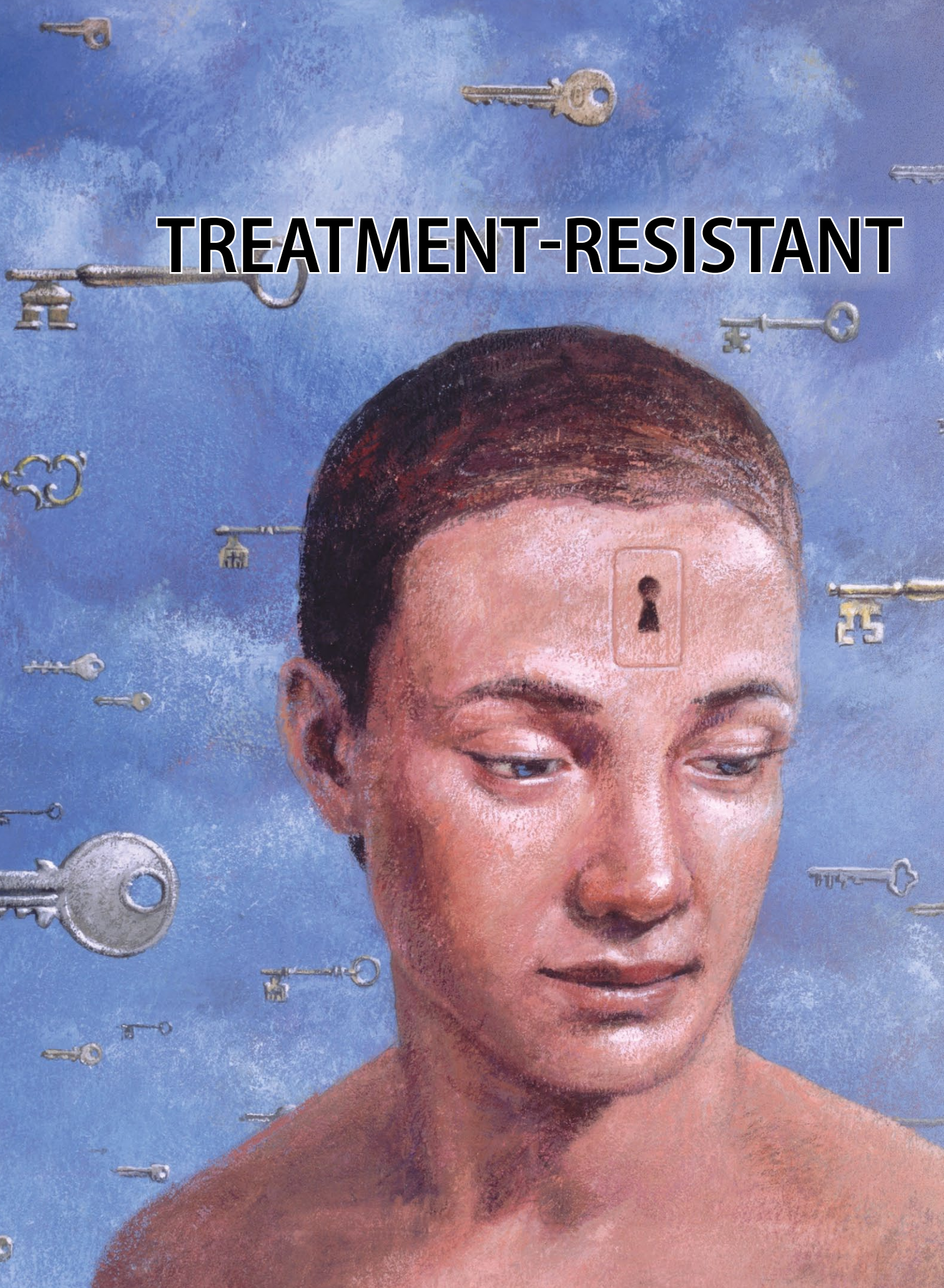


TREATMENT-RESISTANT





SCHIZOPHRENIA: What can we do about it?

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Use pharmacotherapy and other interventions to target the symptoms that matter most to your patient

Patients with treatment-resistant schizophrenia can be broadly defined to include any persons with residual symptoms that cause distress or impairment despite several treatment attempts. Unfortunately, this definition may include most of our patients with schizophrenia.

Clinical trial data on treatment-resistant schizophrenia can be contradictory, leaving “N of 1” empirical treatment trials for individual patients as the current state of the art. This article presents data from clinical trials for pharmacologic and nonpharmacologic options and offers recommendations to try to help our treatment-resistant patients.

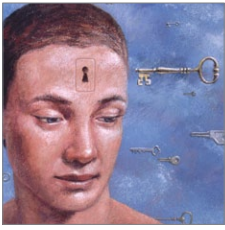
Defining treatment resistance

Research reports regarding treatment-resistant or treatment-refractory schizophrenia have relied on operational criteria such as that found in the pivotal study for clozapine¹:

- at least 3 periods of treatment in the preceding 5 years with neuroleptic agents from at least 2 different chemical classes at dosages equivalent to ≥ 1000 mg/d of chlorpromazine for 6 weeks, each without significant symptomatic relief, and
- no period of good functioning within the preceding 5 years.¹

In that study, patients also underwent a prospective treatment trial with what we now know are high doses of haloperidol (up to 60 mg/d or higher) and benztropine mesylate (6 mg/d) for a period of 6 weeks to confirm lack of drug responsiveness.

continued



Refractory schizophrenia

Clinical Point

Before concluding that a patient is treatment-resistant, consider medication adherence and possible substance use



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Other studies have more relaxed criteria, such as:

- persistent positive symptoms—hallucinations, delusions, or marked thought disorder—after at least 6 contiguous weeks of past or present treatment, with ≥ 1 typical antipsychotics at doses of ≥ 600 mg/d in chlorpromazine equivalents
- a poor level of functioning over the past 2 years, as defined by the lack of competitive employment or enrollment in an academic or vocational program and not having age-expected interpersonal relations with someone outside the biologic family with whom ongoing regular contacts were maintained.²

In this study, no prospective period of treatment to confirm lack of drug responsiveness was required.

The most clinically relevant definition of treatment resistance depends on the patient's individual circumstances. For some patients, targeting positive symptoms is a high priority; for others it may be negative and cognitive symptoms; for others, it may be excitement. Moreover, families may complain of symptoms or behavior that are of little or no concern to your patient.

Although we desire treatment response and remission for our patients, definitions for remission and functional recovery are in flux. Proposed criteria define symptomatic remission as 6-month maintenance of simultaneous ratings of mild or less on delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms.^{3,4} Emsley et al⁴ note that reported remission rates vary widely across studies (17% to 88%) and that patients in remission do better than their non-remitted counterparts in several other outcome domains. Also, patients move in and out of remission over time. Predictors of remission include:

- early treatment response
- baseline symptom severity
- subjective well-being.⁴

Recovery is a more complex construct than remission and includes social outcomes. Although recovery lacks a standard definition, it is the implied goal of treatment. Anything short of recovery can be viewed as inadequate. If we set the bar

at this height, many or most of the patients we treat for schizophrenia could be considered treatment-resistant.

Confounding factors

Before concluding that a patient is treatment-resistant, address medication adherence and possible substance use. Partial or nonadherence with antipsychotic treatment is common—approximately one-half of patients are nonadherent⁵—and associated with relapse and re-hospitalization.⁶ In addition, an estimated one-half of all individuals with schizophrenia also use substances.⁷

Be aware of the optimal dose for any particular antipsychotic and factors that can interfere with achieving adequate plasma levels. This means acknowledging that dosing ranges established during registration studies may not reflect the needs of day-to-day clinical practice.⁸ Pharmacokinetic interactions with other medications, such as carbamazepine or rifampin, can induce liver enzymes and result in subtherapeutic antipsychotic levels. Cigarette smoking also may have this effect. Lowered clozapine or olanzapine plasma levels have been observed in patients who resume smoking after being discharged from a non-smoking inpatient environment. Some antipsychotics, such as ziprasidone and lurasidone, must be taken with food in order to have sufficient bioavailability.⁹

What does a patient want?

Patients with schizophrenia often have limited insight into their psychotic symptoms.¹⁰ Savvy clinicians will attempt to leverage a patient's insight into ancillary symptoms—such as impaired sleep, anxiety, and dysphoria—to encourage a therapeutic alliance and therefore adherence. If patients feel their concerns are not addressed, they may consider treatment inadequate even though the intensity of their hallucinations and delusions may have decreased.

Which antipsychotic is best?

Meta-analyses of randomized controlled trials (RCTs) of antipsychotic treatment

Table 1

Antipsychotic combinations: Few studies support efficacy

Study	Design	Patients	Results
Shiloh et al, 1997 ^a	10-week, double-blind, placebo-controlled	28 patients nonresponsive to typical antipsychotics and partially responsive to clozapine received add-on sulpiride,* 600 mg/d, or placebo	The sulpiride group showed improvements in positive and negative symptoms
Josiassen et al, 2005 ^b	12-week, randomized, double-blind, placebo-controlled	40 schizophrenia patients unresponsive or partially responsive to clozapine randomized to clozapine + placebo or clozapine + risperidone, 6 mg/d	Mean BPRS total and positive symptom subscale scores reduced in both groups but reductions were greater in the clozapine/risperidone group; reduction in SANS also was observed in the clozapine/risperidone group
Genç et al, 2007 ^c	8-week, randomized, single-blind	56 treatment-resistant schizophrenia patients randomly assigned to clozapine + amisulpride* or clozapine + quetiapine	Both groups improved at week 8 as measured by BPRS, SANS, SAPS, and CGI; however, patients receiving amisulpride showed greater improvement
Muscatello et al, 2011 ^d	24-week, randomized, double-blind, placebo-controlled	31 treatment-resistant schizophrenia patients receiving clozapine randomized to receive adjunctive aripiprazole or placebo	Aripiprazole showed beneficial effect on positive and general psychopathologic symptomatology, but no significant effects on executive cognitive function
Takahashi et al, 1999 ^e	8-week, randomized, single-blind, crossover	10 neuroleptic-treated patients received add-on risperidone and mosapramine*	Both additions resulted in significant, yet modest, improvement; no significant difference in PANSS between risperidone and mosapramine

*Not available in the United States

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; PANSS: Positive and Negative Syndrome Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms

Source: For reference citations, see this article at CurrentPsychiatry.com

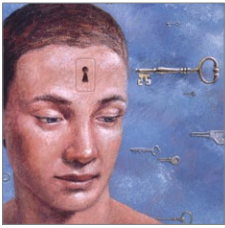
Clinical Point

As monotherapy, clozapine has consistently demonstrated superiority over other antipsychotics

for schizophrenia found that, although individual response will vary, clozapine generally has better efficacy than other antipsychotics.¹¹⁻¹³ Olanzapine, risperidone, and amisulpride (which is not available in the United States) appear to be more efficacious than first-generation antipsychotics. Other second-generation antipsychotics do not consistently show greater efficacy than first-generation antipsychotics, although their tolerability profiles vary greatly.¹¹⁻¹³

Antipsychotic monotherapy. More than 25 RCTs have focused on antipsychotic monotherapy for treatment-resistant patients; for a bibliography of these studies, see this article at CurrentPsychiatry.com. For the most part, clozapine has consistently demonstrated superiority over

comparators. Because not all patients with schizophrenia can tolerate clozapine or are willing to have their blood monitored as required, other second-generation antipsychotics have been suggested as possible substitutes. Olanzapine has established superior efficacy to first-generation antipsychotics¹¹⁻¹³ and perhaps comparable efficacy to clozapine in some studies.^{2,14-17} Risperidone appeared to be comparable to clozapine in some studies,^{18,19} whereas clozapine's superiority was evident in others.^{14,20,21} Although an RCT found comparable efficacy for ziprasidone vs clozapine,²² patients enrolled in this study may not have been treatment-resistant regarding efficacy but instead could not tolerate prior treatments. Enrolling patients on the basis of poor efficacy and/or poor tolerability to their prior antipsychotic regimen



Refractory schizophrenia

Clinical Point

Among mood stabilizers, lamotrigine may be the most promising for treatment-resistant schizophrenia

Table 2

Agents studied as adjuncts to antipsychotics

Acetylsalicylic acid and nonsteroidal anti-inflammatory agents
Anticonvulsants and lithium
Antidepressants
Antiglucocorticoids
Agents used to treat attention-deficit/hyperactivity disorder
Beta blockers
Cholinesterase inhibitors and other agents used to treat Alzheimer's disease
Experimental agents that act on glutamate receptors
GABA _A receptor drugs
Neurosteroids and hormones
Omega-3 fatty acids
Opioid system agents
Peptides
Purinergic agents
Serotonin 5-HT _{1A} receptor agonists
Serotonin 5-HT ₃ receptor antagonists
Wakefulness promoting agents

also has complicated the interpretation of studies comparing olanzapine with clozapine¹⁶ and risperidone with clozapine.¹⁸

Antipsychotic combinations. Combinations of antipsychotics are used commonly when treating chronic schizophrenia.²³ Of the approximately 20 RCTs of antipsychotic combination therapy, most tested clozapine combined with other second-generation antipsychotics, such as risperidone. For a bibliography of these studies, see this article at CurrentPsychiatry.com. Only 5 studies support a combination approach (Table 1, page 55).

What about augmentation?

Adjunctive non-antipsychotics also are commonly used when treating patients with chronic schizophrenia. For example, lithium and anticonvulsants are used in approximately one-half of all inpatients with schizophrenia in facilities operated by the State of New York Office of Mental

Health.^{24,25} The evidence base for these agents as adjuncts to antipsychotics generally is weak.²⁶ Specifically, early reports of benefit with adjunctive lithium have been negated by later studies. Similarly, large trials of adjunctive valproate and lamotrigine have failed to replicate early and promising efficacy signals from smaller trials, although the larger studies did not specifically target treatment-resistant schizophrenia.

Among mood stabilizers, lamotrigine may be the most promising for treatment-resistant schizophrenia. In a meta-analysis of clinical trials examining schizophrenia patients receiving clozapine (N = 161) who were randomized to receive adjunctive lamotrigine or adjunctive placebo, lamotrigine was superior to placebo in total score for psychosis symptoms and scores for positive and negative symptoms.²⁷

More than 125 published RCTs have studied a wide variety of adjunctive agents other than lithium or anticonvulsants for treating persistent schizophrenia symptoms (Table 2).

Only some of the approximately 40 RCTs regarding adjunctive antidepressants in patients with chronic schizophrenia focused on patients with ongoing depressive symptoms. For a bibliography of these studies, see this article at CurrentPsychiatry.com. In a meta-analysis measuring improvement of negative symptoms from 23 trials (N = 819),²⁸ the effect size was moderate in favor of antidepressants. Subgroup analysis revealed significant responses for fluoxetine, trazodone, and ritanserin.

More than 50 RCTs have focused on augmenting medications for cognitive dysfunction in chronic schizophrenia. Unfortunately, agents used to treat Alzheimer's disease have shown disappointing results when tested in patients with schizophrenia, as have agents prescribed for attention-deficit/hyperactivity disorder (methylphenidate, guanfacine, atomoxetine) or agents used to promote alertness (modafinil and armodafinil).

Medications that act on glutamate receptors may offer another potential solution, although not in combination with clozapine.²⁹



Visit this article at CurrentPsychiatry.com for a bibliography of studies of treatment-resistant schizophrenia

Table 3

Cognitive-behavioral therapy for schizophrenia

Study	Design	Patients	Results
Pinto et al, 1999 ^a	6-month, randomized controlled	37 treatment-resistant schizophrenia patients were randomized to CBT plus social skills training or supportive therapy	Both groups showed statistically significant improvement on the BPRS, SAPS, and SANS; however, patients in the CBT group had lower BPRS and SAPS scores. No difference on SANS scores
Barretto et al, 2009 ^b	21-week, controlled (nonrandomized)	Patients refractory to clozapine were placed in a CBT or befriending control group	The CBT group showed significant improvement in PANSS total score and general psychopathology subscale score, as well as an improvement of QLS; improvement persisted at 6-month follow-up

BPRS: Brief Psychiatric Rating Scale; CBT: cognitive-behavioral therapy; PANSS: Positive and Negative Syndrome Scale; QLS: Quality of Life Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms

Source: For reference citations, see this article at CurrentPsychiatry.com

Other agents that require further study where ≥ 2 positive studies have been reported (with ≤ 2 negative studies) include celecoxib, neurosteroids and hormones, purinergic agents, serotonin 5-HT_{1A} receptor agonists, and serotonin 5-HT₃ receptor antagonists.

Therapeutic neuromodulation

More than 10 RCTs of repetitive transcranial magnetic stimulation (rTMS) in patients with refractory symptoms of schizophrenia have been published; the results were mixed. For a bibliography of these studies, see this article at CurrentPsychiatry.com. In a meta-analysis of 9 trials (n = 213),³⁰ prefrontal rTMS for treating negative symptoms demonstrated a small-to-medium effect size. In another meta-analysis³¹ of all prospective studies of rTMS for negative symptoms and for auditory hallucinations and overall positive symptoms in refractory schizophrenia, the effect sizes showed moderate effects.

Fewer controlled trials are available for electroconvulsive therapy,^{32,33} but its use with clozapine appears encouraging.³⁴

Psychological and behavioral intervention. Cognitive-behavioral therapy, although labor-intensive, can be helpful even in patients considered treatment-resistant (Table 3). These interventions generally are provided together with pharmacotherapy.

Complementary and alternative therapies. Patients and their families may ask about complementary and alternative therapies, particularly when conventional approaches have not been successful. A meta-analysis of 6 studies (n = 828)³⁵ that reviewed adjunctive use of ginkgo in patients with chronic schizophrenia found statistically significant moderate improvement in total and negative symptoms. Negative reports also are available, including a 5-month study of adjunctive megavitamins that did not demonstrate any benefits.³⁶ In a review of 13 RCTs of acupuncture for schizophrenia, Lee et al found the overall methodological quality was too low to draw firm conclusions.³⁷

Clinical recommendations

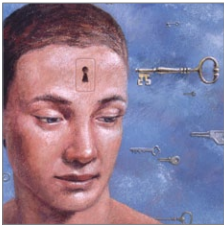
Before declaring a patient with schizophrenia as treatment-resistant, ensure that an adequate trial of medication did take place. This includes consideration of adequate dosing and pharmacokinetic issues. Awareness of potential substance use and/or partial adherence or nonadherence also is critical because these factors can impact treatment response.

When prescribing for a treatment-resistant schizophrenia patient, identify specific target symptoms to better inform medication selection—especially for symptoms that the patient feels are important.

Clinical Point

Studies of repetitive transcranial magnetic stimulation for refractory symptoms of schizophrenia have been mixed

continued



Refractory schizophrenia

Clinical Point

Identify specific target symptoms when prescribing for a treatment-resistant schizophrenia patient

Related Resources

- Cochrane Database of Systematic Reviews. www.cochrane.org/reviews. This database contains reviews of additional therapeutic options for patients with treatment-resistant schizophrenia. As of February 23, 2011, 157 reviews were available.
- Citrome L. Treatment-refractory schizophrenia: What it is and what's been done about it. *Neuropsychiatry*. 2011. Epub ahead of print.
- Citrome L. Clozapine for schizophrenia. Life-threatening or life-saving treatment? *Current Psychiatry*. 2009;8(12):56-63.

Drug Brand Names

Aripiprazole • Abilify	Lurasidone • Latuda
Armodafinil • Nuvigil	Methylphenidate • Ritalin,
Atomoxetine • Strattera	Methylin, others
Benzotropine mesylate	Modafinil • Provigil
• Cogentin	Olanzapine • Zyprexa
Carbamazepine • Tegretol	Quetiapine • Seroquel
Celecoxib • Celebrex	Rifampin • Rifadin
Chlorpromazine • Thorazine	Risperidone • Risperdal
Clozapine • Clozaril	Trazodone • Desyrel, Oleptro
Fluoxetine • Prozac	Valproate (Divalproex)
Guanfacine • Tenex	• Depakote, Depakote ER
Haloperidol • Haldol	Ziprasidone • Geodon
Lamotrigine • Lamictal	
Lithium • Eskalith,	
Lithobid, others	

Disclosure

No writing assistance or external financial support was used for this article. Dr. Citrome is a consultant for, has received honoraria from, or has conducted clinical research supported by Abbott Laboratories, AstraZeneca Pharmaceuticals, Avanir Pharmaceuticals, Azur Pharma Inc., Barr Laboratories, Bristol-Myers Squibb, Eli Lilly and Company, Forest Research Institute, GlaxoSmithKline, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Merck, Novartis, Pfizer Inc., Sunovion, Valeant Pharmaceuticals, and Vanda Pharmaceuticals.

For example, consider an antidepressant for patients who have negative or depressive symptoms. Also take into account other patient-centered concerns, such as tolerability issues that may have interfered with adherence and response in the past.

Clozapine remains the medication of choice for treatment-resistant schizophrenia. Despite dozens of RCTs of potential adjunctive agents for treatment-resistant schizophrenia, no single approach has con-

sistently shown efficacy in reducing symptoms, improving cognition, or increasing a patient's level of function. Individual response can vary, and our search for the "outlier" who does respond to an adjunctive agent can explain our use of these strategies in clinical practice.

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Bottom Line

For many patients with schizophrenia, relief from positive symptoms with antipsychotics may be incomplete. For such patients, efficacy appears to be greater for clozapine, followed by olanzapine and risperidone. Randomized controlled trials have not consistently established efficacy for combining antipsychotics or other augmentation strategies.

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Table 1

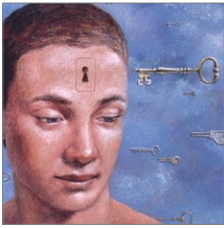
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Refractory schizophrenia

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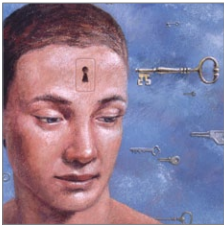
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