Though unsupported by evidence, using >1 antipsychotic may make sense for some treatment-resistant patients
In a perfect world, every treatment decision would fall under the protective umbrella of evidence-based medicine. The reality is that up to 30% of schizophrenia patients respond poorly to antipsychotic monotherapy, and addressing their chronic debilitating illness requires clinicians to step outside the realm of evidence.

This does not have to be a blind step, however. Guided by logic, you can apply knowledge of receptor binding profiles, adverse effects, and kinetic considerations when choosing antipsychotic polypharmacy. This article offers evidence to answer 2 questions:

• What clinical evidence and/or pharmacologic rationale support using >1 antipsychotic?
• When might it be appropriate to use 2 antipsychotics in patients with treatment-resistant psychosis?

Antipsychotic polypharmacy defined
“Polypharmacy” can carry a negative connotation, but not all forms are bad. In some circumstances, antipsychotic polypharmacy may be necessary to provide optimum benefit and prevent harm to the patient and/or staff.

Short-term polypharmacy often occurs when switching patients from 1 antipsychotic to another. This “crossover phase” is justified to provide a smooth transition between the 2 agents, as abrupt antipsychotic discontinuation may cause a rebound worsening of psychosis. Other short-term antipsychotic polypharmacy strategies may be necessary in inpatient settings, particularly for a patient who is acutely psychotic or aggressive.
Clinical Point
Adding risperidone to clozapine did not significantly improve schizophrenia’s positive or negative symptoms in short-term controlled trials.

Table 1
Take-home points about antipsychotic polypharmacy

| Long-term antipsychotic polypharmacy is common, even in schizophrenia patients without treatment-refractory psychosis |
| Controlled clinical trials do not support antipsychotic polypharmacy; many clinicians use this strategy, however, so it may have perceived value |
| Which antipsychotic combinations are best—in terms of efficacy and safety—is unclear |
| Controlled trials of combination antipsychotic therapy are difficult to conduct, which limits the availability of evidence to inform clinical practice |
| Whenever you initiate antipsychotic polypharmacy, document your rationale and the alternatives you considered |

Box
Other pharmacologic adjuncts proposed for antipsychotics

As our understanding of psychosis’s pathophysiology of improves, more options will come for treatment-resistant cases. Changes in the glutamatergic system, for example, have been implicated in schizophrenia’s pathophysiology. Lamotrigine—a second-generation anticonvulsant with antiglutamatergic activity—has been studied as augmentation to antipsychotics in patients with schizophrenia. Several randomized, controlled trials suggested clinical benefit from adjunctive lamotrigine, but 2 recent multicenter, randomized, double-blind trials failed to support that finding.

Although not adequately studied, other possible augmentation options may include GABA agonists, COX-2 inhibitors, and selective serotonin reuptake inhibitors.

Long-term polypharmacy

In patients with schizophrenia, which this article addresses, occurs when a clinician elects to use >1 antipsychotic. When a patient improves during cross-titration of 2 antipsychotics, for example, the clinician may decide not to fully complete the switch and continue treatment with both agents.

Experience-based treatment?

Antipsychotic polypharmacy is prevalent (reported in up to 25% of outpatients and 50% of inpatients with schizophrenia), costly for patients and insurers, and likely to be associated with increased risk of adverse effects and drug-drug interactions. Despite what is known, a wide gap exists between the science and clinical practice of combination antipsychotic therapy in schizophrenia (Table 1).

Clinical trials. The efficacy and safety of antipsychotic combinations in schizophrenia (with options including FGA + FGA, FGA + SGA, and SGA + SGA) has not been studied adequately in well-controlled, systematic trials. Four short-term—6 to 26 weeks—randomized, double-blind, controlled trials have examined antipsychotic polypharmacy (clozapine + risperidone) in patients with schizophrenia:

- In 3 studies, adding risperidone to clozapine did not significantly improve positive or negative symptoms.
- In all 4 studies, clozapine + risperidone was associated with increased sedation, akathisia, hyperprolactinemia, and elevated fasting blood glucose.

These studies do not support a favorable benefit-risk profile for clozapine + risperidone treatment, and this combination’s long-term efficacy and safety has not been examined. Evidence for other antipsychotic combinations (such as olanzapine + risperidone or quetiapine + risperidone) is restricted to open-label, uncontrolled trials and case reports. Other options will likely develop for augmenting antipsychotic therapy for treatment-resistant schizophrenia, but none are available and supported by adequate data at this time (Box).
continued from page 42

Table 2

Questions to consider before initiating antipsychotic polypharmacy

Ask yourself, ‘Have I . . .

<table>
<thead>
<tr>
<th>Determined</th>
<th>if my patient is taking the prescribed medication correctly or even at all?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allowed for</td>
<td>an adequate trial—dosage and duration—of antipsychotic monotherapy?</td>
</tr>
<tr>
<td>Maximized the dosage</td>
<td>of the current antipsychotic?</td>
</tr>
<tr>
<td>Tried at least 2 to 3 trials</td>
<td>of a first-generation and/or second-generation antipsychotic?</td>
</tr>
<tr>
<td>Tried an adequate trial</td>
<td>of clozapine?</td>
</tr>
<tr>
<td>Re-evaluated</td>
<td>my patient’s diagnosis?</td>
</tr>
<tr>
<td>Considered tolerability</td>
<td>and safety issues associated with adding another antipsychotic?</td>
</tr>
<tr>
<td>Considered drug-drug interactions</td>
<td>that may occur as a result of adding another antipsychotic?</td>
</tr>
<tr>
<td>Considered nonpharmacologic alternatives,</td>
<td>including psychosocial interventions?</td>
</tr>
<tr>
<td>Augmented</td>
<td>with a nonantipsychotic medication, such as valproic acid?</td>
</tr>
<tr>
<td>Considered my patient’s</td>
<td>ability to pay for an additional antipsychotic?</td>
</tr>
<tr>
<td>Considered whether I can monitor</td>
<td>my patient more closely while he/she is on multiple antipsychotics?</td>
</tr>
</tbody>
</table>

Mortality risk? Two independent, longitudinal cohort studies have found antipsychotic polypharmacy to be a statistically significant predictor of reduced survival.21,22 Although these studies have identified a possible association, additional research is required to determine whether increased mortality in schizophrenia is attributable to the disorder, comorbid medical conditions, antipsychotic medications, or a complex interaction of factors.

Treatment guidelines—such as the Texas Medication Algorithm Project’s updated treatment algorithm for schizophrenia23—reflect the paucity of controlled studies of antipsychotic combinations. The expert consensus panel that developed the TMAP algorithm recommends clozapine augmentation with an FGA or SGA, or electroconvulsive therapy after adequate trials of antipsychotic monotherapy, including clozapine. The panel recommends reserving other antipsychotic combinations as a last-line strategy (see Related Resources, page 53).

‘Sensible’ pharmacology

Despite the lack of supporting evidence, many clinicians apparently are using antipsychotic polypharmacy for schizophrenia patients with treatment-resistant psychosis. Moreover, reports that up to one-fourth of outpatients and one-half of inpatients may receive antipsychotic polypharmacy2–7 suggest that this approach is not being reserved for treatment-resistant psychosis. Rather, it is being used in non-treatment-refractory schizophrenia patients as well—a practice Stahl labeled a “dirty little secret.”24

Before you consider using antipsychotic polypharmacy for a schizophrenia patient, we suggest that you answer a series of questions to rationalize your decision (Table 2). These questions seem intuitive, but they represent appropriate clinical practice and may support the use of multiple antipsychotics in selected patients.

Which combination? If you determine that a patient is an appropriate candidate for antipsychotic polypharmacy, think about the pharmacologic profiles of available agents. Administering 2 antipsychotics may augment pharmacologic activity, provide an additive effect, or worsen your patient’s symptoms.

Although data from well-controlled studies of clozapine + risperidone do not support its efficacy,2–12 this combination is rational from a pharmacologic perspective. Clozapine shows a lower D2 receptor occupancy (16% to 68%) than that of risperidone (63% to 89%),25 so risperidone’s additional D2 receptor occupancy may enhance a patient’s response to clozapine. Table 3 (page 51) lists other potentially “sensible” antipsychotic-antipsychotic combinations.

Not all combinations make pharmacologic sense, however, such as adding haloperidol to aripiprazole. Haloperidol’s...
Table 3

Theoretically beneficial antipsychotic combinations

<table>
<thead>
<tr>
<th>Antipsychotic #1</th>
<th>Antipsychotic #2</th>
<th>Theoretical pharmacologic benefit</th>
<th>Theoretical safety/tolerability concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Olanzapine</td>
<td>Additional D2 receptor occupancy</td>
<td>Anticholinergic effects, metabolic adverse events, orthostasis, sedation</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Quetiapine</td>
<td>D2 agonist/antagonist in addition to ‘fast on/fast off’ D2 blockade; unique 5HT activity</td>
<td>Sedation</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Olanzapine</td>
<td>Differing D2 blockade properties with minimal increase in EPS risk; 2 agents with structural similarity to clozapine</td>
<td>Anticholinergic effects, metabolic adverse events, orthostasis, sedation</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Loxapine</td>
<td>D2 agonist/antagonist plus a typical antipsychotic that has atypical properties at low doses; 2 agents thought to not potentiate weight gain</td>
<td>Orthostasis, sedation</td>
</tr>
</tbody>
</table>

D2: dopamine; 5HT: serotonergic; EPS: extrapyramidal symptoms

pharmacologic binding profile (potent D2 blockade) may cancel out any benefits with regard to extrapyramidal symptoms and hyperprolactinemia from aripiprazole’s receptor binding profile (D2 agonist/antagonist). In theory, any displacement of antipsychotic medication from D2 receptors because of competing inhibition may increase risk of symptom exacerbation.

Safety/tolerability

Reduced dosages. Combining antipsychotics may allow you to increase treatment efficacy and improve patient tolerability. Lower dosages of 2 antipsychotics may cause fewer side effects than a high dosage of 1 antipsychotic.

For example, case reports and retrospective studies suggest that adding aripiprazole to clozapine may improve antipsychotic efficacy and reduce metabolic adverse events in treatment-resistant patients. In these cases, clozapine dosages were lower than those usually used in patients with schizophrenia.

Metabolic effects. Carefully weigh the propensity of some antipsychotics to induce weight gain, hyperlipidemia, or glucose dysregulation if you plan to use these agents as part of a polypharmacy regimen. Among SGAs, clozapine and olanzapine are associated with the highest risks of metabolic adverse effects, followed by quetiapine and risperidone. Aripiprazole and ziprasidone are less likely than other SGAs to cause these effects.

A recent study found a higher incidence of metabolic syndrome in patients receiving antipsychotic polypharmacy. The increased incidence was linked to demographics and clinical risk factors, however, and was not independently associated with the use of multiple antipsychotics. Because evidence is scarce and inconclusive, the risk of metabolic adverse events is unknown when antipsychotics are combined. Exercise caution when combining antipsychotics—particular those known to cause adverse metabolic effects—in case the risk is additive.

Tardive dyskinesia (TD). SGAs are associated with a lower incidence of TD compared with FGAs, but adding an FGA to an SGA may increase the patient’s TD risk. Also assess patients regularly (as often as weekly during acute treatment and every 6 to 12 months during maintenance...
Antipsychotic combinations

Clinical Point

Exercise caution when combining antipsychotics known to cause adverse metabolic effects, in case the risk is additive.

QTc effects. Because antipsychotics can increase QTc intervals, follow patients closely with cardiac monitoring and electrocardiography. Monitoring is especially important if you use ziprasidone in combination therapy, as it may increase the QTc interval more than other SGAs.28

Other adverse effects. The concurrent use of 2 antipsychotics may amplify side effects that are generally considered mild, such as sedation. For example, risperidone and ziprasidone are considered to cause low to moderate sedation. This combination may result in an additive sedative effect that could negatively impact the patient’s psychosocial functioning.

Anticholinergic effects may also be potentiated, especially if a particular combination of antipsychotics warrants anticholinergic medication use for extrapyramidal symptoms.

References


Bottom Line

Evidence does not support the practice, but many clinicians use antipsychotic polypharmacy for selected schizophrenia patients with treatment-resistant psychosis. If your decision to combine antipsychotics is within appropriate clinical practice, choose agents with compatible pharmacologic profiles. Monitor closely for increased risk of adverse events, including metabolic side effects, tardive dyskinesia, and prolonged QTc interval.
Related Resources


Drug Brand Names

- Aripiprazole - Abilify
- Clozapine - Clozaril
- Haloperidol - Haldol
- Lamotrigine - Lamictal
- Lamotrigine - Lamictal
- Loxapine - Loxitane
- Olanzapine - Zyproxa
- Quetiapine - Seroquel
- Risperidone - Risperdal
- Valproic acid - Depakene
- Ziprasidone - Geodon

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