

# What Are We Looking for in New Antipsychotics?

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Antipsychotics are the cornerstone of treatment for psychotic and some nonpsychotic disorders. However, despite pharmacologic advances, considerable areas of need remain. This article reviews desirable properties for future antipsychotics and considers how far current agents have come in achieving those objectives. Preferably, new antipsychotics should have a "balanced" pharmacodynamic profile that addresses the need for efficacy without compromising psychiatric or physical well-being; a safe, fast, and convenient pharmacokinetic profile; a definable therapeutic window, and availability in multiple formulations. Compared with available agents, new antipsychotics should ideally have at least similar efficacy for positive symptoms, agitation, and aggression and better efficacy for negative or cognitive symptoms, relapse prevention, treatment-resistant illness, and associated problems such as depression, anxiety, and substance abuse. Improved tolerability and subjective acceptability to patients are also important in promoting adherence and continued treatment. Finally, they should have improved effectiveness in facilitating functioning, subjective well-being, quality of life, and, ultimately, recovery. Given the complexity of schizophrenia, its unknown etiology and pathophysiology, and challenges in clinical trial design and conduct, it is not surprising that it has remained difficult to develop antipsychotics with novel mechanisms. To achieve true breakthroughs, we need greater insight into the pathophysiology underlying specific disease processes and therapeutic and adverse responses. It is hoped that research on drug-specific biomarkers that can predict response in specific patient groups will advance personalized psychiatric care and improve patient outcomes.

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**I**n selecting treatments for schizophrenia, clinicians consider variables related to the patient (eg, age, history of response), the illness (eg, duration, symptom type, comorbidity), the medication (eg, pharmacodynamics, pharmacokinetics, efficacy, tolerability, cost), and the patient's environment (eg, finances, support).<sup>1</sup> Of these, the primary variable the clinician can modify is the medication. Thus, it is important for prescribers and drug developers to be familiar with the profiles of existing antipsychotics. This article reviews desirable properties for future antipsychotics and how far available agents have come in achieving those objectives. Since this discussion relies largely on pooled data analyses and meta-analyses, it does not include data on the 3 most recently introduced antipsychotics, asenapine, iloperidone, and lurasidone, which were not included in available meta-analyses. However, 3 articles in this supplement review these agents' efficacy and tolerability profiles in the context of the aspects of schizophrenia treatment highlighted here.<sup>2–4</sup>

## TREATMENT GOALS

What we desire from an antipsychotic is a medication that can treat psychosis, reduce symptoms (produce response), lead to symptom resolution (symptoms below the threshold to make a diagnosis), and maintain the patient with no more than mild positive and negative symptoms for at least 6 months (remission), with the ultimate goal being recovery. The "ideal medication" would also overcome treatment resistance and effectively protect against relapse.

## PHARMACODYNAMICS

The ideal antipsychotic would reduce excess dopamine levels in the mesolimbic pathway and/or associative striatum<sup>5</sup> to treat psychosis, while maintaining adequate dopamine levels where dopamine is needed, including the mesocortical pathway, where too little dopamine can lead to secondary negative symptoms and cognitive impairment; the nigrostriatal pathway, where too much dopamine blockade can cause extrapyramidal side effects (EPS); and the hypothalamic pathway, where too much dopamine blockade can elevate prolactin levels.<sup>6</sup>

The ideal antipsychotic would cause minimal histaminergic blockade (associated with sedation, weight gain, and metabolic complications), cholinergic blockade (associated with dry mouth, constipation, and impaired cognition), and  $\alpha_1$ -adrenergic blockade (related to orthostasis).<sup>7</sup> It would have  $\alpha_2$  blocking effects (associated with antidepressant activity) and serotonergic or noradrenergic reuptake inhibition (possibly helpful for anxiety and/or depression).<sup>7</sup> Neurotrophic or neurogenic effects, which require further study, would also be desirable. A pharmacodynamic profile that would restore satiety and metabolic signaling in overweight/obese patients would be valuable.

Antipsychotics differ markedly in pharmacodynamic and hence clinical, especially adverse effect, profiles. Since 60%–80% striatal dopamine blockade is considered necessary for antipsychotic efficacy and clinically relevant EPS begin to occur at  $\geq 80\%$  dopamine occupancy, only receptors occupied at a clinically significant level when 60%–80% dopamine blockade is reached are relevant for an antipsychotic's clinical profile.<sup>7</sup>

Although all available antipsychotics were developed based on the dopamine hypothesis of schizophrenia, research on new treatments for psychosis is also focusing on

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other mechanisms (eg, glutamatergic and GABAergic systems). Agents affecting the cholinergic and histaminergic systems are also being explored for negative and cognitive symptoms.

### PHARMACOKINETICS

The ideal antipsychotic would have a sufficiently broad gap between efficacy and toxicity, so that dosing could be increased as needed without triggering excessive side effects. Other desirable characteristics are rapid onset of action, no need for extensive titration, a reliable therapeutic blood level window, a longer half-life to reduce rebound effects and maintain consistent blood levels, multiple formulations, limited potential for drug-drug interactions (DDIs), and metabolism not significantly affected by renal or hepatic dysfunction. The ideal agent could be taken with or without food, and blood levels would not be affected by smoking. Available antipsychotics vary considerably in pharmacokinetic profiles, including potential to cause DDIs.<sup>7</sup>

### EFFICACY

Available antipsychotics are efficacious for positive symptoms, agitation, aggression, and relapse prevention, but, except for clozapine, have limited efficacy for refractory illness.<sup>8</sup> They do not produce clinically significant improvement in negative and cognitive symptoms, provide only inconsistent and/or insufficient relief of social/functional impairment or comorbid psychiatric problems, and can worsen comorbid medical conditions.<sup>8</sup> A recent meta-analysis comparing efficacy of first- and second-generation antipsychotics (FGAs and SGAs) found relatively few differences, except that clozapine was significantly better than the FGAs with a moderate effect size (0.5) and olanzapine, amisulpride, and risperidone were superior to FGAs with minimal to small effect sizes (0.1–0.3).<sup>9</sup> Another meta-analysis comparing SGAs in acute schizophrenia found few differences in efficacy.<sup>10</sup> While, in some analyses, olanzapine was superior to other SGAs, effect sizes were minimal to small (0.1–0.3); even clozapine did not separate from any of the SGAs, except zotepine, unless higher-dose clozapine studies were analyzed separately.<sup>10</sup> (Given their reliance on data from studies of varying quality with at times large methodological differences, meta-analyses should be used to generate rather than test hypotheses.) On the basis of available data, the Schizophrenia Patient Outcomes Research Team (PORT) noted few differences in efficacy between the FGAs and non-clozapine SGAs, except possibly a longer time to treatment discontinuation for olanzapine.<sup>11</sup>

A new antipsychotic should be at least as efficacious for positive symptoms as available agents, with improved efficacy for negative and cognitive symptoms and comorbid psychiatric symptoms. Also desirable would be the ability to improve illness insight, which no agent has been shown to do; reduce suicide risk (clozapine has the only such indication)<sup>8</sup>; and reduce smoking and/or substance craving/abuse. Finally, an ideal antipsychotic would be at least as good as clozapine for treatment-refractory illness without serious side effects.

### Cognitive Deficits

Available antipsychotics have a small effect on cognition.<sup>12</sup> Their side effects can also cause secondary cognitive symptoms (eg, via sedation, EPS, anticholinergic effects).<sup>7,13</sup> Sleep difficulties, anxiety, depression, psychotic disorganization, and substance abuse can also impair cognition. The ideal antipsychotic would cause minimal sedation or EPS, normalize sleep, not contribute to obesity and sleep apnea, alleviate anxiety and depression, treat psychotic disorganization, and reduce substance abuse. Since it is probably overly ambitious to expect one molecule to cover such a wide, complex array of domains, researchers are searching for mechanisms and agents that can target separate domains. Once agents with specific efficacy for domains other than positive symptoms are discovered, they could be used as augmentation in a rational, evidence-based polytherapy strategy.

### Comorbid Psychiatric Conditions

Patients with schizophrenia often have comorbid anxiety and/or depression. While most available antipsychotics have established efficacy for mania,<sup>14</sup> an ideal antipsychotic should also have efficacy for depression and anxiety. A number of SGAs have efficacy for major depression and dysthymia.<sup>15</sup> Only quetiapine has shown efficacy for generalized anxiety disorder.<sup>16</sup> Some antipsychotics may have efficacy in combination with antidepressants for obsessive-compulsive disorder.<sup>17</sup> Efficacy for anxiety and depression, as monotherapy and augmentation, does not seem to be a class effect and most likely depends on extradopaminergic activity.

### Treatment Resistance

Clozapine is the only agent definitively shown effective in treatment-resistant schizophrenia, but its use is limited by serious side effects,<sup>8</sup> highlighting the need for agents that can effectively manage treatment-refractory schizophrenia with a better safety profile.

Many clinicians use 2 antipsychotics for treatment-refractory schizophrenia instead of clozapine because of clozapine's side effects or because patients refuse it. While the efficacy of antipsychotic polytherapy that does not involve clozapine is unclear,<sup>18</sup> the ideal antipsychotic, used adjunctively, would not only enhance efficacy of the first agent, but also potentially reduce side effects.<sup>8</sup>

### SAFETY AND TOLERABILITY

The ideal antipsychotic would cause minimal or no EPS and akathisia<sup>19</sup> and have little risk of tardive dyskinesia (TD).<sup>20</sup> It would be weight neutral, cause no metabolic abnormalities,<sup>21</sup> and reverse weight gain and/or lipid abnormalities. It should cause minimal sedation and anticholinergic effects, little orthostasis, no QTc prolongation, and no blood dyscrasias (ie, no blood tests needed). It should not increase suicidality. It would be safe during pregnancy and in children, adolescents, and the elderly. Although no efficacy mechanisms beyond antidopaminergic effects have been established for schizophrenia since the discovery of chlorpromazine, SGAs represent an advance in terms of a differential reduction in adverse effects associated with FGAs.

More recently introduced SGAs also combine the side effect advantages of earlier SGAs (ie, reduced EPS and TD) with reductions in cardiometabolic effects and subsequent risk of coronary heart disease.<sup>8</sup> The following sections discuss desirable side effect profiles of a new antipsychotic and how available antipsychotics measure up.

### Sedation

Antipsychotic-induced sedation, caused by high affinity for histaminergic relative to dopamine receptors,<sup>7</sup> can interfere with functioning and adherence. Clozapine and quetiapine have the greatest risk of sedation and haloperidol and aripiprazole the least.<sup>9</sup>

### Weight Gain

Histaminergic blockade also seems to be related to weight gain.<sup>21</sup> Clozapine and olanzapine are associated with the most weight gain and aripiprazole and ziprasidone with the least.<sup>9,22</sup>

### Metabolic Effects

The SGAs differ significantly in metabolic effects, with olanzapine producing the greatest increases in lipid and glucose levels and aripiprazole the least.<sup>21,22</sup> It is desirable that switching to an antipsychotic with lower liability for weight gain and metabolic abnormalities produce improvements in these areas, an effect seen with ziprasidone and aripiprazole.<sup>21,23,24</sup> Because some metabolic effects associated with antipsychotics may not be weight-related,<sup>21,25</sup> an ideal antipsychotic should be not only weight neutral, but also metabolically neutral.

### Diabetes

The risk of diabetes varies considerably among antipsychotics, with the highest risk associated with olanzapine, clozapine, and low-potency agents, while aripiprazole seems associated with a reduced diabetes risk.<sup>21,26</sup>

### Muscarinic Effects

Muscarinic effects can interfere with cognition and lead to constipation, dry mouth, blurred vision, urinary retention, tachycardia, and potentially psychosis. Antipsychotics vary in affinity for muscarinic receptors, with olanzapine and quetiapine having the highest affinity.<sup>7</sup> Anticholinergic agents given to treat EPS can block muscarinic receptors; anticholinergic load is associated with cognitive adverse effects.<sup>13</sup>

### Orthostatic Hypotension

Antipsychotics differ in  $\alpha_1$ -adrenergic receptor blockade and potential to cause orthostatic hypotension, with quetiapine, followed by olanzapine and risperidone, having the greatest risk.<sup>7</sup>

### Elevated Prolactin Levels

Elevated prolactin levels can cause amenorrhea in women; galactorrhea, mostly in women; erectile dysfunction in men; and breast enlargement/engorgement, decreased libido, anorgasmia, and osteoporosis due to hypogonadism in both genders.<sup>27</sup> The ideal antipsychotic would not raise prolactin levels. The greatest elevation of prolactin occurs with

risperidone, paliperidone, and haloperidol, while clozapine and quetiapine have little effect, and aripiprazole, even when combined with prolactin-elevating drugs, has been shown to normalize or reduce prolactin levels.<sup>8,27</sup>

### EPS, Akathisia, and TD

The SGAs have a lower risk of EPS than high-potency FGAs but do not differ much from low-potency FGAs, except for clozapine and quetiapine, which have minimal EPS risk.<sup>9</sup> In a recent meta-analysis, risperidone was associated with more use of antiparkinsonian medications than clozapine, olanzapine, quetiapine, and ziprasidone.<sup>19</sup> Relatively low rates of akathisia are important, because this at times very uncomfortable side effect has been associated with treatment discontinuation and, when severe, even suicidality. Pooled data from long-term studies showed significantly reduced rates of TD with SGAs (by 600%) compared with haloperidol.<sup>20</sup>

### Life Expectancy and Sudden Cardiac Death (SCD)

Patients with schizophrenia have a gap in life expectancy of 15–25 years compared with the general population, mostly attributable to premature cardiovascular and cerebrovascular death.<sup>28</sup> Patients with severe mental illness have a higher prevalence of modifiable risk factors for cardiovascular disease (CVD) (eg, smoking, obesity, diabetes, hypertension, dyslipidemia) than the general population, as a result of the disease itself, an unhealthy lifestyle, and antipsychotic side effects.<sup>21,29</sup> FGAs and SGAs are also associated with a similar, dose-related increased risk of SCD.<sup>30</sup> It is not clear if and which antipsychotics lead directly to an increased risk of torsades de pointes and SCD and how much this increased risk is due to changes in cardiac repolarization time and/or ischemic heart disease.<sup>21</sup> An ideal antipsychotic would not cause weight gain, produce metabolic complications, prolong QTc interval, or aggravate obesity and CVD.

## ADHERENCE

Discontinuing antipsychotic treatment for schizophrenia for a short time (eg, 1–10 days) can double the risk of hospitalization; longer gaps can triple or quadruple the risk.<sup>31</sup> Factors contributing to nonadherence include lack of efficacy or intolerability of the medication, cognitive dysfunction, poor insight, comorbid conditions (eg, drug abuse), poor therapeutic alliance, complicated dosing regimen, and environmental/life stressors. An ideal antipsychotic would have properties that encourage adherence (eg, once a day or less frequent dosing), a benign side effect profile, subjective acceptability, and ability to improve well-being and functional levels. It would also be available in oral and short- and long-acting injectable (LAI) formulations. Use of an LAI formulation may improve adherence because patients do not need to take medication daily and nonadherence is identified immediately.<sup>32</sup> Although not all studies have found LAI agents superior to oral agents, enrolling patients who agree to participate in a relapse prevention study may select for more adherent patients. When a population-based all-inclusive approach is used, LAI agents appear superior to

oral antipsychotics in all-cause discontinuation and relapse prevention.<sup>33</sup> LAI formulations are available for risperidone, paliperidone, and olanzapine, and a LAI formulation for aripiprazole is in clinical trials.

### EFFECTIVENESS

The Effectiveness Pyramid (Figure 1) shows that efficacy and tolerability are only the initial focus in achieving effectiveness. The importance of balancing efficacy and tolerability is reflected in recent recommendations that favor effective and relatively safer medications (eg, with reduced cardiometabolic risk).<sup>11</sup> While medications are essential in treating schizophrenia, they should be complemented by psychotherapeutic interventions to achieve full effectiveness.

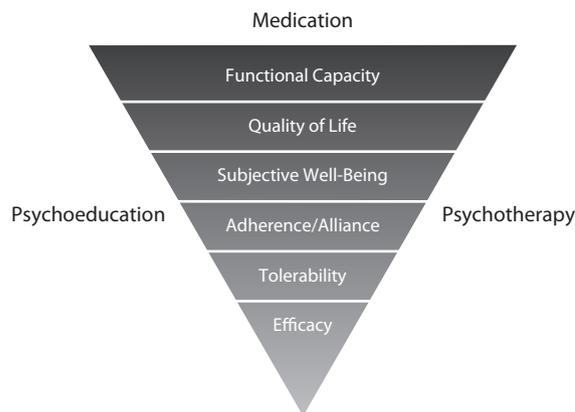
Persistence of treatment is also essential. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, discontinuation for any cause was significantly longer with olanzapine than with the other antipsychotics, but olanzapine was associated with greater increases in weight, glucose, and lipids than the other antipsychotics.<sup>34</sup> However, when patients re-randomized to olanzapine were removed from the analyses, olanzapine was no longer associated with significantly longer time to all-cause discontinuation.<sup>35</sup> The European First Episode Schizophrenia Trial (EUFEST) found lower rates of discontinuation for any cause with amisulpride, olanzapine, quetiapine, and ziprasidone than with haloperidol, but symptom reductions were approximately 60% in all groups.<sup>36</sup> SGAs did show an advantage over haloperidol on the Global Assessment of Functioning and Clinical Global Impressions scales, which may more accurately reflect real-world effectiveness.<sup>36</sup>

The “holy grail” of treatment is recovery. Proposed criteria for recovery specify concurrently sustained improvements for at least 2 years in 4 domains: symptom remission, appropriate role function, performing tasks of day-to-day living without supervision, and social interactions.<sup>37</sup> Unfortunately, a 5-year study in which first-episode patients were treated with antipsychotics in an algorithmic fashion found only a 13.7% recovery rate within or after 5 years.<sup>38</sup> Thus, a great need remains for new antipsychotics that can increase recovery.

### PERSONALIZED CARE

An ideal antipsychotic would promote delivery of “personalized” care through the availability of drug-specific biomarkers for efficacy and tolerability. It is hoped research will identify predictive biomarkers (eg, genetic polymorphisms) and allow for more targeted treatment. A pharmacogenomic analysis of data from the CATIE study found that certain single nucleotide polymorphisms predicted neurocognitive improvement with ziprasidone or olanzapine, but not with the other antipsychotics.<sup>39</sup> The field of metabolomics also holds promise for identifying disease-specific biomarkers. A study that quantified lipid metabolites in patients with schizophrenia found that olanzapine, risperidone, and aripiprazole each had a different metabolomic profile that could potentially be linked to different outcomes in specific patients.<sup>40</sup>

**Figure 1. The Effectiveness Pyramid**



### CONCLUSION

Although there has been clear progress over the past 50 years in developing antipsychotics, clinical needs remain.<sup>8</sup> In terms of efficacy, these include reliance on antidopaminergic activity as the only proven mechanism for treatment of psychosis; limited efficacy for negative and cognitive symptoms; isolated efficacy for comorbid conditions; minimal effects on insight; nonadherence; low functional levels in many, if not most, patients; and availability of only one agent effective for treatment-resistant illness, which is associated with potentially life-threatening adverse effects. In terms of side effects, newer agents produce fewer and less severe neuromotor effects than older agents, and more recently introduced agents combine this with decreased prolactin effects, sedation, anticholinergic load, and/or weight gain and metabolic effects. However, no agent incorporates all of these properties, and it is likely to be impossible to combine all desired effects in one agent. Thus, medications with distinctly different pharmacologic mechanisms need to be developed that target specific aspects of the disease and can be combined in rational, safe, efficacy-enhancing ways.

Given the complexity of schizophrenia, its unknown etiology and pathophysiology, difficulties in measuring clinically meaningful outcomes, and challenges in clinical trial design, it is not surprising that it has remained difficult to develop new treatments.<sup>41</sup> Given the absence of biomarkers and truly personalized medicine, it is important to have treatment options with different advantages and disadvantages that may prove optimal for specific patient subgroups.<sup>42</sup> The introduction of the 3 most recently approved antipsychotics in the United States is a positive development in this regard.<sup>2-4</sup>

To achieve truly personalized prescribing and care for schizophrenia, we need more insight into mechanisms underlying specific disease processes and therapeutic and adverse responses, a goal the National Institute of Mental Health is focusing on in their Research Domain Categories initiative (RDoC) (<http://nimh.nih.gov/research-funding/rdoc/index.shtml>). With this added knowledge, it is very likely that new agents can be developed and available agents and mechanisms can be refined.

**Drug names:** aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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