Olanzapine: a basic science update

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Olanzapine, an atypical antipsychotic, has a broad receptor binding profile, which may account for its pharmacological effects in schizophrenia. *In vitro* receptor binding studies showed a high affinity for dopamine D_2, D_3, and D_4 receptors; all 5-HT_2 receptor subtypes and the 5-HT_6 receptor; muscarinic receptors, especially the M_1 subtype; and α_1-adrenergic receptors. *In vivo* studies showed that olanzapine had potent activity at D_2 and 5-HT_{2A} receptors, but much less activity at D_1 and muscarinic receptors, and that it inhibited dopaminergic neurons in the A10 but not the A9 tract, suggesting that this agent will not cause extrapyramidal side-effects (EPS). Microdialysis studies showed that olanzapine increased the extracellular levels of norepinephrine and dopamine, but not 5-HT, in the prefrontal cortex, and increased extracellular dopamine levels in the neostriatum and nucleus accumbens, areas of the brain associated with schizophrenia. Studies of gene expression showed that olanzapine 10 mg/kg also increased Fos expression in the prefrontal cortex, the dorsolateral striatum, and the nucleus accumbens. These findings are consistent with the effectiveness of olanzapine on both negative and positive symptoms and suggest that, with careful dosing, olanzapine should not cause EPS.

Schizophrenia is a disorder that involves many neurotransmitter systems, and differences in the expression and distribution of neurotransmitter receptor subtypes in various regions of the brain may account for the complex effects of drugs used to treat psychiatric disorders. Typical antipsychotic compounds, such as haloperidol, bind primarily to dopamine receptors, while the atypical antipsychotic agents, such as clozapine, interact with a number of these neurotransmitter systems through binding at multiple receptor sites. Dopamine receptor binding does not account for all the actions of atypical antipsychotic agents. Indeed, the broad receptor binding profile of clozapine may be responsible for its impressive clinical efficacy in schizophrenia and its lack of extrapyramidal side-effects (EPS). The atypical antipsychotic agent olanzapine also interacts with a number of different neurotransmitter systems. These interactions may provide insight into olanzapine's beneficial activity in schizophrenia.

OLANZAPINE RECEPTOR BINDING *IN VITRO*

The many differences in binding profiles of antipsychotic compounds probably contribute to their great pharmacological diversity. Olanzapine has a broad receptor binding profile as has been shown by *in vitro* radioreceptor binding studies (Table 1).

With respect to dopamine receptors, olanzapine has particularly high affinity for the D_2, D_3, and D_4 subtypes and lower

Table 1 Binding affinities of olanzapine, clozapine and haloperidol for dopamine, serotonin, muscarinic, adrenergic and histamine receptor subtypes (adapted from Bymaster *et al*, 1996*a*; Calligaro *et al*, 1996; Roth *et al*, 1994; and Schickler & Marr, 1996)

Receptor	Olanzapine (K_i, nM)	Clozapine (K_i, nM)	Haloperidol (K_i, nM)
D_1	119±20	85±0.7	25±7
D_2	20±8	125±20	1±0.04
D_3	16±3	84±12	5±1
D_4	26±1.2	47±4	1.6±0.2
D_5	51±2	85±21	12±0.7
5-HT_{1A}	>1000	770±220	7930±500
5-HT_{2A}	2.5±0.4	6.5±0.4	58±16
5-HT_{2B}	11±2	7±1	1450±140
5-HT_{2C}	29±4	36±1	12 375±2650
5-HT_3	57±6	69±8	>1000
5-HT_4	>1000	>1000	–
5-HT_6	2.5±9	4±0.7	>5000
5-HT_7	104±12	6.3±3.7	263±41
M_1	1.9±0.1	1.9±0.4	1475±300
M_2	18.5±5	10±1	1200±180
M_3	25±2	14±1	1600±305
M_4	10±0.6	6±0.5	>1500
M_5	6±0.8	5±1.2	8120±912
α_1-adrenergic	19±1	7±4	46±6
α_2-adrenergic	230±40	8±3	360±100
β-adrenergic	>10 000	>10 000	>10 000
H_1	7±0.3	6±2	3630±85
H_2	>1000	>1000	–
H_3	>1000	708	–

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affinity for the D_1 and D_5 subtypes, a pattern somewhat similar to that of clozapine (Bymaster *et al*, 1996*a*; Calligaro *et al*, 1996). In contrast, the dominant domain of haloperidol is the D_2 receptor. Haloperidol's very effective blockade of this receptor may explain why it causes EPS. In functional studies, the effect of olanzapine on dopamine D_1-receptor-stimulated adenylate cyclase activity in the rat retina was compared with that of the selective D_1-receptor antagonist Sch23390 (Truex, personal communication). Sch23390 effectively antagonised D_1-receptor-stimulated adenylate cyclase activity; olanzapine also blocked adenylate cyclase activity, but only at much greater concentrations, suggesting that its potency to block D_1-receptors is modest.

With respect to serotonin (5-HT) receptors, olanzapine has particularly high affinity for all 5-HT_2 subtypes (particularly the 5-HT_{2A} subtype) and the 5-HT_6 receptor (Roth *et al*, 1994), but it possesses modest affinity for the 5-HT_3 receptor. Clozapine has a similar profile, but it has a high affinity for the 5-HT_7 receptor as well (Roth *et al*, 1994). Among atypical antipsychotic agents, risperidone and ziprasidone also have very high affinities for the 5-HT_{2A} subtype. The functional effects of olanzapine, clozapine, and haloperidol at 5-HT_2 receptor subtypes were studied by determining the effect of these compounds on 5-HT-induced inositol triphosphate formation in AV12 cells transfected with 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptor subtypes (Lucaites *et al*, 1995). The compounds had no agonist effects at 5-HT_2 receptors, but olanzapine and clozapine effectively blocked the 5-HT_{2A} and 5-HT_{2B} receptors. Surprisingly, they did not effectively block the 5-HT_{2C} receptor, despite fairly good binding affinity.

The interaction between olanzapine and muscarinic receptors remains controversial. Nevertheless, in radioreceptor binding studies, olanzapine has been found to have very high affinity for muscarinic receptors, particularly the M_1 subtype (Bymaster *et al*, 1996*a*). Clozapine has a very similar profile, whereas haloperidol is essentially inactive at muscarinic receptors. Olanzapine and clozapine are clearly antagonists at the M_1, M_2, M_3, and M_5 subtypes. Some data suggest that both may have some agonist activity at the M_4 subtype (Zeng *et al*, 1997), but possibly only in cell lines that have large receptor reserves. We have found that neither olanzapine nor clozapine had any agonist activity at any muscarinic receptor subtype (Lucaites *et al*, 1995; Bymaster *et al*, 1996*c*). Perhaps these compounds act as very weak partial agonists or as antagonists at the M_4 receptor *in vivo*. Olanzapine is about 1/100 as potent as atropine at blocking increases in second messengers at the M_1–M_5 subtypes induced by muscarinic agonists, suggesting that olanzapine is only a weak antagonist at the muscarinic receptors.

Olanzapine, and especially clozapine, have high affinity for α_1-adrenergic receptors, but olanzapine has much lower affinity than clozapine for α_2-adrenergic receptors (Bymaster *et al*, 1996*a*). The low affinity of olanzapine for α_2-adrenergic receptors may result in reduced cardiovascular side-effects. Olanzapine and clozapine both have low affinity for β-adrenergic receptors, and both agents have high affinity for the histamine H_1 receptor but not for histamine H_2 and histamine H_3 receptors (Schickler & Marr, 1996).

Olanzapine has been found to have very little affinity for a number of other receptors (some of which are implicated in schizophrenia), uptake transporters, and enzymes (Table 2). For example, olanzapine's low affinity for ion-channel receptors, including the MK-801 and phencyclidine binding sites, may limit certain side-effects.

Table 2 Receptors, enzymes and key neuronal proteins for which the affinity of olanzapine is low ($IC_{50} > 1$ μm)

Receptors
Adenosine, purinergic
$GABA_A$ and $GABA_B$, benzodiazepine
Glutamate (AMPA, kainate, NMDA)
Glycine
Nicotinic (neuronal)
Sigma (nonselective)
Opiate (μ, κ, δ)
Peptide (CCK_A, CCK_B, NK1, NK2, NPY, NT)
Ion channel receptors
Ca^{++} (L and N)
Cl^-
Glutamate (MK-801, PCP)
Na^{++} (APT, Ca, Volt+ and −)
Uptake transporters
Choline, GABA, norepinephrine, 5-HT, dopamine
Enzymes
Acetylcholinesterase
Choline acetyltransferase
MAO A and B

IN VIVO STUDIES

A better understanding of olanzapine's activity at, and interaction with, receptors *in vivo* may provide insight into this compound's effects in schizophrenia.

Activity

Increased serum corticosterone concentrations can be induced in an animal model by stimulation of D_2 receptors with pergolide or by stimulation of 5-HT_2 receptors (probably 5-HT_{2A}) with the 5-HT_2 agonist quipazine. Using this model, Fuller & Snoddy studied the antagonist effects of olanzapine, clozapine, and haloperidol at the D_2 and 5-HT_2 receptors (Fuller & Snoddy, 1992). One hour after administration of one of the three antipsychotic agents and one hour before measurement of the serum corticosterone levels, pergolide mesylate (0.3 mg/kg) was injected intraperitoneally or quipazine maleate (2.5 mg/kg) subcutaneously. Clozapine was relatively ineffective in inhibiting the pergolide-induced D_2-receptor-mediated increase in serum corticosterone, but effectively blocked the quipazine-induced increase in serum corticosterone. In contrast, haloperidol was only active in blocking the D_2-mediated increase in serum corticosterone. Olanzapine effectively blocked both D_2- and 5-HT_{2A}-mediated increases in serum corticosterone and was more potent at the 5-HT_{2A} receptor (Table 3).

The A10 dopamine tract, which projects from the ventral tegmental area to the mesolimbic area, is thought to be involved in schizophrenia. A key finding in schizophrenia research has been that chronic administration of clozapine selectively decreases the spontaneous firing of dopaminergic cells in the mesolimbic A10 tract. On the other hand, excessive blockade of the A9 dopamine tract, which projects from the substantia nigra to the motor areas in the striatum, is thought to cause EPS. A number of studies have shown that chronic treatment with clozapine produces no inhibitory effect on the nigrostriatal A9 motor tract. This is consistent with the efficacy of clozapine in schizophrenia and the lack of EPS.

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Table 3 Antagonism of pergolide (D_2)- and quipazine (5-HT_{2A})-induced increase in serum corticosterone by antipsychotic agents[1] (Bymaster *et al*, 1997*b*, derived in part from Fuller & Snoddy, 1992) (Reproduced by kind permission of Physicians Postgraduate Press)

Compound	Pergolide-induced (ED_{50}, mg/kg IP)	Quipazine-induced (ED_{50}, mg/kg SC)
Olanzapine	3	0.57
Clozapine	>10	2.6
Haloperidol	0.18	>1

1. Pergolide mesylate (0.3 mg/kg IP) or quipazine maleate (2.5 mg/kg SC) was injected in an animal model 1 hour after antipsychotics and 1 hour prior to sacrifice: IP, intraperitoneal administration; SC, subcutaneous administration.

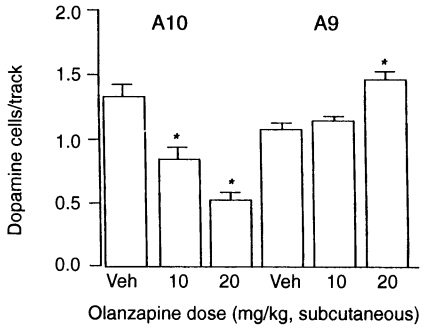


Fig. 1 Effect of chronic treatment with olanzapine on the number of spontaneously firing dopamine cells in the substantia nigra (A9) and ventral tegmental areas (A10) of rats. Olanzapine was administered in osmotic minipumps at the indicated doses for 21 days: *$P<0.001$ (Stockton & Rasmussen, 1996). (Reproduced by kind permission of the American College of Neuropsychopharmacology.)

Stockton & Rasmussen (1996) conducted electrophysiological studies of olanzapine's effect on the A10 and A9 tracts. Olanzapine administered for 21 days inhibited spontaneous firing of dopaminergic neurons in the A10 tract in a dose-related manner, whereas there was no inhibition and, in fact, some stimulation of dopaminergic neurons in the A9 tract (Fig. 1). A review of the literature showed that chronic administration of antipsychotic compounds inhibited firing of A10 dopaminergic neurones (Skarsfeldt, 1995; Stockton & Rasmussen, 1996). However, chronic administration of the typical antipsychotic agents haloperidol and chlorpromazine also inhibited firing of A9 dopaminergic neurons. Olanzapine, clozapine, and sertindole have no effect on the A9 tract, which suggests that these agents will not cause EPS. The only reported study of the affects of ziprasidone and risperidone on the A9 tract showed that these agents inhibited firing of A9 dopaminergic neurons. Whether quetiapine inhibits the A9 tract remains controversial.

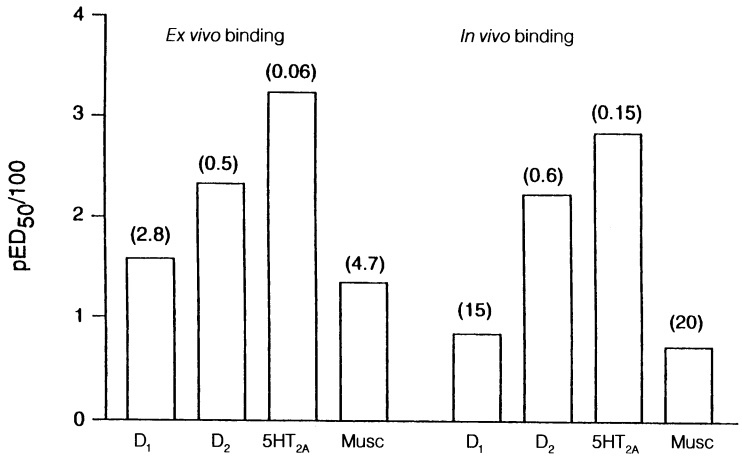


Fig. 2 Receptor occupancy of olanzapine using *ex vivo* autoradiography and *in vivo* binding techniques. Values are pED_{50}/100 and numbers in parentheses are actual effective dose (ED_{50}) values. *Ex vivo* autoradiography was determined after administration of olanzapine subcutaneously for 2 hours (Schotte *et al*, 1996). *In vivo* receptor occupancy was determined by giving olanzapine intraperitoneally 15–30 min prior to administration of ^{3}H-SCH23390 (D_1), ^{3}H-raclopride (D_2), ^{3}H-spiperone (5-HT_{2A}), and ^{3}H-QNB (muscarinic); rats were killed at specified times thereafter. Specific binding was determined in the striatum for D_1 and D_2 receptors, frontal cortex for 5-HT_{2A}, and hippocampus for muscarinic receptors. D, dopamine; Musc, muscarinic.

Receptor binding

Receptor binding studies using *ex vivo* autoradiography (Fig. 2) have demonstrated that olanzapine *in vivo* occupies 5-HT_{2A} and dopamine D_2 receptors with much higher potency than muscarinic or D_1 receptors (Schotte *et al*, 1996). A study was conducted to compare the *in vivo* occupancy of olanzapine for D_1, D_2, muscarinic, and 5-HT_{2A} (in the frontal cortex) receptors in rats by inhibition of ^{3}H-radioligand binding with Sch23390, raclopride, quinuclidinyl benzilate (QNB), and spiperone, respectively (Bymaster *et al*, 1997*a*). The results showed that olanzapine potently inhibited both D_2- and 5-HT_{2A}-receptor binding *in vivo*. Interestingly, olanzapine only inhibited a maximum of 80% of the D_2-receptor binding. This finding is generally consistent for atypical compounds, which do not totally occupy the D_2 receptor. In contrast, haloperidol readily occupies 100% of the D_2 receptor. *In vivo*, olanzapine inhibited the D_2 receptor more potently than the D_1 receptor, particularly when compared to the *in vitro* binding results. Olanzapine had rather low potency in inhibiting QNB binding at the muscarinic receptor, perhaps due to the ligand (QNB has a very high affinity for muscarinic receptors and is difficult to inhibit). Nevertheless, these data suggest that olanzapine *in vivo* may have only modest affinity for muscarinic receptors, and they are consistent with previous *ex vivo* binding data (Schotte *et al*, 1996).

The affinity of olanzapine for dopamine receptors has also been measured by its ability to block the irreversible receptor-inactivating agent 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (Bymaster *et al*, 1996*b*). If olanzapine binds to dopamine receptors, pretreatment with this compound should block subsequent receptor inactivation by EEDQ as measured by ^{3}H-radioligand binding. Results showed that olanzapine can block irreversible striatal dopamine receptor inactivation by EEDQ in a dose-dependent manner. Moreover, olanzapine blocked D_2 receptors more potently than D_1 receptors (Bymaster *et al*, 1996*b*).

Microdialysis

The prefrontal cortex probably represents a key region involved in the negative symptoms of schizophrenia. Using a novel technique, Li and coworkers measured the effect of olanzapine, clozapine, and haloperidol on extracellular levels of norepinephrine,

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dopamine, and serotonin in the same dialysate sample taken from the prefrontal cortex (Bymaster *et al*, 1997*a*; Li, 1998). Olanzapine increased the extracellular levels of dopamine (Fig. 3) and norepinephrine (data not shown), but not 5-HT, in a dose-related manner. Clozapine also increased the extracellular concentrations of norepinephrine and dopamine in the prefrontal cortex. However, haloperidol had no effect on either neurotransmitter, suggesting that increased release of these neurotransmitters is not mediated by dopamine D_2 autoreceptors but possibly by 5-HT_2 or α_1-adrenergic receptors (data not shown). Olanzapine also increased extracellular dopamine concentrations in a dose-related manner in two other areas of the brain associated with schizophrenia, the neostriatum and the nucleus accumbens, probably through blockade at dopamine D_2 autoreceptors.

Gene expression

Changes in neuronal activity caused by antipsychotic agents can induce the expression of the immediate-early gene c-fos and its protein product Fos, which then can be measured. Robertson and Fibiger studied the effect of haloperidol, clozapine, and olanzapine on the expression of Fos-like immunoreactivity in the prefrontal cortex (the presumed site of origin of negative symptoms of schizophrenia), the nucleus accumbens, and the dorsolateral striatum (Fig. 4) (Robertson & Fibiger, 1992). Haloperidol had little effect on Fos expression in the prefrontal cortex, but it considerably increased Fos expression in the nucleus accumbens and greatly increased Fos expression in the dorsolateral striatum. These results are consistent with the effect of haloperidol on positive symptoms only of schizophrenia and the induction of EPS. In contrast, clozapine increased Fos expression in the prefrontal cortex and the nucleus accumbens but not in the dorsolateral striatum. These results are consistent with the effectiveness of clozapine on both positive and negative symptoms of schizophrenia with no induction of EPS. Olanzapine was studied at two different doses, 5 mg/kg and 10 mg/kg (Robertson & Fibiger, 1996). At the 10 mg dose, olanzapine produced an increase in Fos expression in the prefrontal cortex, a large increase in the nucleus accumbens, and an intermediate increase in the dorsolateral striatum. These findings are consistent with the effectiveness of olanzapine on both negative and positive symptoms and suggest that, with careful dosing, olanzapine should not cause EPS.

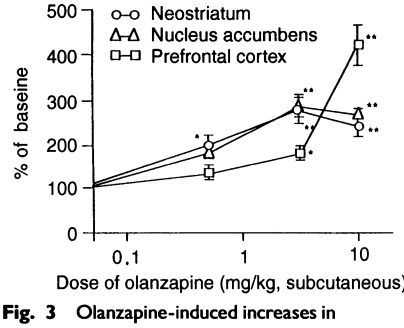


Fig. 3 Olanzapine-induced increases in extracellular levels of dopamine in brain regions. Determined by microdialysis in conscious rats. The points represent the peak increases in extracellular levels of dopamine in the neostriatum, nucleus accumbens, and prefrontal cortex after sequential administration of olanzapine: $*P<0.05$; $**P<0.001$ (Li *et al*, 1998).

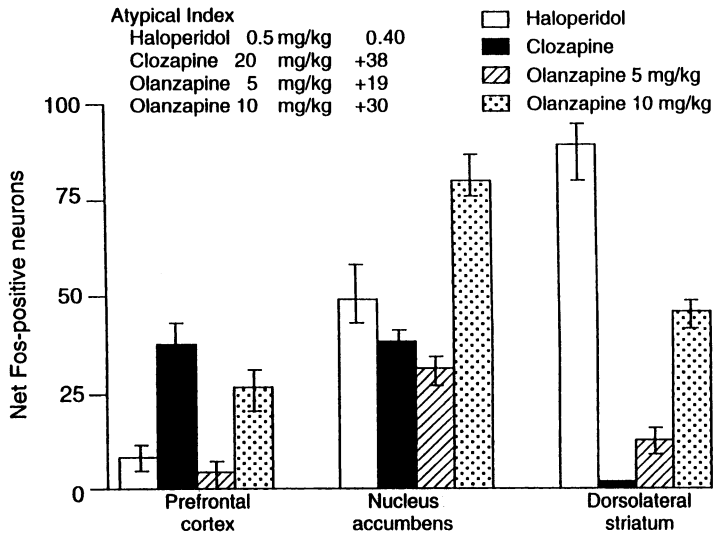


Fig. 4 Effect of antipsychotics on expression of Fos-like immunoreactivity in brain regions. The antipsychotics were administered subcutaneously 2 hours prior to killing. The atypical index was calculated by subtracting the net Fos-positive neurons in the dorsolateral striatum from the net Fos-positive neurons in the nucleus accumbens (Robertson & Fibiger, 1992, 1996).

DISCUSSION

Olanzapine is an atypical antipsychotic with a broad binding and pharmacological profile (Bymaster *et al*, 1996*a*). Olanzapine's pleotrophic pharmacology (including interaction with dopaminergic, serotonergic, muscarinic, and α_1-adrenergic receptors) undoubtedly contributes to its beneficial therapeutic profile. Of particular interest is the novel effect of olanzapine in increasing extracellular levels of dopamine and norepinephrine in the prefrontal cortex, which is probably mediated by interaction with some of the aforementioned receptors.

In vivo, olanzapine occupies dopamine D_2 and 5-HT_{2A} receptors more readily than dopamine D_1 or muscarinic receptors. Presumably, most of the antipsychotic effects of olanzapine are mediated by the blockade of D_2 and 5-HT_{2A} receptors. Since blockade of muscarinic and dopamine D_1 receptors can produce cognitive dysfunction, and since olanzapine has minimal interaction with these receptors, it would be expected to produce minimal cognitive disturbances. Results of treatment with olanzapine are consistent with these expectations – antipsychotic efficacy can be achieved clinically with minimal anticholinergic effects.

It has been hypothesised that a decreased dopamine function in the prefrontal cortex may cause the negative symptoms of schizophrenia (Deutch, 1992). Dopamine inhibits the firing of excitatory amino acid tracts that project from the prefrontal cortex to the ventral tegmental area (A10) and the nucleus accumbens. If dopamine is decreased, these tracts may fire excessively, causing greater dopamine release in the nucleus accumbens and producing or increasing the positive symptoms of schizophrenia. Olanzapine increases dopamine release in the prefrontal cortex, which may decrease the firing of excitatory amino acid

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tracts, thereby inhibiting dopamine release in the nucleus accumbens, and reducing the positive symptoms of schizophrenia. Thus olanzapine produces a dopamine-mimetic effect in the prefrontal cortex and is not believed to block postsynaptic D_1 receptors appreciably.

Olanzapine may reduce the positive symptoms of schizophrenia by selective inhibition of A10 dopamine neurons, resulting in reduced firing and presumably decreased release of dopamine. In addition, olanzapine may have an effect on positive symptoms by blocking postsynaptic D_2 receptors in the mesolimbic areas and by reducing the firing of glutamate tracts, thereby reducing a forward feed phenomenon from the prefrontal cortex to the ventral tegmental area.

The absence of EPS with olanzapine may be related to this agent's incomplete blockade of D_2 receptors, lack of A9 depolarisation blockade, and interaction with other receptors. In particular, olanzapine may block or partially block 5-HT_2 and muscarinic receptors which are known to affect EPS.

Finally, olanzapine-induced increases in norepinephrine release in the prefrontal cortex may have an enabling effect on dopamine, or may have a direct role in reducing the negative symptoms of schizophrenia. Dopamine and norepinephrine may also play important roles in arousal, mood, and stimulation of memory. Norepinephrine, specifically, may increase arousal and improve mood. Thus, olanzapine may improve mood and cognition by its effects on norepinephrine and dopamine release. Activation of D_1 receptors in the prefrontal cortex may improve memory, particularly working memory.

Thus, the interaction of olanzapine with a number of neuronal receptors, as well as its effects on dopamine and norepinephrine release, may play a role in its beneficial effects in the treatment of schizophrenia and its reduced side-effect profile.

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