist properties. The anticholinergic scopolamine produced a marked increase in escape latency, path length, and speed (Figure 4). 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.

Therapeutic Index: Mesolimbic Selectivity

It is generally thought that mesolimbic dopamine receptors mediate the therapeutic effects of antipsychotic drugs while striatal dopamine receptors mediate their extrapyramidal side effects. Thus, any tendency of a drug to preferentially or selectively interact with mesolimbic dopamine receptors would suggest that the drug in question would have fewer extrapyramidal side effects. It is thus of importance that earlier studies on olanzapine have suggested that it may have mesolimbic selectivity (see Bymaster et al,²⁷ this issue).

Figure 3. Effect of Olanzapine on Latency, Path Length, Swim Speed, and Side Wall Factor in a Water Maze†



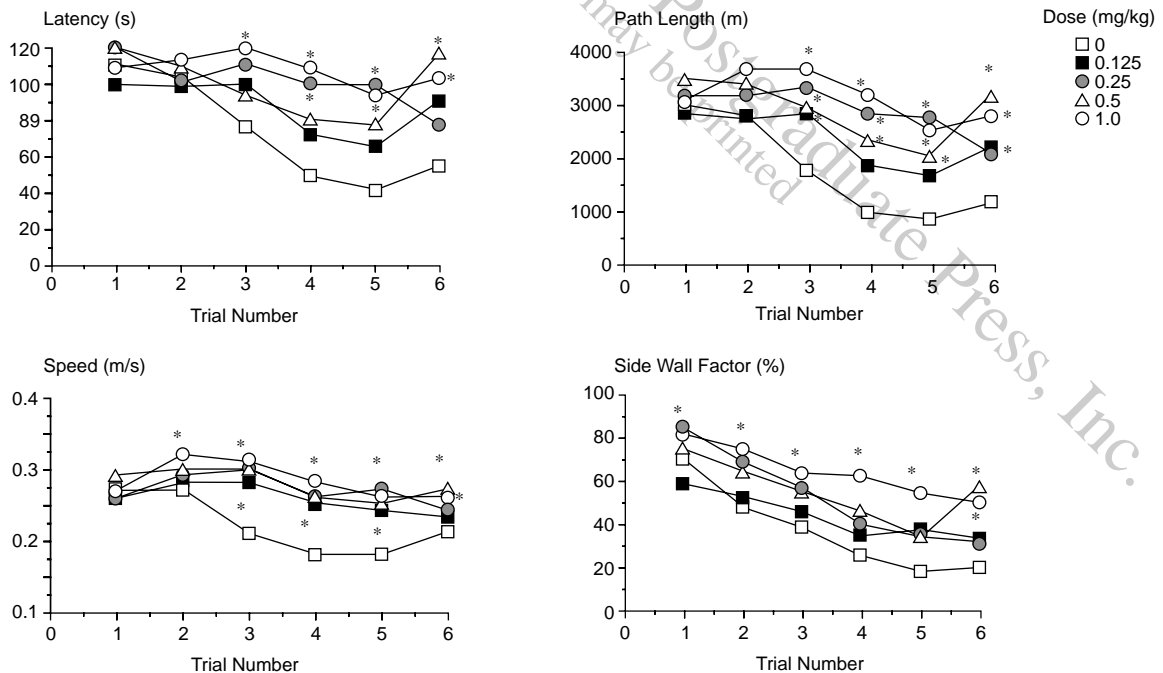
†Data from reference 10. The results are expressed as the mean \pm SE for groups of 10 rats.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Figure 4. Effect of Scopolamine on Latency, Path Length, Swim Speed, and Side Wall Factor in a Water Maze†



†Data from reference 10. The results are expressed as the mean \pm SE for groups of 10 rats.

* $p < .05$.

One can also generate data indicative of mesolimbic selectivity for olanzapine using assays for inhibition of stimulant-induced hyperactivity. For example, a recent report⁴ indicated that a number of newer antipsychotic agents, including olanzapine, preferentially block the hypermotility induced by a low dose of amphetamine (0.5 mg/kg) compared to a higher dose of amphetamine (2.0 mg/kg), while typical antipsychotic agents failed to demonstrate the same degree of selectivity. The reason this suggests mesolimbic selectivity is that it is well known that low doses of dopamine agonists stimulate locomotor behavior (walking, running) which is thought to be mediated by mesolimbic dopamine receptors; high doses of the same dopamine agonists stimulate stereotypic behaviors (sniffing, licking, gnawing, etc.) that are believed to be mediated by dopamine receptors in striatum.⁴

In our own laboratory, olanzapine (2.5 to 10 mg/kg) produced, in rats, a significant reduction of cocaine (20 mg/kg, i.p.)-induced hyperactivity, whereas olanzapine did not antagonize hyperactivity induced by amphetamine (2.5 mg/kg, i.p.).³ It could be argued that the cocaine data represent increased locomotion involving activity of mesolimbic dopamine receptors, whereas the amphetamine data, at the particular amphetamine dose used, reflect increased stereotypic behaviors mediated by striatal dopamine receptors.

Therapeutic Index: Other Tests

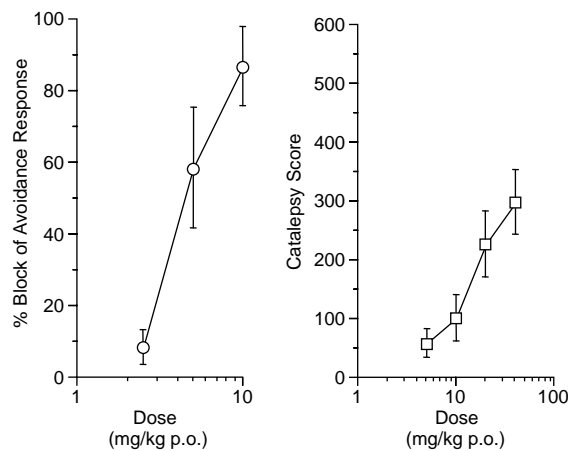
Although biochemical and behavioral data suggest that olanzapine may have antipsychotic properties, this can also lead to motor disturbance because dopamine receptors mediate both efficacy and extrapyramidal side effects of antipsychotic drugs. The Therapeutic Index (TI) was therefore determined (TI = difference between efficacy dose vs. dose producing EPS). One way to evaluate the TI is to divide the dose causing extrapyramidal side effects (or its experimental surrogate) by the efficacious dose (or its experimental surrogate). Such a comparison will indicate the extent to which olanzapine can be clinically used at a dose that is therapeutic yet low enough to avoid extrapyramidal side effects. The ability to block the conditioned avoidance response (which is thought to predict efficacy) without inducing catalepsy (which predicts extrapyramidal side effects) would suggest a high TI.

Conditioned Avoidance Versus Catalepsy

Inhibition of a conditioned avoidance response has been widely used as a test predictive of antipsychotic potential, while the induction of catalepsy in rats is predictive of extrapyramidal symptoms in the clinic.^{6,7,18} Thus, by comparing the dose required to antagonize conditioned avoidance or to induce catalepsy, it is possible to obtain some indication of the likely therapeutic index of a new agent.

In the conditioned avoidance test, animals are trained to move from one side of a box to the other upon hearing a

Figure 5. Effect of Olanzapine on Conditioned Avoidance Responding in Rats (left panel)^a and Olanzapine-Induced Catalepsy in Rats (right panel)^{b*}



*Reprinted with permission from Moore et al, 1992.⁵

^aResults are expressed as the mean \pm SE percentage block of avoidance responding for groups of seven rats.

^bResults are expressed as the mean \pm SE total catalepsy time assessed at hourly intervals for 5 hours. A score of 600 is the maximum possible for each animal.

tone. If they do not move when they hear the tone, they get a mild shock through the grid floor, and then they can escape by moving to the other side of the cage. Well-trained animals will avoid the shock by responding after hearing the tone. Dopamine antagonists block this trained response and thus decrease avoidance responding.

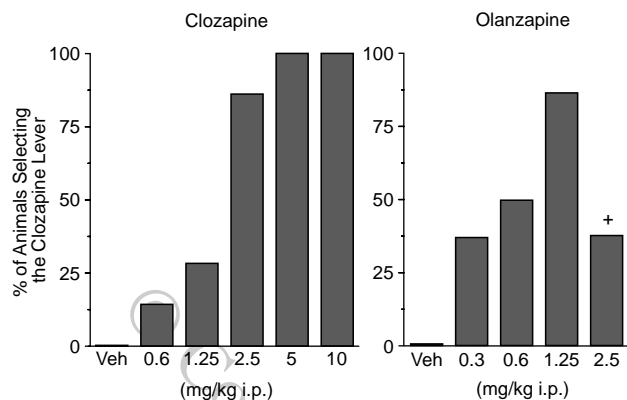
Figure 5 shows that olanzapine can induce almost 100% block of the conditioned avoidance response (CAR), suggesting potential antipsychotic efficacy.⁵ Moreover, the figure shows that at a dose of olanzapine (10 mg/kg) that produces nearly 100% inhibition of avoidance, there is very little induction of catalepsy (CAT; relative immobility in rats). From these data we have generated ED₅₀ values for these effects (CAR: 4.7 [95% CI: 3.6 to 6.1] mg/kg; CAT: 39.4 [95% CI: 24.5 to 63.2] mg/kg; CAT/CAR ratio = 8.4).⁵ These data suggested that olanzapine will be less likely to induce EPS at therapeutic doses.

For typical antipsychotics such as haloperidol (CAR: 0.5 [95% CI: 0.4 to 0.6]; CAT: 1.1 [95% CI: 1.0 to 1.3]; CAT/CAR ratio = 2.6), there is less separation between the dose that inhibits avoidance responding and the dose that induces catalepsy. And clinically, too, typical antipsychotics such as haloperidol elicit extrapyramidal side effects to a greater degree than atypical antipsychotics such as clozapine.⁵ It is interesting to note that clinically olanzapine produces significantly less EPS than haloperidol (see Beasley, et al. this issue²⁸).

Paw Test (HRT) Versus Paw Test (FRT)

In the rat paw retraction test,⁶ olanzapine produced a similar "atypical"-like profile to that of clozapine, increas-

Figure 6. Effect of Clozapine or Olanzapine in Rats Trained to Discriminate 5.0 mg/kg i.p. Clozapine From Vehicle*



*Reprinted from Moore et al, 1992.⁵ Each column represents the percentage of animals selecting the clozapine appropriate lever. “+” denotes a marked disruption in responding.

ing hindlimb retraction time (HRT) at doses much lower ($ED_{min} = 0.5$ mg/kg) than those necessary to increase forelimb retraction time (FRT) ($ED_{min} = 10$ mg/kg).⁸

On the basis of these observations, it is likely that olanzapine will have a wide therapeutic index and produce fewer extrapyramidal side effects than typical antipsychotic agents.

Other Clozapine-Like Actions of Olanzapine

Other assays have been used to evaluate similarities between olanzapine and clozapine, and we will discuss several of them including (1) drug discrimination (clozapine discrimination) in rats; (2) schedule-controlled behavior (conflict behavior) in rats; and (3) effects of olanzapine on the ability of antagonists at the NMDA glutamate receptor to induce behavioral changes as assessed by (a) PCP-induced deficits in prepulse inhibition, (b) PCP-induced social isolation, and (c) PCP-induced hyperactivity.

Drug discrimination (clozapine discrimination) in rats. The question being asked is: Does olanzapine have a clozapine-like action in a clozapine drug discrimination assay? Drug discrimination studies can be used to establish the pharmacologic similarities between compounds.¹⁹ Clozapine provides a discriminative stimulus in this assay^{20,21} in which rats are trained to discriminate an injection of clozapine from an injection of vehicle. When clozapine (5 mg/kg, i.p.) is administered, they press one lever for food reward. When vehicle is administered, they press a different lever and again are rewarded for a correct response. Over a period of about 40 days the animals learned to discriminate clozapine from vehicle.¹⁵

Seven of eight animals trained on clozapine but then treated only with olanzapine (1.25 mg/kg) selected the clozapine lever (Figure 6).⁵ The animals apparently perceived some property of olanzapine as being similar to that of clozapine. At higher olanzapine doses, the rate of

responding goes down as does the discrimination, both probably due to the effect of dopamine receptor antagonism on motor function.

Schedule-controlled behavior (conflict behavior) in rats. Another test in which olanzapine shows a profile of activity very similar to clozapine is in a schedule-controlled conflict behavior model which is normally a test associated with anxiolytic-like activity.

There are three components to this test. In the first component, animals are trained to press a lever for food reward (Figure 7). During the second component, the time-out component, all the lights are turned off, the animal is in darkness, and there are no programmed consequences. In the third or “conflict” component, every tenth press receives a food pellet, but, at the same time, the animal gets a mild shock through the grid floor. Thus, a conflict is established between wanting to obtain the food and wanting to avoid the shock. This conflict suppresses baseline responding.

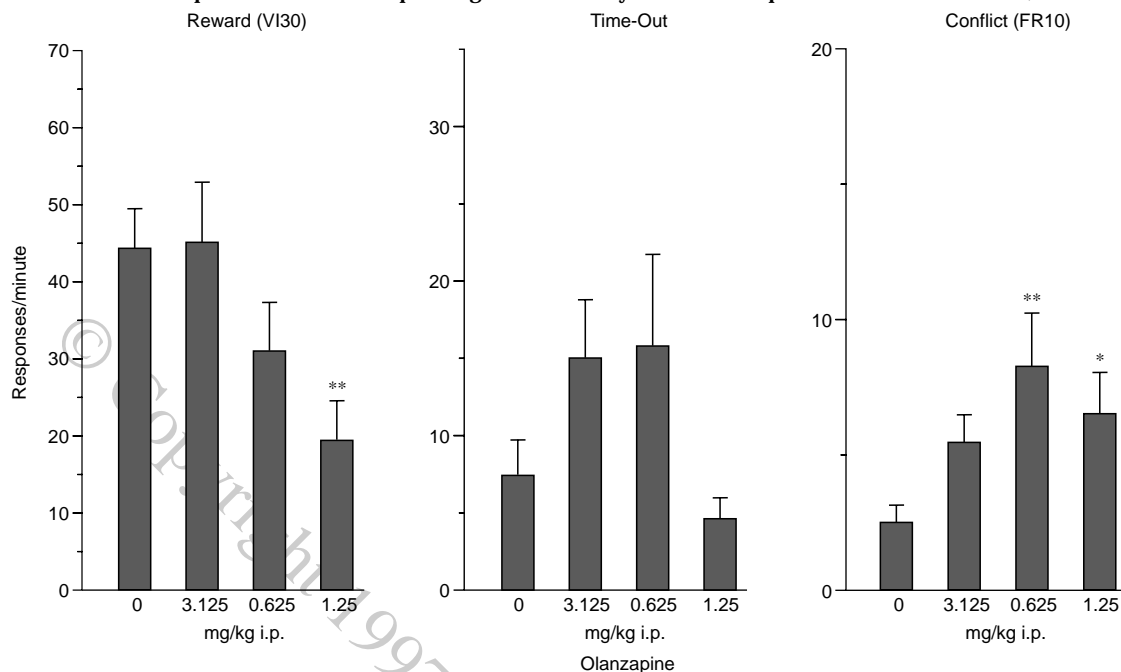
A number of reports have shown that clozapine differs from “typical” antipsychotics in its effects on schedule-controlled behavior (for review, see Bruhwyler et al.²²). For example, clozapine increased punished responding in rats, squirrel monkeys, pigeons, and mice.^{5,13,23,24}

When we administered clozapine, it produced a dose-related reduction of responding in the reward component. There was also a slight, nonsignificant effect on the time-out responding. Finally, there was a small but significant increase in responding during the conflict component.^{5,14} This last effect of clozapine was smaller than what would be observed if an anxiolytic such as a benzodiazepine were used, but the clozapine effect is very reproducible.^{5,13,23,24} In contrast, haloperidol, a “typical” antipsychotic drug, decreased the rate of responding during all three components.¹⁴

Figure 7 shows the effect of olanzapine in this model. Similar to clozapine, olanzapine (1.25 mg/kg) suppressed responding during the reward period. There was a slight effect during the time-out component. But, during the conflict component, there was a clear increase in responding, similar to the effect of clozapine.^{5,14} Similar results have also been reported in rats and pigeons.^{13,25} Hence, during the conflict phase, there is a suppression of baseline responding, and agents like clozapine and olanzapine disinhibit this suppression, releasing the behavior. Although speculative, it is interesting to consider the possibility that the effects of these atypical antipsychotics in this assay are related to their effectiveness in treating the negative symptoms of schizophrenia. Of course, such a hypothesis needs rigorous testing that includes other agents that are also effective against negative symptoms.

Effects of olanzapine on the ability of antagonists at the NMDA glutamate receptor to induce behavioral changes: (a) PCP-induced deficits in prepulse inhibition, (b) PCP-induced social isolation, (c) PCP-induced hyperactivity. There has recently been increased interest in the role of glutamate and glutamate receptors in schizophrenia (for

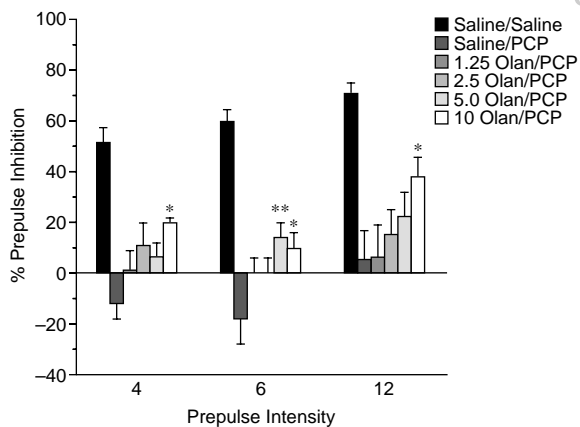
Figure 7. Effect of Olanzapine on Rates of Responding Maintained by a Three-Component Conflict Schedule†



†Redrawn from Moore et al, 1994.¹⁴ Each column represents the mean ± SE rate of responding for groups of 24 rats.

*p < .05.
**p < .01.

Figure 8. Effects of Olanzapine on Phencyclidine (PCP)-Induced Deficits in Prepulse Inhibition (PPI)†



†Reprinted with permission from Bakshi and Geyer, 1995.¹¹

Values represent mean ± SE for each treatment.

*p < .05, **p < .01 compared to Saline/PCP group.

review see Olney and Farber²⁶). For instance, some non-competitive NMDA glutamate receptor antagonists such as phencyclidine (PCP) are psychotomimetic in man, inducing certain symptoms that are indistinguishable from schizophrenia.

PCP-induced deficits in prepulse inhibition. One hallmark of schizophrenia is the inability of patients to filter or “gate” extraneous auditory stimuli. This deficit,

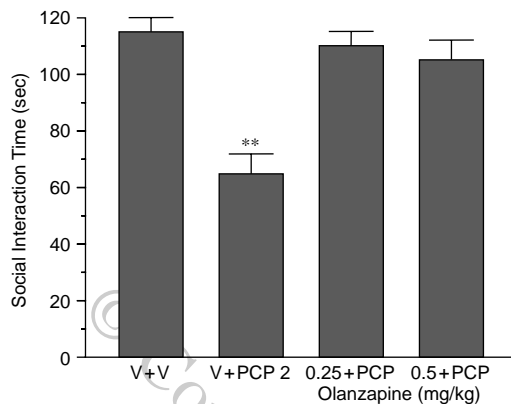
which can be modeled in animals by administration of *d*-amphetamine or noncompetitive NMDA antagonists such as PCP, results in a decrease in the prepulse inhibition (PPI) of the startle reflex. In animal studies, preadministration of olanzapine or clozapine—but not administration of “typical” antipsychotic agents—negated the PCP-induced deficit in PPI (Figure 8¹¹).

PCP-induced social isolation. PCP has also been shown to induce a syndrome of social isolation in rats, a possible model of some aspects of the negative symptoms of schizophrenia. Corbett et al.¹² reported that PCP reduced the amount of time pairs of rats interacted without affecting overall rates of activity. Clozapine and olanzapine reversed this deficit while the other agents tested had no effect (Figure 9).

PCP-induced hyperactivity. PCP also induces a hyperactivity syndrome in rats and mice that is reversed by “atypical” antipsychotic agents such as clozapine and olanzapine (Table 1). The PCP-induced hyperactivity is also antagonized by 5-HT₂ antagonists, suggesting that the antagonism observed with olanzapine and clozapine is probably related to their 5-HT₂ antagonist properties.^{16,17}

SUMMARY

As an antipsychotic, olanzapine appears to have an atypical profile. This is based on the fact that (1) it shows mesolimbic selectivity, (2) it preferentially blocks 5-HT

Figure 9. Effect of Olanzapine on PCP-Induced Social Deficits in Rats in a Social Interaction Paradigm†

†Reprinted with permission from Corbett et al, 1995.¹² Abbreviations: V = vehicle, 2 = 2 mg/kg PCP.

***p* < .01 compared to V + V group one-way ANOVA followed by Dunnett's test.

Table 1. Minimal Effective Doses (ED_{min}, mg/kg) of Olanzapine and Various Other Agents for Decreasing Spontaneous Activity or Antagonizing Hyperlocomotion Produced by 3 mg/kg Phencyclidine (PCP) in Mice*

Compound	Spontaneous Activity (ED _{min} , mg/kg)	PCP-Induced Hyperactivity (ED _{min} , mg/kg)	Spon/PCP
Olanzapine	1.0	0.03	33
Clozapine	3.0	0.3	10
Ritanserin	> 1.0	0.01	> 100
LY53857	> 3.0	0.1	> 30
MDL 100,907	0.3	0.003	100
Haloperidol	0.3	0.1	3

*Reprinted from Gleason and Shannon, 1997.¹⁷ The ratio of ED_{min} for decreasing spontaneous activity to antagonizing PCP-induced hyperlocomotion is also indicated.

receptors compared to dopamine receptors, and (3) it inhibits the conditioned avoidance response (predictive of antipsychotic efficacy) at doses that are much lower than those required to induce catalepsy (predictive of extrapyramidal side effects). In addition to these characteristics, olanzapine has many similarities to clozapine, which is known to be atypical. Thus, olanzapine's receptor profile (see Bymaster et al.,²⁷ this issue), like that of clozapine, is one which shows high affinity interactions with a broad range of neuronal receptors (dopamine, 5-HT, α -adrenergic, histamine, muscarinic cholinergic). Olanzapine also substitutes for clozapine in a drug discrimination assay. Also, unlike "typical" antipsychotics, olanzapine increases responding in a conflict behavioral model. In addition, olanzapine, like clozapine, reverses changes induced by antagonists of the NMDA receptor, changes that may model some of the negative symptoms of schizophrenia (e.g., social isolation). Based on this behavioral profile, we would predict that olanzapine will be an efficacious antipsychotic, effective against both positive and

negative symptoms while producing few extrapyramidal side effects.

Drug names: clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa).

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