

Quetiapine: Preclinical Studies, Pharmacokinetics, Drug Interactions, and Dosing

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Quetiapine is a novel dibenzothiazepine atypical antipsychotic. Quetiapine shows affinity for various neurotransmitter receptors including serotonin, dopamine, histamine, and adrenergic receptors and has binding characteristics at the dopamine-2 receptor similar to those of clozapine. In animal models, the drug has a preclinical profile suggestive of antipsychotic activity with a reduced tendency to cause extrapyramidal symptoms (EPS) and sustained prolactin elevation. For example, quetiapine alters neurotensin neurotransmission and *c-fos* expression in limbic but not motor brain regions. The drug also demonstrates clozapine-like activity in a range of behavioral and biochemical tests and may possess neuroprotective properties. In humans, quetiapine exhibits linear pharmacokinetics with a mean terminal half-life of 7 hours. The primary route of elimination of quetiapine is through hepatic metabolism. Although not affected by smoking, alterations in quetiapine disposition due to age or hepatic impairment are manageable by appropriate dosage reduction. The optimal dosing range for quetiapine is 150 to 750 mg/day, and recent results suggest that once-daily dosing may be suitable for some patients. Finally, imaging studies with positron emission tomography confirm significant differences between quetiapine and typical antipsychotics that may be indicative of their differences in mechanism of action and propensity for producing EPS.

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The treatment of schizophrenia changed in the 1950s with the discovery of typical antipsychotics such as chlorpromazine and haloperidol. However, not all patients responded to these drugs, and significant numbers of patients experienced serious side effects such as extrapyramidal symptoms (EPS), which include akathisia, dystonia, and parkinsonism.

The first of the atypical antipsychotics, clozapine, was patented in the 1960s and used in clinical trials in the 1960s and 1970s. Agranulocytosis, which occurred in 1% to 2% of patients, forced the removal of clozapine from the market in 1975. Clozapine was reintroduced in 1990 with improved hematologic monitoring. However, although clozapine showed efficacy in the treatment of psychosis associated with schizophrenia, its propensity to produce agranulocytosis has kept it from widespread use.

A research goal at AstraZeneca (formerly Zeneca, formerly ICI Pharmaceuticals) during the 1980s was the development of a clozapine-like drug that did not cause hematopathology (as clozapine did) or EPS (as typical antipsychotics did). Drug candidates were synthesized based on structural activity relationships using perlapine and fluperlapine, 2 drugs related to clozapine but structurally dissimilar enough to possibly lower the risk of agranulocytosis (thought to be related to the clozapine molecule itself). Pharmacologic evaluation was accomplished in a variety of species and a battery of behavioral, electrophysiologic, and biochemical tests predicting antipsychotic activity and EPS liability. In 1984, ICI 204,636—later named quetiapine—was discovered to have a clozapine-like pharmacologic profile but with an improved safety profile. Quetiapine was approved by the U.S. Food and Drug Administration in September 1997 and is currently marketed in the United States to treat schizophrenia. It is also approved for this indication in more than 70 countries worldwide, including Canada, Japan, and most European countries.

PRECLINICAL STUDIES

Receptor Profile

Quetiapine is a multiple receptor antagonist. It shows a low affinity for the dopamine-2 (D₂) receptor and a higher affinity for the serotonin-2A (5-HT_{2A}) receptor, which is

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Table 1. In Vitro Receptor Binding of Quetiapine on Human Brain Receptors^a

Receptor	Mean K _d (nM)
α ₁ -Adrenergic	8.1
α ₂ -Adrenergic	80
Dopamine D ₂	770
Histamine H ₁	19
Muscarinic	1400
5-HT _{1A}	300
5-HT _{1D}	560
5-HT _{2A}	31
5-HT _{2C}	3500

^aData from Richelson and Souder.² The smaller the K_d value, the greater the binding.

generally considered predictive of an atypical antipsychotic.¹ The equilibrium dissociation constants (K_d) for the receptor binding affinities for quetiapine are summarized in Table 1.

In Vivo Tests

A variety of animal models showed that quetiapine had a preclinical profile similar to clozapine, suggesting antipsychotic activity but with a reduced tendency to cause motor disturbances (Table 2). For example, in conditioned avoidance tests in squirrel monkeys and paradigms using apomorphine and amphetamine-induced behavioral alterations, quetiapine was more potent than clozapine in higher species (cats and monkeys), but less potent in rodents.³ In functional tests based on neurochemical indices, such as elevation of dopamine metabolites, quetiapine exhibited the properties of a dopamine receptor antagonist.⁴ In other tests in rats, quetiapine only transiently elevated plasma prolactin levels, and chronic administration did not produce D₂ receptor supersensitivity—both of which are properties shared by clozapine but not by haloperidol. Furthermore, unlike typical antipsychotics, quetiapine produced few or no dyskinetic reactions in haloperidol-sensitized monkeys, which is considered predictive of low tardive dyskinesia liability.³ In a variety of preclinical tests conducted to predict an atypical antipsychotic drug profile, quetiapine produced results similar to clozapine. Quetiapine reversed the disruptive effects of apomorphine, ketamine, phencyclidine, and isolation rearing on prepulse inhibition of the startle reflex in rats (an animal model for sensorimotor gating deficits in schizophrenia)⁵⁻⁹ and reversed amphetamine-induced social isolation in monkeys (an animal model for the negative symptoms in schizophrenia).¹⁰ Finally, electrophysiologic tests also predicted antipsychotic activity and low propensity for producing EPS. Chronic administration of quetiapine reversed the inhibitory effects of amphetamine on midbrain dopamine neurons and produced depolarization inactivation of limbic-related A10 dopamine neurons but not the motor-related A9 dopamine neurons.¹¹ This difference from haloperidol, which caused depolarization inac-

tivation of both regions, suggests that quetiapine was less likely to produce EPS than typical antipsychotics. In summary, in vivo functional studies all provide evidence that quetiapine has a preferential effect on limbic as opposed to striatal D₂ receptors. EPS are associated with D₂ occupancy in the striatum, which therefore predicts a therapeutic effect with placebo levels of EPS for quetiapine.

In Vitro Studies

The pathophysiology of schizophrenia has been actively studied for the past 50 years. Although D₂ receptors are implicated, a wide variety of other mechanisms have also been proposed as modulating influences.¹²⁻¹⁵ Consequently, many in vitro studies have been conducted to characterize the physiologic actions of quetiapine.

Dopamine receptors. The efficacy of different antipsychotics has been related to the magnitude of D₂ receptor antagonism,¹⁶ with some of the differences between the abilities of antipsychotics to produce EPS related to up-regulation of dopamine receptors.¹⁷ In one study of the effects of the atypical antipsychotics quetiapine, olanzapine, and risperidone on dopamine receptor density, rats were treated for 28 days with the various antipsychotics.¹⁸ Olanzapine and risperidone, but not quetiapine, exhibited significantly increased D₂ binding in various brain regions in the caudate-putamen, nucleus accumbens, and hippocampus. Furthermore, olanzapine and risperidone, but not quetiapine, produced an even greater up-regulation of D₄ receptors in the caudate-putamen, nucleus accumbens, and hippocampus. At the same time, D₁ and D₃ receptors in all regions were unaltered by any treatment. Thus, there are differences among atypical antipsychotics in their effects on the various dopamine receptors, and the lack of effect of quetiapine on dopamine receptors in the basal ganglia provides more evidence to suggest placebo levels of EPS in humans with treatment with quetiapine.

Neurotensin. There is evidence from a variety of experimental approaches implicating the neuropeptide neurotensin in both the mechanism of action of antipsychotic drugs and the pathophysiology of schizophrenia.^{13,19,20} In a series of studies measuring neurotensin concentrations in cerebrospinal fluid (CSF) of schizophrenic patients before and after antipsychotic drug treatment, reduced CSF neurotensin concentrations were found in a sizable subset of drug-free schizophrenic patients (for a review, see Binder et al.¹³). Clinically effective antipsychotic drug treatment normalized CSF neurotensin concentrations in the subgroup of schizophrenic patients with lower CSF neurotensin concentrations. A recent study suggests that there are region-specific changes in the levels of neurotensin receptor binding in mesial temporal lobe in patients with schizophrenia, particularly a decreased neurotensin receptor density in layer II of the entorhinal cortex.²¹ All of this research has led to the hypothesis that increased neurotensin neurotransmission is

Table 2. Animal Behavioral Tests of Antipsychotic Activity^a

Test	Description	Result With Quetiapine
Conditioned avoidance response paradigm	Subjects (usually rodents) conditioned to make an active response to avoid foot shock Antipsychotics produce a deficit in avoidance responses Predictive of antipsychotic activity	Quetiapine was more potent than clozapine in higher species but less potent in rodents ³
Paw retraction	In rodents, typical antipsychotics affect both forelimb and hindlimb retraction time; atypical antipsychotics more effective in increasing hindlimb retraction time Predictive of EPS liability	Quetiapine selectively affected forelimb vs hindlimb retraction time ¹⁰
Catalepsy	Antipsychotic-induced catalepsy in rodents resulting from blockade of striatal dopamine receptors Predictive of EPS liability	Quetiapine produced a weak effect at 20 and 40 mg/kg ³
Haloperidol-sensitized monkeys	Monkeys dosed with haloperidol until dyskinetic reactions occur; other drugs then administered Predictive of tardive dyskinesia liability	Quetiapine produced few or no dyskinetic reactions ³
Prepulse inhibition of acoustic startle reflex	Weak nonstartling stimulus followed by an intense acoustic stimulus Model for sensorimotor gating deficits in schizophrenia	Quetiapine reversed the effects of apomorphine and isolation rearing and restored the startle reflex ^{6,7,9}
Monkey social interaction	Amphetamine-induced social isolation in monkeys Model for negative symptoms in schizophrenia	Quetiapine reversed the social isolation in monkeys ¹⁰

^aAbbreviation: EPS = extrapyramidal symptoms.

involved in the clinically relevant effects of antipsychotic drugs.^{13,19,20}

To date, all clinically effective antipsychotic drugs that have been examined significantly alter neurotensin neurotransmission.^{22–26} In general, typical antipsychotic drugs such as haloperidol alter neurotensin neurotransmission in both limbic and motor brain regions. In contrast, atypical antipsychotic drugs, including quetiapine, alter neurotensin neurotransmission, specifically in limbic brain regions. In an effort to demonstrate that antipsychotic drug-induced alterations in neurotensin neurotransmission are actually involved in clinically relevant behavioral effects, we examined the role of neurotensin neurotransmission in restoration of isolation rearing–induced deficits of prepulse inhibition (PPI) by antipsychotic drugs.⁹ Although the neurotensin receptor antagonist alone had no effect on PPI, pretreatment with the neurotensin antagonist blocked the restoration of PPI seen with haloperidol and quetiapine in isolation-reared animals. These data suggest that increased neurotensin neurotransmission may be a common denominator that produces the behavioral effects of clinically effective antipsychotic drugs.

Modulation of immediate early gene expression. Immediate early genes are a class of genes that show rapid and transient increases in expression to extracellular signals such as growth factors and neurotransmitters. Antipsychotic drugs selectively increase the expression of the immediate early gene protein *c-fos*; therefore, *c-fos* protein immunocytochemistry is used as a metabolic marker for tracing the sites of action of neuroactive drugs.²⁷ Both acute haloperidol and clozapine treatments induce *c-fos* in the shell compartment of the nucleus accumbens and in the lateral septal nucleus, whereas haloperidol additionally induces *c-fos* in both the core of the nucleus accumbens and in the dorsal striatum.²⁸ Activation of *c-fos* in the

nucleus accumbens and medial striatum has been hypothesized to reflect potential antipsychotic activity,²⁹ whereas activation of dorsolateral striatal *c-fos* has been hypothesized to result from the blockade of D₂ receptors and thus to reflect the propensity for producing EPS.²⁹ Unlike haloperidol, clozapine characteristically induces *c-fos* in the prefrontal cortex, and this region has been proposed as a site underlying the unique effects of clozapine treatment on the negative symptoms of schizophrenia.²⁹

Quetiapine selectively elevated the immediate early gene product *c-fos* in the limbic-related (e.g., nucleus accumbens, lateral septum, prefrontal cortex) but not the motor-related (e.g., dorsolateral striatum) regions of the brain.²⁹ Thus, quetiapine is predicted to have antipsychotic activity, with placebo levels of EPS.

Ionotropic glutamate receptors. Another neurotransmitter implicated in the pathogenesis of schizophrenia is glutamate. Glutamatergic neurons are the major excitatory pathways linking the cortex, limbic system, and thalamus—regions that have been implicated in schizophrenia. The *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor may be particularly important because blockade of this receptor by the dissociative anesthetics reproduces in normal subjects many of the symptoms of schizophrenia.³⁰ Furthermore, postmortem studies reveal variable alterations in glutamate receptors in patients with schizophrenia.³¹ Consequently, one hypothesis of the pathophysiology of schizophrenia involves hypofunction of a subpopulation of corticolimbic NMDA receptors.^{14,30,32}

Although antipsychotics do not directly bind to glutamatergic receptors, they may have indirect influences on the expression of different subunits. In a recent study, the mRNA levels for NMDA and α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor sub-

units were measured after chronic treatment with quetiapine compared with haloperidol and clozapine.³³ Quetiapine and clozapine reduced mRNA expression in the nucleus accumbens for 2 NMDA-forming subunits, NR-1 and NR-2C. Furthermore, quetiapine, but not haloperidol or clozapine, increased the expression in the hippocampus of mRNA for the AMPA subunits GluR-B and GluR-C. These differences between typical and atypical antipsychotics may be relevant for their mechanism of action and different propensities for producing EPS.

Brain-derived neurotrophic factor. It has been suggested that neurotrophins might be involved in the actions of antipsychotic drugs.³⁴ For example, brain-derived neurotrophic factor (BDNF) promotes the function, sprouting, and regrowth of 5-HT-containing neurons in the brains of adult rats,³⁵ and BDNF protein is reported to be elevated in the hippocampus of patients with schizophrenia who were treated with neuroleptic drugs.³⁴ The hippocampus is the brain region that expresses the highest levels of BDNF³⁶ and is also implicated in the pathogenesis of schizophrenia.^{37,38} Chronic stress is associated with exacerbation of some neuropsychiatric disorders, including schizophrenia,³⁹ and neurotrophins may be involved, either directly or indirectly. For example, in rats stressed by immobilization, the expression of BDNF in the hippocampus was typically reduced; however, pretreatment with quetiapine markedly reduced the stress-induced decrease in BDNF protein.⁴⁰ This result suggests that quetiapine may possess neuroprotective properties that may be important for its antipsychotic activity.

PHARMACOKINETICS

The absorption of quetiapine in the body is rapid, with a median time to reach maximum observed plasma concentration ranging from 1 to 2 hours.⁴¹ Quetiapine absorption is unaffected by food in the stomach,⁴ and the drug is approximately 83% bound to serum proteins.⁴¹ The mean terminal half-life of quetiapine is approximately 7 hours.

Quetiapine exhibits linear pharmacokinetics, so that blood levels change roughly as a proportion of dose taken.⁴¹ Furthermore, its pharmacokinetics do not appear to be affected by ethnic background, gender, body weight, or cigarette smoking. In pharmacokinetic studies, there were no apparent differences in adolescents compared with adults.⁴² In elderly patients, the mean plasma clearance of quetiapine is reduced by 30% to 50% compared with younger patients, so the initial target dosing may need to be lowered by an equivalent amount. No clinically significant differences were found for pharmacokinetic parameters for patients with renal or hepatic impairment compared with those for healthy control subjects.⁴³

The primary route of elimination of quetiapine in the body is through hepatic metabolism. It is metabolized in the liver by the cytochrome P450 (CYP) system with the

CYP3A4 isoenzyme being the primary pathway. After administration of [¹⁴C]quetiapine, approximately 73% of the radioactivity was excreted in urine and 21% was excreted in feces.⁴¹ Eleven metabolites formed through hepatic oxidation have been identified. Two of these metabolites were found to be pharmacologically active, but, because they circulate in the plasma at levels that are 2% to 12% that of quetiapine, they are unlikely to contribute substantially to the pharmacologic effects of the drug.

DRUG INTERACTIONS

Although quetiapine does not inhibit any of the CYP450 isoenzymes, nor does it appear to induce the CYP3A4 isoenzymes,⁴¹ drugs that alter the activity of the CYP3A4 isoenzymes have the potential for drug-drug interactions with quetiapine. For example, drugs such as erythromycin that are potent inhibitors of CYP3A4 are likely to raise quetiapine levels, and drugs that induce CYP3A4, such as carbamazepine and phenytoin, will decrease quetiapine levels.

Various studies have been conducted to examine whether drug-drug interactions occur between quetiapine and other drugs. Haloperidol and risperidone do not affect plasma quetiapine concentrations; thus, concomitant administration does not require any change in quetiapine dosage.⁴⁴ However, because coadministration of quetiapine with thioridazine does result in lower plasma quetiapine levels, doses of quetiapine may need to be increased when it is coprescribed with thioridazine.⁴⁴ Fluoxetine and imipramine do not affect plasma quetiapine levels,⁴⁵ and lithium levels are not changed by quetiapine.⁴⁶ Also, no clinically relevant alterations in quetiapine pharmacokinetics were observed after the coadministration of cimetidine in patients with psychotic disorders.⁴⁷ Finally, oral clearance of quetiapine was increased 5-fold when it was coadministered with phenytoin, indicating that dosage adjustment of quetiapine may be necessary when both drugs are given concurrently.⁴⁸ Thus, caution may be required when administering quetiapine along with drugs that inhibit or induce cytochromes, particularly CYP3A4.

DOSING

Current dosing recommendations suggest titration to 400 mg/day using the following schedule, administered b.i.d. in divided doses: day 1, 50 mg; day 2, 100 mg; day 3, 200 mg; day 4, 300 mg; day 5, 400 mg.⁴⁹ In patients who respond to quetiapine, therapy should be continued at the optimal dose that maintains remission, within the range of 150 to 750 mg/day.

Although the terminal half-life for quetiapine of 7 hours suggests that twice-daily dosing is necessary, the results from a receptor occupancy trial show a dissociation in time course between receptor occupancy and plasma concentra-

tions of quetiapine at both D_2 and 5-HT_2 receptors, leaving open the possibility of once-daily dosing.⁵⁰

The option of once-daily administration of quetiapine was studied in a randomized, double-blind clinical trial in patients with schizophrenia or schizoaffective disorder.⁵¹ In this study of once-daily versus twice-daily administration of quetiapine, there were 3 phases of drug administration, each 4 weeks long. In phase 1, baseline to week 4, the previous antipsychotic agent was withdrawn and treatment with quetiapine was initiated. In phase 2, week 4 to week 8, the patients were randomly assigned to once-daily or twice-daily dosing of quetiapine. Finally, in phase 3, week 8 to week 12, there was a double-blind crossover for an additional 4 weeks. Nineteen of 21 patients successfully completed the study. At the first switch at phase 2, none of the 10 patients randomly assigned to once-daily dosing worsened at this switch point. At the next switch point at phase 3, 3 patients showed worsening of symptoms; however, all but 1 of these patients showed eventual improvement. Adverse effects were noted mostly in the first 4 to 8 weeks of treatment and were mild to moderate in severity. Four patients experienced symptomatic postural hypotension during the titration phase of the study. Four patients had tardive dyskinesia at baseline; however, symptoms resolved in 6 to 8 weeks of treatment. No new cases of akathisia or other EPS were noted in the double-blind phases of study. Thus, these results suggest it may be possible to switch many patients who are receiving a therapeutic dose of quetiapine b.i.d. to once daily.

Switching or crossover strategies in stable patients can lead to a flare-up of psychotic symptoms and may also result in withdrawal effects. These flare-ups can appear as reemergence or worsening of psychosis, rebound or unmasked dyskinesia, and cholinergic-rebound phenomena. In a trial of 50 patients assessing the safety of abruptly switching from one of 4 usual-care treatment strategies to quetiapine, an abrupt switch to quetiapine and an abrupt discontinuation of quetiapine were well tolerated.⁵² Only 2 patients (4%) had a psychotic relapse with the abrupt switch to quetiapine, and somnolence was the most common adverse event. After the abrupt discontinuation of quetiapine, there was some deterioration in psychotic symptoms; the nonpsychiatric symptoms consisted primarily of nausea and vomiting, most of which were mild to moderate in intensity. Consequently, switching to and from quetiapine can be accomplished without much difficulty.

IMAGING STUDIES

The dopamine hypothesis of schizophrenia postulates that the symptoms of the disease are related to increased dopaminergic transmission and that drugs that possess antipsychotic potency block D_2 receptors. Imaging studies using positron emission tomography or single photon

emission computed tomography have examined the relationship between clinical efficacy, receptor occupancy at the D_2 receptor, and the development of adverse events such as EPS and hyperprolactinemia. With typical antipsychotics such as haloperidol, the likelihood of a clinical response increased significantly as the D_2 occupancy exceeded 65%.⁵³ In addition, hyperprolactinemia and EPS were associated with higher D_2 occupancies of 72% and 78%, respectively. Although data from typical antipsychotics are consistent with the dopamine hypothesis for the mechanism of action of antipsychotics, clozapine and quetiapine seem to be exceptions because they are associated with very low receptor occupancies.

Imaging studies have further characterized the receptor-binding properties of quetiapine. Mean D_2 receptor occupancies of 30% and 41% were observed for quetiapine doses of 450 and 750 mg/day.⁵⁴ Higher 5-HT_{2A} receptor occupancies of 57% and 74% were observed for doses of 450 and 750 mg/day. A significantly lower striatal D_2 occupancy rate was observed for quetiapine and clozapine compared with haloperidol.⁵⁵ In another study, quetiapine showed transiently high D_2 occupancy (58%–64%) 2 to 3 hours after a single dose, which then decreased to low levels in 12 hours.⁵⁶ Finally, it has been suggested that because clozapine and quetiapine are loosely bound to D_2 receptors, their rapid release from D_2 receptors may contribute to their low D_2 receptor occupancy and lower propensity to produce EPS.⁵⁷

Other studies reveal regional differences in the binding properties of quetiapine that confirm its atypical characteristics. A limbic selective blockade similar to that for clozapine was observed with a D_2/D_3 receptor occupancy by quetiapine of 32% in the striatum and 60.1% in the temporal cortex.⁵⁸ In other studies, quetiapine blocked cortical 5-HT_{2A} receptors, similar to other atypical antipsychotics, and this antagonism may contribute to the lack of EPS.⁵⁹ Hence, imaging studies reveal significant differences between quetiapine and typical antipsychotics that may be indicative of their differences in mechanism of action and tendency to produce EPS.

SUMMARY

Quetiapine was discovered in 1984 by scientists at AstraZeneca Pharmaceuticals (formerly Zeneca, formerly ICI Pharmaceuticals) who were searching for a drug with antipsychotic properties like those of clozapine but that had a better safety profile. Like many antipsychotics, quetiapine shows affinity for various neurotransmitter receptors, such as serotonin, dopamine, histamine, and adrenergic receptors. In animal models, the drug has a preclinical profile suggestive of antipsychotic efficacy with a reduced tendency to cause EPS. In vitro studies have revealed that quetiapine has an effect on many different proteins/peptides in the central nervous system, such as dopamine

receptors, neurotensin, ionotropic glutamate receptors, and BDNF. These modulatory interactions may be related to the mechanism of action of the drug as an antipsychotic or may be indicative of additional benefits, such as neuroprotection.

In clinical studies, quetiapine exhibits linear pharmacokinetics with a terminal half-life of 7 hours. It is metabolized in the liver by the CYP3A4 isoenzyme; however, quetiapine itself does not inhibit any of the CYP450 isoenzymes, nor does it appear to induce the CYP3A4 isoenzymes. Plasma levels of quetiapine are not affected by concurrent administration of risperidone, haloperidol, fluoxetine, imipramine, or cimetidine. However, dosage adjustment may be required when quetiapine is coadministered with thioridazine or phenytoin.

The dosing range for quetiapine is 150 to 750 mg/day, but clinical experience suggests that target doses are 400 mg/day and above. Recent results suggest that once-daily dosing may be suitable for some patients. Clinical studies show that patients can be switched to and from quetiapine without much difficulty.

Imaging studies with positron emission tomography confirm regional differences in binding properties for quetiapine that are consistent with being an atypical antipsychotic. Because of its loose binding to D₂ receptors, quetiapine shows transiently high D₂ occupancy that subsequently decreases to low levels. Thus, many different experimental approaches suggest that quetiapine is an atypical antipsychotic with a reduced propensity for producing EPS.

Drug names: amphetamine (Adderall), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), cimetidine (Tagamet and others), clozapine (Clozaril and others), erythromycin (Ery-Tab, E-Base, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil, Surmontil), ketamine (Ketalar and others), olanzapine (Zyprexa), phenytoin (Dilantin), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril).

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