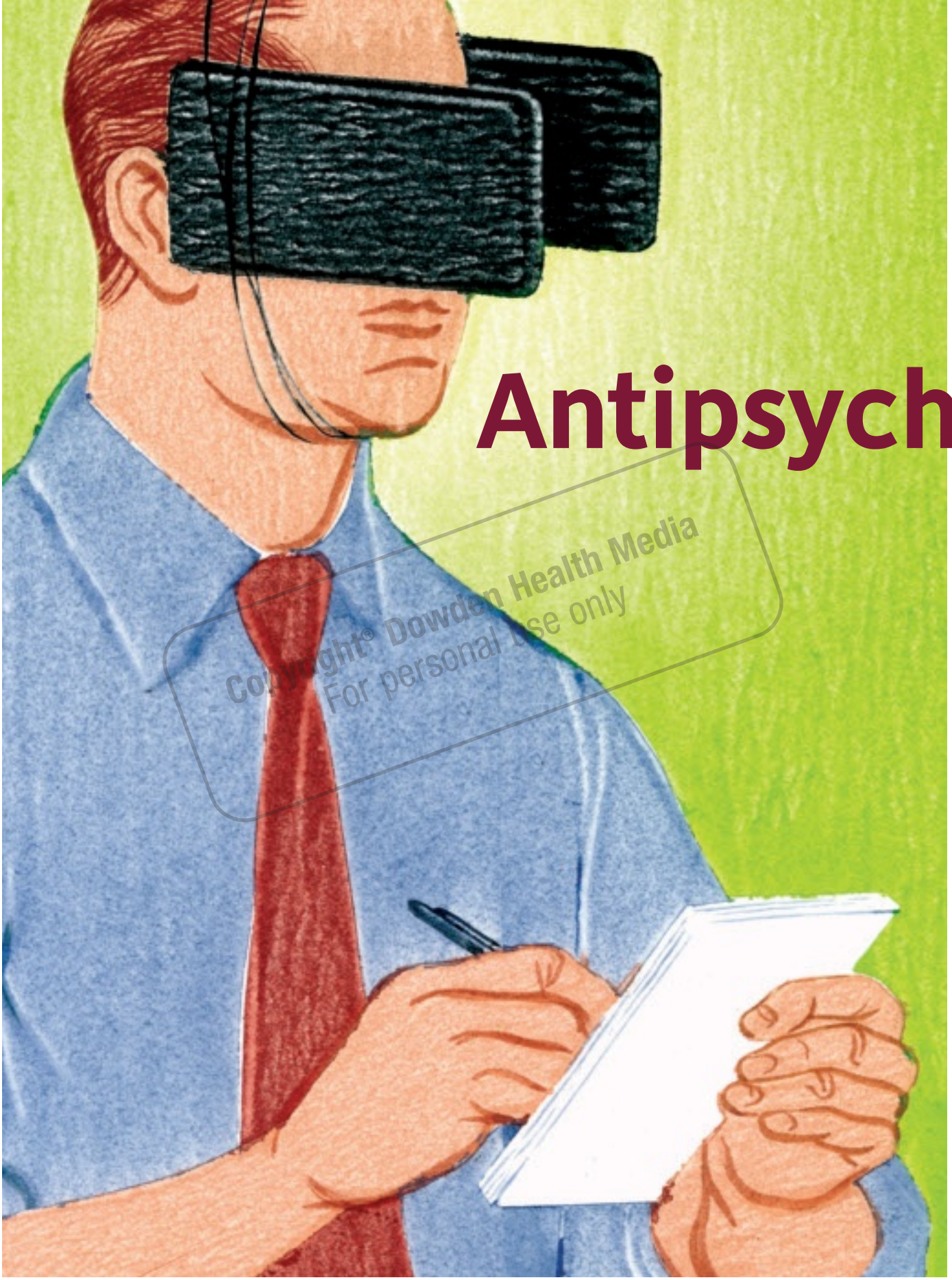
Antipsych



ALEX NABAUM FOR CURRENT PSYCHIATRY

Though unsupported by evidence, using >1 antipsychotic may make sense for some treatment-resistant patients

Current PSYCHIATRY

otic combinations

Blind step or logical?

Aaron P. Gibson, PharmD, MS
Assistant professor
College of pharmacy
University of New Mexico
Albuquerque

Nick C. Patel, PharmD, PhD
Assistant professor
College of pharmacy
University of Georgia
Augusta

John Lauriello, MD
Professor and vice chair
Department of psychiatry
University of New Mexico

Peter F. Buckley, MD
Professor and chair
Department of psychiatry & health behavior
Medical College of Georgia
Augusta

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,[1] 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.

continued

Antipsychotic combinations

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' 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.[15]

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,[16-18] but 2 recent multicenter, randomized, double-blind trials failed to support that finding.[19]

Although not adequately studied, other possible augmentation options may include GABA agonists, COX-2 inhibitors, and selective serotonin reuptake inhibitors.[20]

The use of a first-generation antipsychotic (FGA) to lead in a second-generation antipsychotic (SGA) is a justifiable treatment strategy. In addition, sedative antipsychotics such as quetiapine often are used during initial treatment of acutely ill patients and subsequently withdrawn.

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),[2-7] costly for patients and insurers,[8] 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 studies[9-12] have examined antipsychotic polypharmacy (clozapine + risperidone) in patients with schizophrenia:

- In 3 studies,[9,11,12] 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.[13,14] 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***).[15-20]

continued on page 46

continued from page 42

Antipsychotic combinations

Clinical Point

Depending on the drugs' pharmacologic profiles, combining 2 antipsychotics may provide an additive effect or worsen your patient's symptoms

Table 2

Questions to consider before initiating antipsychotic polypharmacy

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

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 schizophrenia[23]—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 polypharmacy[2-7] 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,[9-12] 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

continued on page 51

continued from page 46

Table 3

Theoretically beneficial antipsychotic combinations

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

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[26,27] 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.[28]

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.[29]

Because evidence is scarce and inconclusive, the risk of metabolic adverse events is unknown when antipsychotics are combined. Exercise caution when combining antipsychotics—particularly 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.[30] Also assess patients regularly (as often as weekly during acute treatment and every 6 to 12 months during maintenance

Clinical Point

Lower dosages of 2 antipsychotics may cause fewer side effects than a high dosage of 1 antipsychotic

TO COMMENT ON THIS ARTICLE OR OTHER TOPICS IN THIS ISSUE, VISIT
CurrentPsychiatry.com and click on the "Send Letters" link or write to Erica Vonderheid, erica.vonderheid@dowdenhealth.com

Clinical Point

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

treatment)[31] for extrapyramidal symptoms, including akathisia. Administer appropriate rating scales (such as the Abnormal Involuntary Movements Scale [AIMS], Barnes Akathisia Rating Scale [BARS], or Simpson-Angus Rating Scale [SARS]), and treat these adverse events as clinically indicated.

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

1. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353(12):1209-23.
2. Chakos MH, Glick ID, Miller AL, et al. Baseline use of concomitant psychotropic medications to treat schizophrenia in the CATIE trial. *Psychiatr Serv* 2006;57(8):1094-101.
3. Botts S, Hines H, Littrell R. Antipsychotic polypharmacy in the ambulatory care setting, 1993-2000. *Psychiatr Serv* 2003;54(8):1086.
4. Tapp A, Wood AE, Secrest L, et al. Combination antipsychotic therapy in clinical practice. *Psychiatr Serv* 2003;54(1):55-9.
5. Paton C, Lelliott P, Harrington M, et al. Patterns of antipsychotic and anticholinergic prescribing for hospital inpatients. *J Psychopharmacol* 2003;17(2):223-9.
6. Tempier RP, Pawliuk NH. Conventional, atypical, and combination antipsychotic prescriptions: a 2-year comparison. *J Clin Psychiatry* 2003;64(6):673-9.
7. Jaffe AB, Levine J. Antipsychotic medication coprescribing in a large state hospital system. *Pharmacoepidemiol Drug Saf* 2003;12(1):41-8.
8. Valuck RJ, Morrato EH, Dodd S, et al. How expensive is antipsychotic polypharmacy? Experience from five US state Medicaid programs. *Curr Med Res Opin* 2007;23(10):2567-76.
9. Freudenreich O, Henderson DC, Walsh JP, et al. Risperidone augmentation for schizophrenia partially responsive to clozapine: a double-blind, placebo-controlled trial. *Schizophr Res* 2007;92(1-3):90-4.
10. Josiassen RC, Joseph A, Kohegyi E, et al. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 2005;162(1):130-6.
11. Honer WG, Thornton AE, Chen EY, et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. *N Engl J Med* 2006;354(5):472-82.
12. Anil Yağcioğlu AE, Kivircik Akdede BB, Turgut TI, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. *J Clin Psychiatry* 2005;66(1):63-72.
13. Chan J, Sweeting M. Combination therapy with non-clozapine atypical antipsychotic medication: a review of current evidence. *J Psychopharmacol* 2007;21(6):657-64.
14. Lerner V, Libov I, Kotler M, Strous RD. Combination of "atypical" antipsychotic medication in the management of treatment-resistant schizophrenia and schizoaffective disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;28(1):89-98.
15. Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am J Psychiatry* 2001;158(9):1367-77.
16. Kremer I, Vass A, Gorelik I, et al. Placebo-controlled trial of lamotrigine added to conventional and atypical antipsychotics in schizophrenia. *Biol Psychiatry* 2004;56(6):441-6.
17. Tiihonen J, Hallikainen T, Ryynänen OP, et al. Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. *Biol Psychiatry* 2003;54(11):1241-8.
18. Zoccali R, Muscatello MR, Bruno A, et al. The effect of lamotrigine augmentation of clozapine in a sample of treatment-resistant schizophrenic patients: a double-blind, placebo-controlled study. *Schizophr Res* 2007;93(1-3):109-16.
19. Goff DC, Keefe R, Citrome L, et al. Lamotrigine as add-on therapy in schizophrenia: results of 2 placebo-controlled trials. *J Clin Psychopharmacol* 2007;27(6):582-9.
20. Nasrallah HA. Innovative polypharmacy: when dopamine blockade is not enough [editorial]. *Current Psychiatry* 2007;6(11):17-18.

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

- Texas Medication Algorithm Project (TMAP). Schizophrenia antipsychotic treatment algorithm. www.dshs.state.tx.us/mhprograms/TIMA.shtm.
- Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, 2nd ed. *Am J Psychiatry* 2004;161(suppl):1-56.

Drug Brand Names

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

Disclosures

Dr. Gibson reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products. He receives research support from the PhRMA Foundation.

Dr. Patel receives grant support from Takeda Pharmaceuticals and is a consultant for Eli Lilly and Company and Shire Pharmaceuticals.

Dr. Lauriello receives grant support from Eli Lilly and Company and serves as a consultant to Eli Lilly and Company and Vanda Pharmaceuticals.

Dr. Buckley receives grant support from AstraZeneca, National Institute of Mental Health, Pfizer Inc., Solvay, and Wyeth and is a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Janssen Pharmaceutica, Lundbeck, Pfizer Inc., Solvay, and Wyeth. He receives honoraria from Bristol Myers-Squibb, Janssen Pharmaceutica, Lundbeck, and Pfizer Inc.

21. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. *Br J Psychiatry* 1998;173:325-9.
22. Joukamaa M, Heliovaara M, Knekt P, et al. Schizophrenia, neuroleptic medication and mortality. *Br J Psychiatry* 2006;188:122-7.
23. Moore TA, Buchanan RW, Buckley PF, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry* 2007;68(11):1751-62.
24. Stahl SM. Antipsychotic polypharmacy, part 1: therapeutic option or dirty little secret? *J Clin Psychiatry* 1999;60(7):425-6.
25. Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry* 1999;156(2):286-93.
26. Lim S, Pralea C, Schnitt J, et al. Possible increased efficacy of low-dosed clozapine when combined with aripiprazole. *J Clin Psychiatry* 2004;65(9):1284-5.
27. Karunakaran K, Tungaraza TE, Harborne GC. Is clozapine-aripiprazole combination a useful regimen in the management of treatment-resistant schizophrenia? *J Psychopharmacol* 2007;21(4):453-6.
28. Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs* 2007;21(11):911-36.
29. Correll CU, Frederickson AM, Kane JM, et al. Does antipsychotic polypharmacy increase the risk of metabolic syndrome? *Schizophr Res* 2007;89(1-3):91-100.
30. Haddad PM, Dursun SM. Neurologic complications of psychiatric drugs: clinical features and management. *Hum Psychopharmacol* 2008;23(suppl 1):15-26.
31. Marder SR, Essock S, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry* 2004;161(8):1334-49.