

A close-up photograph of a hand with fingers spread, holding several small, textured, golden-brown question marks. The background is a warm, textured surface in shades of orange and brown. The text 'Treatment-resistant psychosis' is overlaid on the upper part of the image.

Treatment-resistant psychosis

Are **2** antipsychotics more effective than **1**?

Combining antipsychotics is 'safe' for schizophrenia patients when the benefits outweigh the risks of ineffective single-drug therapy

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Off-label prescribing of two or more antipsychotics for treatment-resistant psychosis carries inherent risks for both schizophrenia patients and their psychiatrists. You can reduce these risks by demonstrating that your patient will benefit more from combining antipsychotics than from monotherapy alternatives.

Until more empiric data become available, clinicians carry the burden of documenting individual patient response to justify combining antipsychotics. This article can help you identify and counsel possible candidates for this therapy, assess the risks and benefits, and defend your treatment choices if necessary.

WHAT DOES 'COMBINING' MEAN?

For this discussion, "combining antipsychotics" does not mean simultaneously using two or more antipsychotics to treat psychosis. Rather, it refers to using two or more antipsychotics for long-term control of psychotic symptoms. It does not apply to short-term tactics, such as overlapping antipsychotics when switching between them or com-



Box

Defining treatment-resistant schizophrenia

Most trials have used criteria from the seminal clozapine study to define “treatment resistant” schizophrenia:

- History of poor response to one or more antipsychotics.
- Demonstrated nonresponse to adequate dosage and duration of a nonclozapine antipsychotic before starting clozapine.²

This work defines treatment resistance as persistent positive symptoms despite treatment with ≥ 2 different antipsychotics other than clozapine.

Newer antipsychotics are different. The original clozapine studies found little likelihood that patients who had not responded to haloperidol would respond to chlorpromazine. Newer-generation antipsychotics are pharmacologically more heterogeneous than the first-generation agents, however, and failure to respond to one might not mean that none of the others will help.

When to start clozapine? Solid evidence is limited, but a consensus panel has recommended starting clozapine after two unsuccessful trials of newer-generation antipsychotics, with the option to try a third antipsychotic (first- or newer-generation) if clinically warranted.³

Symptoms vs function. In clinical practice, defining treatment resistance as persistent positive symptoms may exclude patients impaired by severe negative symptoms and/or disorganized thought processes. The treatment goal is to restore function, not just to reduce psychosis. As treatments evolve, we can expect more emphasis on a recovery model that addresses total patient well-being and combines psychosocial and pharmacologic interventions.

binning a parenteral and an oral antipsychotic when treating an acute episode.

How long must a combination be used to qualify as long-term treatment? No standard exists, but a period >6 weeks exceeds normal short-term treatment.

HOW SAFE ARE COMBINATIONS?

Patient risk. Combination antipsychotics are used to treat 10% to 20% of schizophrenia patients in this country and $>90\%$ of those in some Asian

countries, such as Japan.¹ Statistics on the prevalence of combining antipsychotics seldom:

- distinguish between short- and long-term use
- identify when practitioners use combinations to treat co-existing symptoms such as insomnia, rather than for psychosis.

Even so, these numbers seem to indicate that combination therapy is not unsafe for patients with treatment-resistant schizophrenia (*Box*).^{2,3} Qualitatively greater safety problems with antipsychotic combinations—compared with monotherapy—would show up, even in our relatively crude post-marketing surveillance system.

Clinicians, however, must define safety in terms of risks and benefits. Given that every medication has risks—some (such as allergic reactions) unique to the individual patient—adding another drug to a treatment regimen will always add risk. When considering more than one antipsychotic, ask yourself:

- Do benefits outweigh risks?
- Is a combination the least risky way to achieve these benefits?

Practitioner risk can also influence treatment selection. Medical risks of combining antipsychotics may be small, but a poor outcome from this off-label use might be more likely to lead to a lawsuit than the same poor outcome with another medication choice.

How much does a practitioner’s perception of medicolegal risk influence treatment selection? No doubt, comfort level varies greatly. I have frequently met prescribers who use antipsychotic combinations instead of clozapine for fear of being sued should agranulocytosis occur.

A PRACTICAL VIEW

Medical risks. Treating patients with antipsychotic combinations may be associated with medical risks (*Table 1*). Patients are less likely to adhere to complex medication regimens than to simple ones. Thus, adding a second antipsychotic may decrease adherence to the first antipsychotic and to other medications, such as for hypertension, diabetes, etc.

Increased side-effect risk has been reported with antipsychotic combinations.⁴ Side effects include those expected from one or both drugs in the combination, especially extrapyramidal effects when conventional antipsychotics are included.^{4,5} Because the total antipsychotic dosage can be considerably higher than usual in patients receiving combinations,⁵ some of the increased side effect burden is probably related to high dosing, rather than to the combinations.

Pharmacodynamic or pharmacokinetic interactions or the loss of an agent's advantages are infrequently reported, perhaps because prescribers are not looking for these effects or do not consider them worth reporting. Of particular concern is tardive dyskinesia (TD), which may develop when conventional antipsychotics are added to agents with very low propensity to cause TD—such as clozapine.

Nonmedical risks. Table 1 also lists potential nonmedical risks associated with combining antipsychotics. No literature exists to help you assess how these considerations might affect your practice.

litigation. As noted, some clinicians prefer

Table 1

Potential risks and benefits of combining antipsychotics

Medical risks

- Decreased adherence to multiple medications
- Increased and/or unexpected side effects
- Increased potential for undesirable pharmacokinetic or pharmacodynamic interactions
- Difficulties in making rational dose adjustments
- Loss of advantages of one of the medications

Nonmedical risks

- Lack of evidence to defend practice in medicolegal cases
- Increased costs if combining second-generation antipsychotics
- Increased quality assurance scrutiny and paperwork

Medical benefits

- Reduced symptoms
- Reduced metabolic side effects (such as partially substituting another atypical antipsychotic for a high clozapine dosage)

Side effects include those expected from one or both antipsychotics in the combination

combining antipsychotics instead of using clozapine because they fear legal action should a patient develop agranulocytosis. In the author's view, this fear is not well-grounded. Successful

lawsuits typically find evidence that the clinician committed errors of omission or commission.

In the case of blood monitoring for clozapine-induced neutropenia, the parameters are clear and enforced. You must follow community standards of practice, which provide a strong legal defense.

Administrative scrutiny. Quality assurance programs are increasingly identifying and monitoring antipsychotic combinations—an obvious target by being frequent, lacking a strong evidence base, increasing costs, and raising liability concerns. Typically, such programs discourage antipsychotic combi-



Table 2

Results of studies using combination antipsychotic therapy

Combination	Type of trial	First author	Outcome measures	Results
Clozapine/sulpiride*	RCT	Shiloh ⁸	Positive, negative, and depressive symptoms	Positive
Clozapine/risperidone	RCT	Josiassen ⁹	Positive and negative symptoms	Positive
Clozapine/risperidone	RCT	Yagcioglu ¹⁰	Positive and negative symptoms	Negative
Clozapine/quetiapine	LCS	Reinstein ¹¹	Body weight, serum glucose	Positive
Clozapine/amisulpride*	LCS	Agelink ¹²	Positive and negative symptoms	Positive

RCT: randomized controlled trial; LCS: large case series

*Sulpiride and amisulpride are not available in the United States.

nations and impose administrative hurdles to starting or continuing them.

Gathering data and documenting it in the patient’s medical record—to be discussed later—is key to demonstrating that a combination’s superior efficacy for the individual patient justifies its use.

Medical benefits. Guidelines and algorithms for drug treatment of schizophrenia either omit combination antipsychotics or suggest this strategy when all else has failed.^{6,7} Lack of evidence for a practice is not the same as evidence against it, however. A combination may be better for some patients than any available antipsychotic monotherapy.

Antipsychotic combinations have been examined in more literature reviews than randomized controlled trials—all of which have addressed augmenting clozapine with another antipsychotic (Table 2).⁸⁻¹² Augmentation with psychotropics other than a second antipsychotic has most often

been tested for negative and cognitive symptoms,⁴ but some evidence has shown adjunctive anticonvulsants and cognition-enhancing agents to improve positive symptoms.⁶

All randomized trials have addressed adding another antipsychotic to clozapine therapy

Reducing side effects is not directly related to treatment-resistant psychosis, but some articles describe managing clozapine’s metabolic side effects by partially substituting another atypical antipsychotic.^{11,13}

Because clozapine is the treatment of choice for treatment-resistant psychosis, consider tactics that maintain its benefits while reducing its metabolic liabilities. Reducing the clozapine dosage (if feasible) is the first-line approach, but partially substituting another antipsychotic might help if psychotic symptoms return.

CLINICAL MANAGEMENT HINTS

Document, document, document. Crucial to “non-standard” treatments such as combining antipsy-

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continued from page 16

chotics is using and documenting good medical practices. These include:

- accurately assessing patients
- carefully weighing illness risks vs treatment risks
- talking regularly to patients about their treatment and therapeutic options (*Table 3*).

Documenting these practices is enormously helpful to other clinicians who see your patient and to validate the quality of your treatment to external reviewers, such as quality assurance, the Joint Commission on Accreditation of Healthcare Organizations, or juries. Clearly document failure or refusal of more-standard therapies, as well as your efforts to establish that neither antipsychotic alone has produced as beneficial a response as the two agents combined.

Use objective measures. Brief scales to measure psychotic symptoms are being increasingly used in public mental health settings.⁶ For example, four psychosis items from the Brief Psychiatric Rating Scale (hallucinations, unusual thought content, paranoia, and disorganized thought) can quickly assess and capture much of the variance of the full scale in patients with schizophrenia.¹⁴

When properly used, these objective and reliable scales can document clinical change and track illness course across time and providers. Other objective outcome measures can contribute to quality of care and its documentation. For more information, visit the Substance Abuse and Mental Health Services Administration Web site (*see Related Resources, page 20*).

Although it seems obvious that persistent illness is not a good thing, the risks of persistent psychosis vary from patient to patient. Some function relatively well despite ongoing psychotic thoughts, whereas others are terribly impaired, demoralized, and/or suicidal. The rationale for

Table 3

3 tips for managing risk and medications

Use objective, quantifiable symptom measures at regular intervals

Document patient's risk of persistent psychosis, based on history

Discuss risks and benefits of other treatment options with the patient and/or family at regular intervals

nonstandard treatment such as an antipsychotic combination is to reduce patient suffering and risk and/or to increase function.

Discuss options with patients. Finally, schizophrenia patients (and involved significant others) need to understand and participate in treatment. Ongoing discussion of treatment options is an important part of this process. For example, initially reluctant patients often come to accept clozapine treatment after discussing its risks and benefits with clinicians and other patients who are taking clozapine. Documenting these discussions is as beneficial to the patient and clinician as is documenting symptoms and treatment effects.

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Long-term, off-label use of combination antipsychotics for persistent psychotic symptoms lacks a strong evidence base. Combining antipsychotics can pose risks to both patients and clinicians. Discuss options with the patient, and document response and side effects to show that a treatment's benefits outweigh its risks.

BottomLine



Combining antipsychotics

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Related resources

- ▶ How to use medication in a systematic and effective way, as part of the overall treatment for severe mental illness. In: *Evidence-based practices: Shaping mental health services toward recovery. Medication management approaches in psychiatry*. Substance Abuse and Mental Health Services Administration. U.S. Department of Health and Human Services. <http://mentalhealth.samhsa.gov/cmhs/communitysupport/toolkits/medication/>.
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DRUG BRAND NAMES

Clozapine • Clozaril
Haloperidol • Haldol
Quetiapine • Seroquel

Risperidone • Risperdal
Ziprasidone • Geodon

DISCLOSURES

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