

# Antipsychotics From Theory to Practice: Integrating Clinical and Basic Data

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The recent introduction of the atypical antipsychotics into the treatment arena for psychoses and related disorders comes with justifiable excitement. These newer antipsychotics offer several clinical benefits over the conventional antipsychotics, which have been the mainstays of care thus far. The primary advantage of these atypical agents is their superior side effect profiles, particularly with regard to extrapyramidal side effects (EPS). The implications from a reduction in EPS touch on virtually every aspect of pathology in schizophrenic illness, including short- and long-term movement disorders, negative symptoms, noncompliance, cognitive dysfunction, and dysphoria. It should be emphasized that while atypical antipsychotics share many clinical attributes, there are also substantial differences among them. This review will examine the pharmacology, clinical efficacy, and side effect profiles of the atypical antipsychotics and attempt to relate the attributes observed in clinical practice and clinical trials to their basic pharmacologic profiles. There is a fair, but not perfect, correspondence between the pharmacologic profiles of the different atypical antipsychotics and their respective clinical attributes. After a comparative overview of their receptor-binding profiles, a brief pharmacokinetic summary will be provided. Finally, the clinical profiles of these agents will be summarized with regard to both their efficacy and adverse effects.

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**A**ntipsychotic drugs are primarily used to treat signs and symptoms of psychosis. Their beneficial effects on psychotic symptoms are observed in a range of conditions such as schizophrenia, psychotic depression, psychotic mania, paranoia, psychosis associated with dementia, delirium, and medical disorders. These medications are also frequently employed to treat agitation, marked mood instability, and aggressive behavior even in the absence of overt psychotic symptoms. While such use was previously discouraged because of the significant adverse effects associated with conventional antipsychotics and the availability of alternative, better-tolerated medications in other classes, the new atypical antipsychotics with their improved adverse effect profiles may make this practice more acceptable.

Antipsychotics were previously referred to as *major tranquilizers* and *neuroleptics*; however, both these terms are misnomers, as they reflect nonessential properties of the drugs in this class of medications that are separate from their antipsychotic effect. Because all compounds in this class cause some degree of sedation, they were previously considered major tranquilizers. This labeling led to the erroneous impression that the antipsychotic effects were secondary to, or otherwise related to, their sedative

effects. The older or *conventional antipsychotics* also consistently caused extrapyramidal side effects (EPS), leading to their being referred to as neuroleptics (“seize the neuron”). The introduction of clozapine and other atypical antipsychotics has demonstrated that it is possible to have antipsychotic efficacy without producing these adverse neurologic effects; in fact, these agents are called *atypical* because they separate the antipsychotic therapeutic effect from the extrapyramidal side effect. Consequently, this class of medications should collectively be referred to as *antipsychotics* and not neuroleptics or major tranquilizers.

The past decade has witnessed an unprecedented development of new atypical antipsychotics. As with their neuroleptic predecessors, these medications are effective in reducing the delusional thinking, hallucinatory experiences, and thought disorganization that are the hallmarks of psychosis. However, compared to older medications, the atypical agents are chemically and pharmacologically unique, have fewer side effects, and hold the promise of greater clinical efficacy.<sup>1</sup>

Conventional antipsychotics or neuroleptics have been exceedingly useful in the treatment of schizophrenia and other psychotic disorders. Among their benefits are control of active psychotic symptoms, reduction of assaultive behavior, and management of severe agitation; all conventional antipsychotics appear to be equally effective in accomplishing these objectives. Conventional antipsychotics also have inherent limitations of efficacy; they are ineffective in a substantial proportion of patients and have a narrow spectrum of clinical activity, showing limited effectiveness in treating negative and cognitive symptoms.<sup>2</sup>

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Conventional antipsychotics also cause prominent and pervasive side effects. In particular, they are characterized by a high occurrence of EPS (occurring in up to 50% of patients) and a high occurrence of tardive dyskinesia (cumulatively occurring in 3% to 5% of patients per year of antipsychotic exposure).<sup>3</sup> Further, as a group, the conventional antipsychotics cause persistent elevations of prolactin levels, which can result in menstrual and sexual side effects.<sup>4</sup>

Potential benefits to be sought from the new antipsychotics include (1) effectiveness in a greater proportion of patients, particularly neuroleptic-refractory patients; (2) a broader spectrum of efficacy, including an increased effectiveness in reducing negative symptoms, cognitive impairment, mood symptoms, and suicide risk, as well as better control of aggression and agitation; (3) minimal EPS; (4) reduced risk of tardive dyskinesia; and (5) absence of prolactin elevation and related side effects. The broadest definitions of atypical antipsychotics include elements of each of these factors. More narrowly, atypical antipsychotics are defined simply as those associated with minimal risk of EPS. With conventional antipsychotics, EPS occur in the same dose range at which psychotic symptoms respond, making it very difficult to obtain clinical benefits in the absence of side effects. Among the newer agents, symptom relief occurs in the absence of EPS, or at doses of medication below those at which EPS become significant. This separation between the antipsychotic and EPS dose-response curves with atypical antipsychotics represents their fundamental advantage over conventional antipsychotics.

How are the pharmacologic profiles of atypical antipsychotics distinct from those of conventional antipsychotics, and how do different atypicals compare to one another with regard to their pharmacologic characteristics? How do atypical antipsychotics differ from conventional antipsychotics in terms of efficacy and adverse effects? How do different atypicals compare to one another with regard to their clinical properties? Finally, how are the comparative clinical profiles (efficacy and adverse effects) of atypical agents understandable in terms of their pharmacologic attributes? This review of pharmacology, clinical efficacy, and adverse effects will lay the foundation for answering these questions.

## PHARMACOLOGY

The pharmacologic basis of atypicality has been a target of intensive study, with 2 broad approaches being used to explain the distinction between atypical and conventional antipsychotics. The first strategy has focused on a drug's selectivity for certain brain regions and on its ability to separate antipsychotic from EPS effects. The second approach has focused on differences between the 2 classes of drugs with regard to neurotransmitter receptor affinities.

## Limbic Selectivity

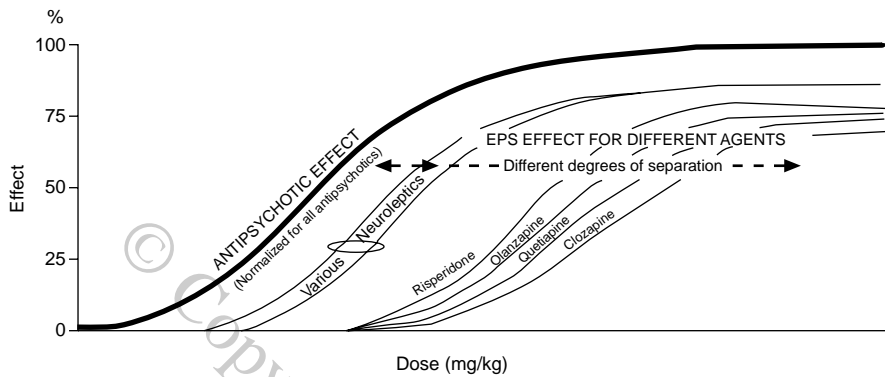
The most obvious explanation for the separation of the dose-response relationship between the development of EPS and antipsychotic efficacy in atypical antipsychotics is that these agents have a preference for the mesolimbic or "emotional" dopamine system versus the extrapyramidal or "motor" dopamine system. Therapeutic effects of antipsychotics are believed to be the result of a blockade of postsynaptic receptors in the mesolimbic dopamine system, whereas a blockade of dopamine receptors in the nigrostriatal system is considered responsible for causing EPS.<sup>5</sup> Conventional antipsychotics block both limbic and striatal dopamine-2 (D<sub>2</sub>) receptors with relatively equal potency, whereas atypical agents have a differential effect, with greater selectivity for mesolimbic neuronal systems. Regional anatomic and behavioral strategies have been used to define this limbic versus nigrostriatal selectivity and provide a comparison between different atypical agents in this regard.<sup>6-8</sup>

Approaches utilized to define regional selectivity anatomically include (1) biochemical, such as microdialytic measures of dopamine turnover, where an antipsychotic is administered and the amounts of dopamine released in the limbic and striatal areas are compared; (2) electrophysiologic, such as measures of the development of depolarization blockade in the ventral tegmental area (where the mesolimbic dopamine tract originates) compared to the substantia nigra (where the nigrostriatal dopamine tract originates); and (3) molecular, such as measures of expression of *c-fos* and related early genes in different brain regions following administration of the drug. Each of these strategies has proven useful in discriminating between atypical and conventional antipsychotics and among atypical antipsychotics. There is fair, but not perfect, congruence between the observed findings using the various strategies.

Behavioral animal models designed to assess limbic versus nigrostriatal selectivity are used to compare drugs for their antipsychotic versus extrapyramidal effects.<sup>6</sup> The relative dose of a particular agent that produces a limbic versus nigrostriatal effect defines the degree of atypicality for the drug. Animal models employed to represent an antipsychotic or limbic effect include (1) inhibition of hypermotility induced by dopaminergic drugs (e.g., amphetamine or apomorphine), (2) inhibition of conditioned avoidance responses, and (3) correction of deficits in prepulse inhibition of acoustic startle response induced by dopaminergic agents. Animal models employed to represent an extrapyramidal or nigrostriatal effect include (1) inhibition of stereotyped behaviors induced by dopaminergic drugs and (2) the induction of catalepsy.

Although there is not perfect correspondence among indices of atypicality obtained for different agents using these modeling strategies, some patterns are evident. Figure 1 represents our effort to integrate all information and

Figure 1. Dose-Response Curve for Antipsychotic and EPS Effects for Conventional and Atypical Antipsychotics<sup>a</sup>



<sup>a</sup>From Jibson and Tandon,<sup>2</sup> with permission.

compare a number of atypical and conventional antipsychotic agents with regard to the degree of separation between limbic or antipsychotic effect and the nigrostriatal or EPS effect. As is apparent from the schematic, there is a broader degree of separation for all atypical antipsychotics in comparison to conventional antipsychotics, a finding that is consistent with the lower propensity of atypical agents to cause EPS. Among atypical antipsychotics, there are different degrees of separation; these differences are likely to be reflected in the relative propensity of these drugs to cause EPS with increasing doses.

### Neurotransmitter Receptor Affinities

The receptor profile of an antipsychotic agent is used to predict the relative potency with which the antipsychotic is likely to act at various neurotransmitter receptors, presumably with predictive implications for the drug's efficacy and side effect profile in humans. Receptor profiles are usually presented in terms of the drug's affinity constants (inhibition constant  $IC_{50}$ ) for each receptor tested. The data are typically derived from *in vitro* studies with homogenates of brain tissue or cells that have been selected because they have specifically expressed, cloned receptors. When evaluating *in vitro* receptor affinity data, it is important to remember that the inferences from the data are approximate and do not correspond directly to what happens in human brain. While receptor affinity profiles are typically derived from *in vitro* studies, other strategies to profile neurotransmitter receptors include (1) *in vivo* ligand-binding studies, (2) *in vivo* receptor-binding studies with positron emission tomography (PET) and single photon emission computed tomography (SPECT), and (3) behavioral assays of *in vivo* effects to assess the drug's potency in blocking particular behaviors induced by specific agonists at different receptors. It should be noted that receptor-binding information derived for individual antipsychotics using these 4 methods may be discrepant and, consequently, should be interpreted

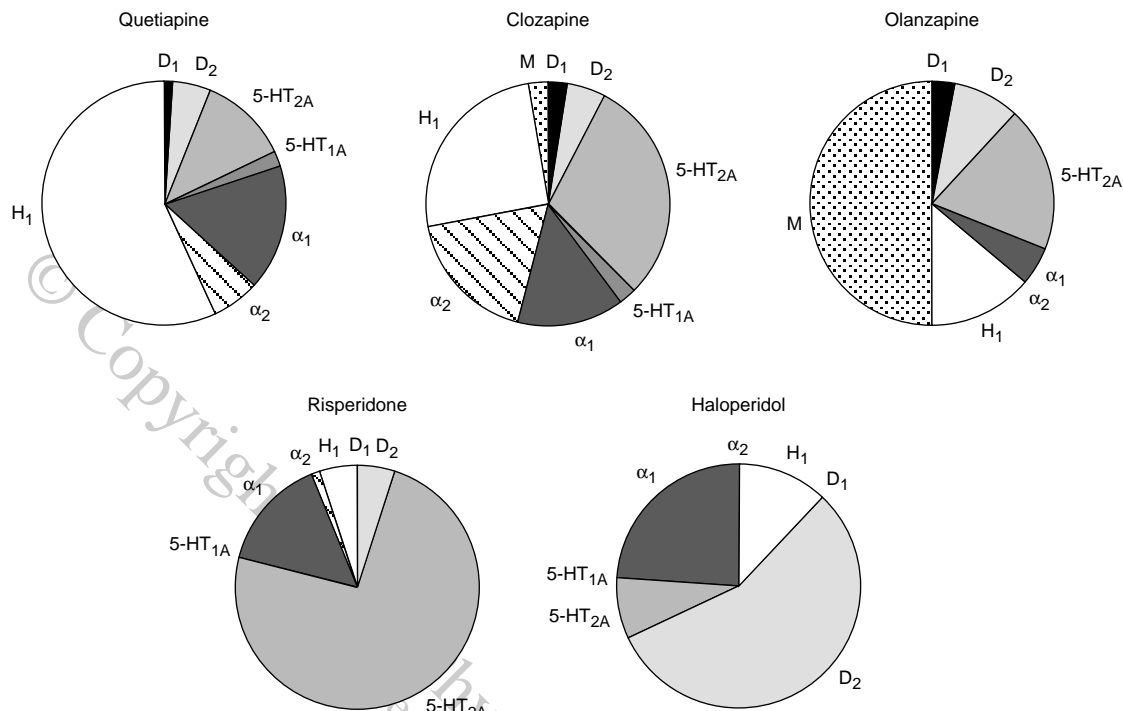
with some caution.<sup>8</sup> Furthermore, while antipsychotics are generally considered to be antagonists at all the sites for which they show high affinity, clozapine acts as a partial agonist at some muscarinic receptors (e.g.,  $M_1$ ,  $M_4$ ),<sup>9,10</sup> and ziprasidone acts as a weak agonist at the 5-hydroxytryptamine ( $5-HT_{1A}$ ) (serotonergic) receptor.<sup>11</sup> The pharmacologic profiles of the atypical antipsychotics are shown in Figure 2.

With the caveats mentioned above, it is evident that there are some similarities and also pronounced differences in the pharmacologic profiles of the atypical antipsychotics.

These agents retain the antipsychotic property of  $D_2$  antagonism, albeit to differing extents, with risperidone and olanzapine being potent antagonists, and clozapine and quetiapine being relatively weak antagonists. In addition, the atypical antipsychotics as a class possess the property of potent antagonism at the serotonergic ( $5-HT_{2A}$ ) receptor. On the other hand, these agents exhibit significant differences in activity at muscarinic cholinergic (particularly  $M_1$ ,  $M_2$ ), histaminergic ( $H_1$ ), noradrenergic ( $\alpha_1$  and  $\alpha_2$ ), and other serotonergic receptors. The probable clinical significance of a blockade of various receptors is shown in Table 1.<sup>2,12</sup> From a therapeutic standpoint, a  $D_2$  receptor blockade appears to be necessary for antipsychotic effect. It is noteworthy that currently there are no effective antipsychotics that are devoid of this property.<sup>1</sup> Antagonism at the  $5-HT_{2A}$  receptor appears to confer a lesser propensity for EPS, an attribute that distinguishes atypical from typical antipsychotics.<sup>13</sup> Possible benefits of other pharmacologic activities have been suggested but remain speculative.<sup>7,14</sup> The receptor profiles of the atypical agents are consistent with the observation that each of these drugs has a distinct set of side effects (Tables 1 and 2, Figure 2).

**Relative potency.** The relative antipsychotic potencies of the atypical antipsychotics in chlorpromazine equivalents (the dose of atypical antipsychotic whose activity is approximately equal to that of 100 mg of chlorpromazine) are noted in Table 3. The recommended range of optimal dosages for the atypical antipsychotics is listed in Table 4 for both young adult and elderly patients. It should be emphasized that the relative antipsychotic potencies noted are approximate and may vary at high and low dosages. It should also be noted that there is a wide variation in the dose of antipsychotic that is optimal for an individual patient. In general, the optimal dose for an elderly patient is 25% of that given to a younger patient. The suggested dose ranges are approximations of the average dose of different

Figure 2. Comparative Receptor-Binding Profiles<sup>a</sup>



<sup>a</sup>From Goldstein,<sup>44</sup> with permission.

Table 1. Clinical Implications of Blockade of Various Receptors by Antipsychotics

Receptors	Possible Benefits	Possible Side Effects
Dopamine D <sub>2</sub> receptor	Antipsychotic effect Efficacy on positive symptoms	Extrapyramidal movement disorders (EPS) (dystonia, pseudo-parkinsonism, akathisia, akinesia, tardive dyskinesia) Endocrine changes (prolactin elevation causing galactorrhea, gynecomastia, menstrual changes, sexual dysfunction)
Serotonin 5-HT receptors		
5-HT <sub>2A</sub> receptors	Reduced EPS <sup>a</sup>	?? Sexual dysfunction
5-HT <sub>2C</sub> receptors	Not known <sup>a</sup>	?? Weight gain
Histamine H <sub>1</sub> receptor	Not known <sup>a</sup>	Sedation, increased appetite, weight gain
Muscarinic receptor	Less EPS <sup>a</sup>	Peripheral: blurred vision, dry mouth, constipation, urinary retention Cardiac: sinus tachycardia, tachyarrhythmia Central: learning and memory dysfunction
α <sub>1</sub> -Adrenergic receptor	Not known <sup>a</sup>	Postural hypotension, dizziness, reflex tachycardia
α <sub>2</sub> -Adrenergic receptor	Not known <sup>a</sup>	Drug interactions

<sup>a</sup>Speculation of possible additional therapeutic benefit but unproven.

Table 2. Side Effect Profiles of Atypical and Selected Conventional Antipsychotics<sup>a</sup>

Side Effect	Chlorpromazine	Thioridazine	Haloperidol	Clozapine	Risperidone	Olanzapine	Quetiapine
EPS	+ to ++	+	+++	0 to ±	0 to ±	0 to ±	0 to ±
Dose-related EPS	++	++	+++	0	++	± to +	0 to ±
Tardive dyskinesia	+++	+++	+++	0	?	?	?
Prolactin elevation	++	++	+++	0	++	±	±
Agranulocytosis	±	±	±	++	±	±	±
Anticholinergic	++	+++	±	+++	±	+ to ++	±
AST/ALT elevation	+	+	+	+	±	±	±
Hypotension	+++	+++	+	+++	+ to ++	+	+ to ++
Sedation	+++	+++	+	+++	+	+ to ++	+ to ++
Seizures	+	+	±	++	±	±	±
Weight gain	+	+	+	+++	++	++ to +++	++

<sup>a</sup>From Tandon,<sup>1</sup> with permission. Symbols: 0 = absent; ± = minimal; + = mild; ++ = moderate; +++ = severe; ? = not known.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; EPS = extrapyramidal side effects.

Table 3. Pharmacokinetics and Clinical Potency of Atypical Antipsychotics<sup>a</sup>

Variable	Conventional Antipsychotics	Clozapine	Risperidone	Olanzapine	Quetiapine
Drug class	Various	Dibenzodiazepine	Benzoxazole	Thienobenzodiazepine	Dibenzothiazepine
Potency <sup>b</sup>	2–100	50	1	4	80
T <sub>max</sub> (hours)	Varies	3	1.5	5	1.5
Protein binding (%)	75–99	92–95	90	93	83
Active metabolite	Varies	No	Yes	No	No
Route of metabolism	CYP1A2 CYP2D6	CYP1A2 CYP3A4	CYP2D6	CYP1A2 CYP2D6	CYP3A4
t <sub>1/2</sub> (hours)	Varies	10–100	6–24	20–70	4–10

<sup>a</sup>Data from reference 1.<sup>b</sup>mg of drug = 1.0 mg chlorpromazine equivalents.Table 4. Optimal Doses for Atypical Antipsychotics (mg/day)<sup>a</sup>

Patients	Clozapine	Risperidone	Olanzapine	Quetiapine
Adults	300–600	3–6	10–20	300–600
Elderly	25–200	0.5–2.0	2.5–10	50–200

<sup>a</sup>Data from reference 1.

medications currently considered optimal; dosages for a specific patient must be individualized.

### Pharmacokinetics

The pharmacokinetics of the atypical antipsychotics are summarized in Table 3. Having a long elimination half-life (t<sub>1/2</sub>) is an advantage in as much as it allows the drug to be given less often, an attribute that has implications for patient compliance. At this time, clozapine, risperidone, and olanzapine are approved for once-daily dosing, whereas quetiapine is approved for twice-daily dosing. Having a long half-life accompanied by a significant H<sub>1</sub> blocking activity (e.g., olanzapine and clozapine) results in substantial sedation. The time from administration of the drug to maximum plasma concentration (T<sub>max</sub>) relates to the rapidity and likelihood of developing side effects such as postural hypotension. Having a short T<sub>max</sub> accompanied by substantial adrenergic (α<sub>1</sub>) antagonism (e.g., risperidone and quetiapine) is associated with increased risk of postural hypotension, necessitating a gradual titration to the desired daily dose of the drug. Atypical antipsychotics are eliminated predominantly by hepatic metabolism, using the cytochrome P450 (CYP) system<sup>15</sup>; the specific CYP isoenzyme used by each agent is noted in Table 3. While atypical antipsychotics do not induce or inhibit CYP enzymes to any significant extent, inducers and inhibitors of CYP enzymes (e.g., selective serotonin reuptake inhibitors, smoking) can affect their bioavailability. Because different atypicals are metabolized by different CYP isoenzymes, agents that induce or inhibit CYP enzymes can affect their bioavailability in different ways.

### Pharmacology of Specific Atypical Antipsychotic Agents (see Figure 2, Table 3)

**Clozapine.** Clozapine produces a significant blockade at serotonergic (5-HT<sub>2A</sub>), adrenergic (α<sub>1</sub> and α<sub>2</sub>), and his-

taminergic (H<sub>1</sub>) receptors. Its affinity for dopaminergic (D<sub>1</sub> and D<sub>2</sub>) and muscarinic cholinergic receptors is somewhat lower. The standard dose range for clozapine is 300–600 mg/day, usually given twice daily to minimize side effects, although its long elimination half-life

(14 hours) makes once-daily dosing possible. Lower doses may be effective in some patients, including the elderly. Doses up to 900 mg/day may be used in neuroleptic-refractory patients. The drug is 92% to 95% protein-bound. Bioavailability is not affected by food. Clozapine is eliminated principally by the hepatic CYP1A2 and CYP3A4 isoenzymes; CYP1A2 inducers such as smoking can reduce clozapine's half-life, while CYP1A2 inhibitors such as fluvoxamine can increase its duration of action.<sup>1,16</sup>

**Risperidone.** Risperidone is primarily active in the blockade of the 5-HT<sub>2A</sub> and D<sub>2</sub> receptors and has a somewhat lower affinity for α<sub>1</sub>, α<sub>2</sub>, and H<sub>1</sub> receptor sites.<sup>17,18</sup> Its pharmacologic profile is markedly different from both conventional antipsychotics and clozapine. As expected from the 20-hour half-life, risperidone (including its active metabolite, 9-hydroxyrisperidone) can be administered once daily.<sup>19</sup> The dose range of 3–6 mg/day appears to be optimal for most patients. Lower doses may be effective in selected patients, including the elderly, for whom the recent introduction of a 1-mg/mL oral solution may prove advantageous. Although several studies have been conducted at doses up to 16 mg/day, the side effect profile for risperidone is significantly worse at doses greater than 6–8 mg/day, making these higher doses less tolerated.<sup>20</sup> Bioavailability of both tablet and solution is about 65%.<sup>21</sup> Food and smoking do not modify the pharmacokinetics of risperidone.<sup>22</sup>

**Olanzapine.** Olanzapine has a high affinity for 5-HT<sub>2A</sub> and M<sub>1</sub> receptors, a somewhat lower affinity for D<sub>1</sub>, D<sub>2</sub>, H<sub>1</sub>, and α<sub>1</sub> receptors, and a minimal α<sub>2</sub> antagonism.<sup>23</sup> A dose range of 10–20 mg/day appears to be optimal for most patients.<sup>24</sup> Once-daily dosing appears to be as effective and tolerated as divided daily doses, consistent with the drug's 30-hour elimination half-life.<sup>25,26</sup> Olanzapine is readily oxidized in air when its protective coating is removed, which occurs when the tablets are cut or crushed; consequently, the portion of the medication not immediately consumed must be discarded. Its bioavailability is unaffected by food. It is eliminated principally by the hepatic CYP1A2 and CYP2D6 isoenzymes; consequently, CYP1A2 inducers such as smoking can reduce its half-life, necessitating higher doses. Because there is a high

prevalence of cigarette smoking among patients with schizophrenia, the modal dose of olanzapine used to treat schizophrenic patients in the clinic (15–20 mg/day) is substantially higher than suggested by the data from the clinical trials (10 mg/day).<sup>27</sup> Although the package insert specifies a maximum dose of 20 mg/day, clinicians are increasingly using higher doses (off-label), particularly while treating somewhat refractory young patients.<sup>27,28</sup>

**Quetiapine.** Quetiapine's pharmacologic profile includes a high affinity for 5-HT<sub>2A</sub>,  $\alpha_1$ , and H<sub>1</sub> receptors, a somewhat lower affinity for the D<sub>2</sub> and  $\alpha_2$  receptors, a low affinity for the D<sub>1</sub> receptor, and no M<sub>1</sub> activity.<sup>29</sup> Quetiapine has been shown to act selectively on the limbic system. The steady-state half-life of the drug is 6.9 hours, suggesting that twice-daily dosing is necessary. The optimal dose range for quetiapine is 300–600 mg per day, although lower doses may be effective in older patients.<sup>30</sup> Its bioavailability is unaffected by food. Quetiapine is metabolized predominantly by the CYP3A4 isoenzyme, and therefore smoking does not modify its blood concentrations.<sup>31</sup>

### CLINICAL EFFICACY

When comparing the efficacy of atypical antipsychotics to conventional agents, 4 issues warrant consideration: (1) speed of response; (2) proportion of patients responding; (3) responsiveness of neuroleptic-refractory patients to treatment with atypical antipsychotics; and (4) spectrum of activity, with particular reference to negative and cognitive symptoms.

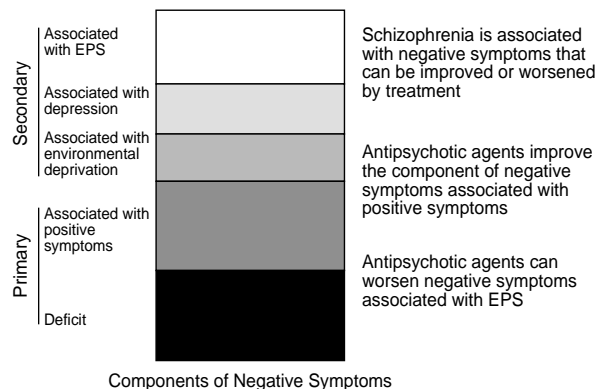
#### Speed of Response

There are no data to suggest that the speed with which schizophrenic patients respond to treatment with various antipsychotic agents differs.<sup>1,32</sup> Symptoms of sleep disturbance, agitation, and aggressive behavior tend to respond most rapidly. Positive symptoms (e.g., delusions, hallucinations, thought disorder) and inattention tend to respond with intermediate rapidity, with maximal response occurring over 3 to 6 weeks. Negative symptoms respond more slowly, with the maximal response occurring over a period of 6–12 weeks. Cognitive and neuropsychological improvements, which are related significantly to the improvement in attention, may progress for up to 6 months.

#### Proportion of Patients Responding

In the short-term trials (4–8 weeks), each of the atypical antipsychotics reviewed here has been shown to be as effective as conventional agents in treating psychotic symptoms.<sup>11,20,33,34</sup> Some studies suggest a better response with the atypical antipsychotics compared to conventional antipsychotics because of a higher proportion of responding patients, a greater proportion of patients showing a greater degree of response, or a greater mean reduction in

Figure 3. Spectrum of Activity: Negative Symptoms<sup>a</sup>



<sup>a</sup>Adapted from DeQuardo and Tandon,<sup>27</sup> with permission.

symptom scores. However, concluding that there are different rates of efficacy among the conventional and atypical antipsychotics based on these studies is premature because of methodological limitations and some inconsistencies in the findings.

#### Response of Neuroleptic-Refractory Patients to Atypical Antipsychotics

Clozapine has clearly been demonstrated to be more effective than conventional antipsychotics in the treatment of neuroleptic-refractory patients.<sup>35</sup> It has been shown to be effective in approximately 30% to 50% of such patients. To date, no definitive evidence has been presented to suggest that other atypical antipsychotics share clozapine's efficacy in patients refractory to treatment with conventional antipsychotics. Although several clinical trials with atypical agents to study this question are underway, no results have been reported thus far.

#### Spectrum of Activity

Psychotic disorders such as schizophrenia are characterized by a broad array of symptoms, and it is desirable that an antipsychotic be effective against the entire range of symptoms (positive—delusions, hallucinations, and thought disorganization; negative—anhedonia, blunted affect, impoverished speech and thinking; and cognitive—neuropsychological impairments)<sup>36</sup> as well as against affective symptoms, agitation, and aggressive behavior. Conventional antipsychotics, while very effective in treating positive symptoms and fairly effective in treating agitation, are only modestly effective in treating negative and cognitive symptoms.

Clinical trials have revealed atypical antipsychotics to be superior to or at least as effective as conventional agents in reducing negative symptoms.<sup>11,20,33–35</sup> Negative symptoms have several contributing factors, however, and much of the superiority of atypical agents appears to be related to their lesser propensity to cause EPS (Figure 3).<sup>2</sup>

Cognitive dysfunction is an important dimension of schizophrenic psychopathology, strongly related to the severity of functional impairment. Conventional antipsychotics have only minor effects on most aspects of cognition in schizophrenia, with some beneficial effects on measures of attention and distractibility.<sup>37</sup> Studies suggest that atypical antipsychotics may have a somewhat greater beneficial effect on cognitive function in schizophrenic patients.<sup>38</sup> Aspects of cognitive function in schizophrenia can be positively or negatively impacted by antipsychotic treatment. Improved attention associated with antipsychotic control of positive symptoms results in a broad but modest improvement in neuropsychological measures. Blockade of mesocortical dopamine transmission, on the other hand, adversely impacts aspects of cognitive function. Anticholinergic activity, either intrinsic to the antipsychotic agent or due to drugs used to treat parkinsonian side effects (e.g., trihexyphenidyl or benztropine), adversely affects memory, learning, and other cognitive functions. Because atypical agents are less likely than conventional agents to cause EPS or require the addition of adjunctive anticholinergic medications, modest cognitive advantages can be expected. Again, it should be emphasized that the modest advantages of atypical over conventional agents with regard to cognitive function emanate primarily from their low propensity to cause EPS and not from any presumed cognitive enhancing properties.

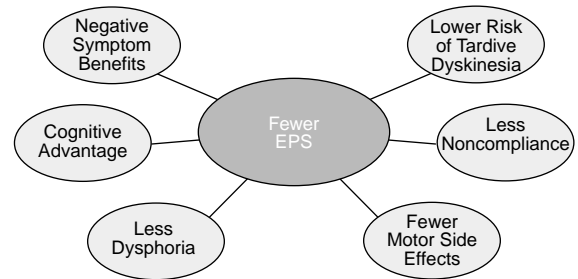
## ADVERSE EFFECTS

### Extrapyramidal Side Effects

Extrapyramidal side effects constitute the biggest problem in the use of conventional antipsychotics for treatment of psychotic disorders.<sup>39</sup> Their reduction or absence with atypical antipsychotics is a major advantage. With conventional antipsychotics, EPS occur in the same dose range at which psychotic symptoms respond, making it very difficult to obtain clinical benefits in the absence of side effects. Among the newer agents, symptom relief occurs in the absence of EPS or at doses of medication below those at which EPS become significant. Various atypical antipsychotics differ in the degree of separation between their antipsychotic and EPS dose-response curves (Figure 1). The smaller the degree of separation, the greater the likelihood that EPS might occur at higher doses of the medication. Tardive dyskinesia is a major concern when using conventional antipsychotics; the risk increases about 4-fold in elderly patients. In comparison to conventional agents, atypical antipsychotics appear to be associated with a significantly lower risk of tardive dyskinesia. While this advantage has been well established for clozapine,<sup>27,40</sup> emerging data with risperidone<sup>41</sup> and olanzapine<sup>42</sup> suggest that other atypical agents may share this property.

The importance of EPS in the context of treatment of psychotic disorders tends to be underestimated. Not only

Figure 4. The EPS Advantage of the Atypical Antipsychotics<sup>a</sup>



<sup>a</sup>From Tandon,<sup>1</sup> with permission.

do the motor parkinsonian side effects limit function and cause distress in their own right, EPS are also associated with several other adverse consequences. Expression of EPS significantly increases the likelihood of subsequent tardive dyskinesia, which, in turn, is associated with increased morbidity and mortality. EPS contribute to secondary negative symptoms, increasing the severity of this symptom dimension and attendant dysfunction. EPS are associated with cognitive dysfunction, attributable directly to unattenuated mesocortical dopamine blockade of the antipsychotic or due to the adjunctive use of other anticholinergic agents to treat EPS.<sup>43</sup> It is not surprising that significant EPS may be correlated with dysphoria. The negative impact of EPS is, thus, not limited to parkinsonian motor manifestations, but extends to increased negative and cognitive symptoms, more dysphoria, higher likelihood of non-compliance, and greater risk of tardive dyskinesia. The defining characteristic of atypical antipsychotics is at least equal efficacy with a significantly lower liability of EPS than conventional agents; consequently, their use would be predicted to yield several benefits that go beyond reduction in motor parkinsonian side effects (Figure 4). Many of these advantages have been confirmed in clinical studies. Therefore, to derive optimal benefits from the use of atypical antipsychotics, it is essential that they be used in a way in which EPS do not occur; if EPS occur in the course of treatment with an atypical antipsychotic, consideration should be given to a reduction in dose or change to another agent. Adequate control of psychotic symptoms accompanied by avoidance of EPS, without the need for adjunctive antiparkinsonian medication, should be the major treatment objective.

### Other Side Effects

The incidence of other side effects differs among the atypical antipsychotics, and they are largely predictable based on the differences in their respective pharmacologic profiles. Table 2 lists the side effect profiles of 3 commonly used conventional antipsychotics (haloperidol, chlorpromazine, thioridazine) and 4 currently approved atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine).

## CONCLUSIONS

The new atypical antipsychotic medications represent a major step forward in the treatment of schizophrenia and other psychotic disorders. These agents are pharmacologically distinct from their neuroleptic predecessors. The primary advantage of the new agents is their superior side effect profiles, particularly with regard to EPS. The implications of EPS reduction touch several domains, including reduced liability for short- and long-term movement disorders, advantages in negative and cognitive symptoms, reduced noncompliance, and reduced dysphoria. The drugs' unique profiles with regard to other side effects may make it possible to individually tailor treatment. Further refinement of our understanding of the clinical utility of these drugs awaits their widespread use in mainstream clinical settings and further controlled studies comparing them to one another.

*Drug names:* benvotropine (Cogentin and others), chlorpromazine (Thorazine), clozapine (Clozaril and others), fluvoxamine (Luvox), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril), trihexyphenidyl (Artane and others).

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