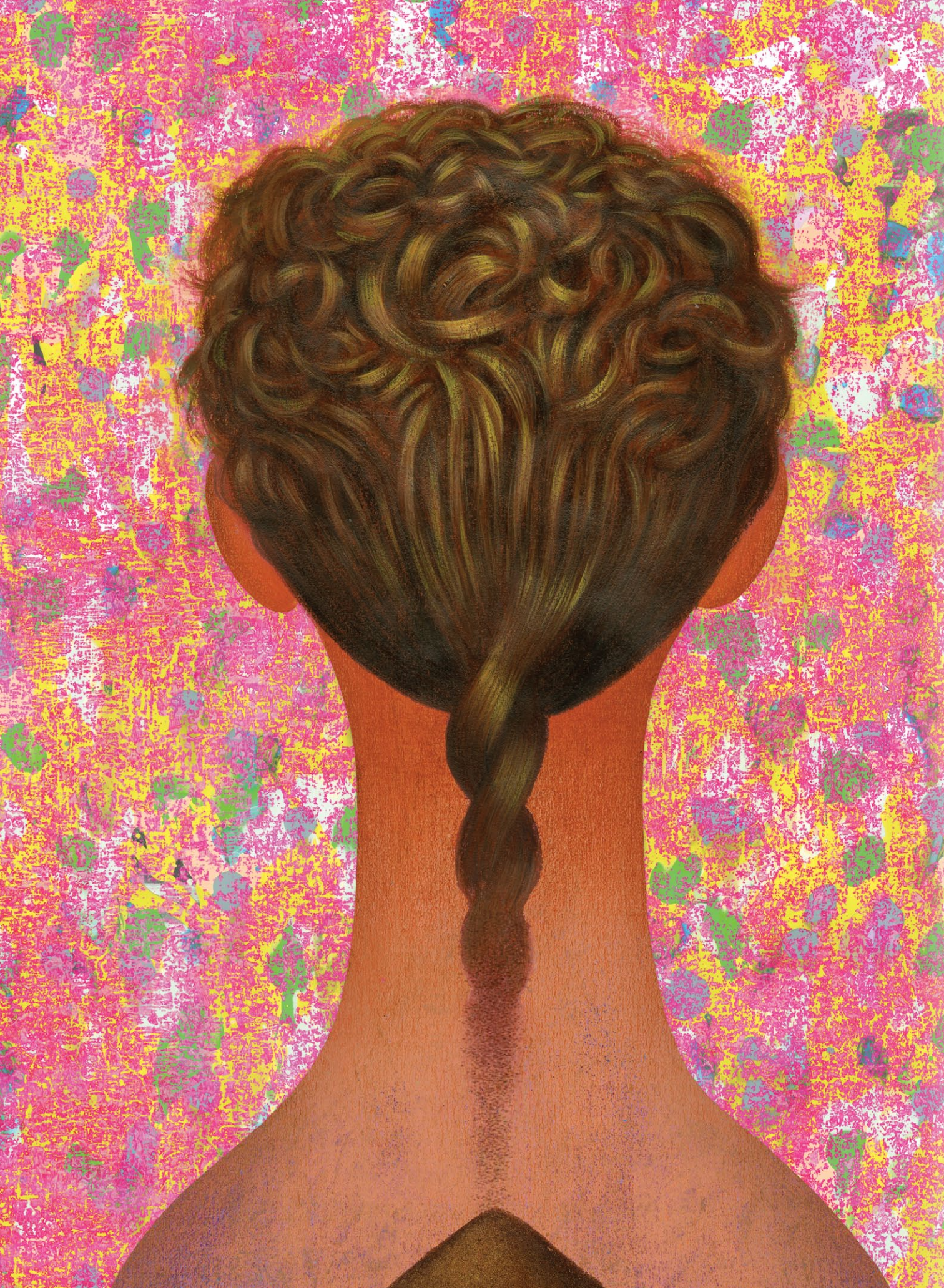

FIRST OF 2 PARTS

MANAGING FIRST-EPISODE PSYCHOSIS
An early stage of schizophrenia with distinct treatment needs

Minimize duration of untreated psychosis; aim for remission

Kristen N. Gardner, PharmD
PGY-2 Psychiatric Pharmacy Resident
Western Missouri Psychiatric Pharmacy Residency Program
Kansas City, Missouri

Henry A. Nasrallah, MD
Sydney W. Souers Endowed Chair and Professor
Department of Neurology and Psychiatry
Saint Louis University School of Medicine
St. Louis, Missouri

Disclosures
Dr. Gardner reports no financial relationships with any companies whose products are mentioned in this article or with manufacturers of competing products.
Dr. Nasrallah is a consultant to Acadia, Alkermes, Lundbeck, Janssen, Merck, Otsuka, and Sunovion, and is a speaker for Alkermes, Lundbeck, Janssen, Otsuka, and Sunovion.

JON KRAUSE FOR CURRENT PSYCHIATRY

The less time that passes between the onset of psychosis and initiation of appropriate treatment, the greater the patient's odds of recovery.[1] However, relapse prevention is a major clinical challenge because >80% of patients will relapse within 5 years, and, on average, 40% to 50% of patients with a first-episode schizophrenia will relapse within 2 years depending on the definition used and patient characteristics.[2] Although there are several explanations and contributing factors to relapses, non-adherence—partial or complete discontinuation of antipsychotics—is a primary risk factor, contributing to a 5-fold increase in relapse risk.[3]

As such, optimal antipsychotic selection, dosing, and monitoring play an important role in managing this illness. Patients with first-episode psychosis (FEP) are unusual in some ways, compared with patients with multiple episodes of psychosis and represent a different stage of schizophrenia.

In this 2-part series, we will discuss pharmacotherapy for FEP. This article focuses on antipsychotic selection, dosage, and duration of treatment among these patients. The second article, in the July 2015 issue, reviews the rationale and evidence for non-standard, first-line therapies, including long-acting injectable antipsychotics and clozapine.

Defining FEP

FEP refers to a patient who has presented, been evaluated, and received treatment for the first psychotic episode associated with a schizophrenia spectrum diagnosis.[4] FEP is part of a trajectory marked by tran-

First-episode psychosis

Clinical Point

The DUP is a predictor of clinical outcome in schizophrenia, including negative symptoms, quality of life, and functional capacity

Discuss this article at www.facebook.com/CurrentPsychiatry

sitional periods. The patient transitions from being "healthy" to a prodromal state characterized by: (1) nonpsychotic behavioral disturbances such as depression or obsessive-compulsive disorder, (2) attenuated psychotic symptoms not requiring treatment, then converting to (3) psychotic symptoms prompting initial presentation for antipsychotic pharmacotherapy, leading to (4) a formal diagnosis of schizophreniform disorder and, subsequently, schizophrenia, requiring treatment to stabilize symptoms.

There are 2 critical periods along this continuum: prodromal stage and the duration of untreated psychosis (DUP). The prodromal period is a retrospectively identified time where the patient shows initial nonpsychotic disturbances (eg, cognitive and behavioral symptoms) before exhibiting clinical diagnostic criteria for a schizophrenia spectrum disorder. Approximately one-third of patients exhibiting these symptoms convert to psychosis within 1 year, and early treatment engagement at this stage has been shown to improve outcomes.[5] The DUP is the time from when a patient has noticeable psychotic symptoms to initiation of drug treatment. The DUP is a consistent predictor of clinical outcome in schizophrenia, including negative symptoms, quality of life, and functional capacity.[1]

Antipsychotic selection

Treatment goals for FEP patients include:

- minimizing the DUP
- rapidly stabilizing psychosis
- achieving full symptomatic remission
- preventing relapse.

Several treatment guidelines for managing schizophrenia offer variable recommendations for initial antipsychotic treatment in patients with first-episode schizophrenia (***Table 1, page 36***).[6-15] Most recommend second-generation antipsychotics (SGAs) over first-generation antipsychotics (FGAs)[6,8,9,13,15] with specific recommendations on minimizing neurologic and metabolic adverse effects—to which FEP patients are susceptible—by avoiding high-potency and neurotoxic FGAs (eg, haloperidol and fluphenazine),[7] clozapine,[11,14] olanzapine,[11] or ziprasidone.[14] Two guidelines—the National Institute for Health and Care Excellence and the Scottish Intercollegiate Guidelines Network—do not state a preference for antipsychotic selection.[10,12]

The rationale for these recommendations is based on efficacy data, tolerability differences, FDA-approved indications, and recent FDA approvals with sparse postmarketing data. Of note, there are a lack of robust data for newer antipsychotics (eg, aripiprazole, paliperidone, iloperidone, asenapine, and lurasidone) in effectively and safely treating FEP; however, given the results of other antipsychotics studies, it is likely the efficacy and tolerability of these drugs can be extrapolated from experience with multi-episode patients.

Study design and demographics. Research studies of FEP share some similarities in study design; however, there is enough variability to make it difficult to compare studies and generalize findings (***Table 2, page 37***).[16] The variability of DUP is a limitation when comparing studies because it is a significant predictor of clinical outcome. Patients who abuse substances—and often are more challenging to treat[17]—typically are excluded from these trials, which could explain the high response rate documented in studies of first-episode schizophrenia.

In addition, some FEP patients included in clinical trials might not be truly antipsychotic naïve; an estimated 25% to 75% of patients in these studies are antipsychotic naïve. This is an important consideration when comparing data on adverse effects that occur early in treatment. Additionally, acknowledging the advantages and disadvantages of how to handle missing data is critical because of the high dropout rate observed in these studies.[18]

Efficacy. There is a high response rate to antipsychotic therapy—ranging from 46% to 96%, depending on the study—in patients with first-episode schizophrenia.[3] The response mainly is seen in reduction of positive symptoms because typically

continued on page 36

continued from page 34

First-episode psychosis

Clinical Point

There is a lack of evidence suggesting that 1 antipsychotic class or agent is more effective than another for first-episode psychosis

Table 1

How do treatment guidelines compare in regard to selecting an antipsychotic for first-episode schizophrenia?

Guideline	Recommendation	Comments
American Psychiatric Association, 2004[6]	SGAs over FGAs	
British Association for Psychopharmacology, 2010[7]	Cautions against the use of high-potency FGAs	Does not discriminate between low-potency FGAs and SGAs
Canadian Psychiatric Association, 2005[8]	SGAs over FGAs	
Expert Consensus Guideline Series – Treatment of Schizophrenia, 1999[9]	SGAs over FGAs	
National Institute for Health and Care Excellence, 2014[10]	Does not preferentially recommend any class or antipsychotic	Least restrictive recommendation
Schizophrenia Patient Outcomes Research Team, 2009[11]	Any antipsychotic except olanzapine and clozapine	Olanzapine is not preferred because of the risk for weight gain and metabolic syndrome development Clozapine is reserved for third-line treatment after therapeutic failure of ≥2 antipsychotics
Scottish Intercollegiate Guidelines Network, 2013[12]	Individual prescribing should consider benefits and harms before choosing therapy	Least restrictive recommendation
Texas Medication Algorithm Project, 2008[13]	SGAs over FGAs	
The Mount Sinai Conference on the Pharmacotherapy of Schizophrenia, 2002[14]	SGAs (except ziprasidone and clozapine) over FGAs	Ziprasidone was not preferred because of cardiac safety concerns at the time of guideline preparation that have since subsided Clozapine is reserved for third-line treatment after therapeutic failure of ≥2 antipsychotics
World Federation Society of Biological Psychiatry, 2012[15]	SGAs over FGAs	

FGA: first-generation antipsychotic; SGA: second-generation antipsychotic

negative and cognitive symptoms do not respond to antipsychotics. One study reported only 29% of patients achieved both positive and negative symptom remission.[19] It is likely that secondary negative symptoms caused by social withdrawal, reduced speech, and avoidance improve when positive symptoms subside, but primary negative symptoms endure.

In general, there is a lack of evidence suggesting that 1 antipsychotic class or agent is more effective than another. Studies mainly assess effectiveness using the primary outcome measure of all-cause discontinuation, such as the Clinical Antipsychotic Trials of Intervention Effectiveness study.[20] This outcome measure is a mixture of patient preference, tolerability, and efficacy that provides a more generalizable gauge on how well the treatment works in the clinic rather than tightly regulated settings such as clinical trials. A recent meta-analysis supports no differences in efficacy among antipsychotics in early-episode psychosis.[21]

Tolerability. Because there are no significant differences among antipsychotic classes or

Table 2

Common study designs and population demographics in clinical trials of first-episode psychosis

Study design component	Characteristics
Inclusion criteria	• Age 16 to 40 • Schizophrenia, schizophreniform, with or without schizoaffective disorder • Mixture of inpatients and outpatients • DUP variable (eg, 1 month to 5 years) • Antipsychotic lifetime use <12 to 16 weeks • Some psychotic symptom criteria
Exclusion criteria	• Prior psychotic disorder with remission • Another axis I diagnosis, including substance abuse • Intellectual developmental disability • Other psychotropic use • Pregnant, lactating, or improper contraception use • Organic brain disease • High suicide risk • Intolerance or contraindication to study drug • History of long-acting injectable antipsychotic use • Emergency medication treatment >3 days • Use of the study drug within past 30 days • Past clozapine use
Common demographics	• Males more than females • Mean age = mid 20s • White • DUP 1 to 2 years • Antipsychotic naïve, 25% to 75%
Common methodology	• Efficacy/effectiveness endpoints: all-cause treatment discontinuation or 20% to 50% reductions in PANSS or BPRS +/- improvements in CGI • Trial durations: 6 weeks to several years • Missing data are handled differently

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impressions Scale; DUP: duration of untreated psychosis; PANSS: Positive and Negative Symptom Scale

Source: Reference 16

Clinical Point

Evidence suggests first-episode patients are more sensitive to adverse effects of antipsychotics, particularly neurologic side effects

agents in terms of efficacy in first-episode schizophrenia, drug selection is guided mainly by (1) the adverse effect profile and (2) what should be avoided depending on patient-specific variables. Evidence suggests first-episode patients are more sensitive to adverse effects of antipsychotics, particularly neurologic side effects (see this article at CurrentPsychiatry.com for a table comparing adverse effects of antipsychotics in first-episode psychosis).[18,22-29] Overall adverse effect profiles remain similar across FEP or multi-episode patients, but tend to be more exaggerated in drug-naïve patients with FEP.

Regarding FGA side effects, McEvoy et al[18] demonstrated the neuroleptic threshold occurs at 50% lower haloperidol dosages in patients with first-episode schizophrenia (2.1 mg/d) compared with multi-episode schizophrenia (4.3 mg/d). Other trials suggest SGAs are associated with a lower risk of extrapyramidal side effects (EPS) or use of adjunctive therapies such as anticholinergic drugs or benzodiazepines.[23-27] An exception to this statement is that higher risperidone dosages (≥4 to 6 mg/d) have been found to have higher rates of EPS and use of adjunctive medications to treat these symptoms in FEP.[26] This is important because studies report higher discontinuation rates with more severe adverse effects of antipsychotics.

Cardiometabolic effects are of particular concern in first-episode patients because most weight gain happens in the first 3 to 4 months of treatment and remains throughout the first year.[18,24,29,30] Studies have shown that olanzapine, quetiapine, and risperidone are associated with

First-episode psychosis

Clinical Point

Treatment guidelines recommend antipsychotic dosages lower than those used for multi-episode schizophrenia, especially FGAs

more clinically significant weight gain compared with haloperidol and ziprasidone.[23-25] Olanzapine-associated weight gain has been reported to be twice that of quetiapine and risperidone.[18] Regardless, the EUFEST trial did not find a difference in clinically significant weight gain after 12 months among the antipsychotics studied, including haloperidol and ziprasidone.[25]

Weight gain associated with these antipsychotics is accompanied by changes in fasting triglycerides, glucose, total cholesterol,[23] and high-density lipoprotein cholesterol as well as an increase in body mass index (BMI) categorization[29] (eg, shift from normal to overweight).[18,25] Patients with lower baseline BMI and in racial minority groups might experience more rapid weight gain regardless of antipsychotic selection.[29,30]

Hyperprolactinemia could be underrecognized and could contribute to early treatment discontinuation.[31] Evidence in patients with first-episode schizophrenia suggests similar outcomes as those seen in multi-episode patients, in whom risperidone is associated with higher prolactin elevations and clinically significant hyperprolactinemia (eg, galactorrhea and gynecomastia) compared with olanzapine, quetiapine, and low-dose haloperidol.[18,23,24] However, there is a lack of studies that assess whether long-term therapy with strong D2 receptor antagonists increases the risk of bone demineralization or pathological fractures when started before patients' bones reach maximum density in their mid-20s.[31]

Antipsychotic dosing

Given the high rate of treatment response in FEP and patients' higher sensitivity to antipsychotic adverse effects, particularly EPS, guidelines recommend antipsychotic dosages lower than those used for multi-episode schizophrenia,[11] especially FGAs. Based on trial data, commonly used dosages include:

- haloperidol, ≤5 mg/d[23-25,29]
- olanzapine, 10 mg/d[18,23,25,29]
- risperidone, ≤4 to 6 mg/d.[18,24,29,32]

In general, haloperidol and risperidone, 2 to 3 mg/d, were well tolerated and effective in trials. Higher quetiapine dosages of 500 to 600 mg/d could be required.[11,18,25]

According to a survey on prescribing practices of antipsychotic selection and dosing in first-episode schizophrenia,[4] clinical prescribing practices tend to use unnecessarily high initial antipsychotic dosing compared with trial data. There also is variability in the usual target antipsychotic dosage ranging from 50% lower dosages to normal dosages in chronic schizophrenia to above FDA-approved maximum dosages for olanzapine (which may be necessary to counteract tobacco-induced cytochrome P450 1A2 enzyme induction).

In addition, these clinicians reported prescribing aripiprazole, an antipsychotic with weaker evidence (eg, case reports, case series, open-label studies) supporting its efficacy and tolerability in FEP. These prescribing practices could reflect attempts to reduce the DUP and achieve symptom remission, so long as tolerability is not a concern.

Essentially, prescribed dosages should be based on symptom improvement and tolerability. This ideal dosage will vary as illustrated by Kapur et al,[33] who reported that FEP patients (N = 20) given haloperidol, 1 mg or 2.5 mg/d, had D2 receptor occupancy rates of 38% to 87%, which was significantly dose-related (1 mg/d mean = 59%, 2.5 mg/d mean = 75%). Clinical response and EPS significantly increased as D2 receptor occupancy exceeded 65% and 78%, respectively.

Antipsychotic response

When should you expect to see symptom improvement in patients with first-episode schizophrenia?

Emsley et al[34] reported a 77.6% response rate among first-episode patients (N = 522) treated with low dosages of risperidone (mean modal dosage [MMD] = 3.3 mg/d) and haloperidol (MMD = 2.9 mg/d). They found variable response times that were evenly dispersed over a 10-week period. Nearly one-quarter (22.5%) did not respond until after week 4 and 11.2% did

Table 3

What predicts successful—and unsuccessful—treatment in first-episode schizophrenia?

Treatment outcome	Predictors
Response	• Shorter duration of untreated psychosis (acute onset) • Good premorbid function • Smaller pituitary volumes • Female sex
Nonresponse	• Poor premorbid function • Lack of insight • Excessive intolerance to side effects • Male sex • Lack of social activities
Relapse	• Antipsychotic discontinuation (nonadherence) • Unemployment • Poor premorbid adaptation to school • Premorbid social withdrawal • Substance use • Comorbid psychiatric disorders
Adherence	• Strong therapeutic alliance/patient–doctor relationship
Nonadherence	• Antipsychotic side effects • Poor insight • Memory deficits • Substance use • Amotivation/apathy

Source: References 1,3,4,23,25,40

not respond until after week 8. In a study of FEP patients (N = 112) treated with olanzapine (MMD = 11.8 mg/d) or risperidone (MMD = 3.9 mg/d), Gallego et al[35] reported a cumulative response of 39.6% at week 8 and 65.1% at week 16.

Although there is evidence that, among multi-episode patients, early nonresponse to antipsychotic therapy could predict subsequent nonresponse,[36] the evidence is mixed for first-episode schizophrenia. Studies by Emsley et al[34] and Gallego et al[35] did not find that early nonresponse at weeks 1 or 2 predicted subsequent nonresponse at week 4 or later. However, other studies support the idea that early nonresponse predicts subsequent nonresponse and early antipsychotic response predicts future response in first-episode patients, with good specificity and sensitivity.[37,38]

Overall, treatment response in first-episode schizophrenia is variable. An adequate antipsychotic trial may be longer, 8 to 16 weeks, compared with 4 to 8 weeks in multi-episode patients. Because research suggests that failure to respond to treatment may lead to medication nonadherence,[39] it is reasonable to consider switching antipsychotics when a patient experiences minimal or no response to antipsychotic therapy at week 2; however, this should be a patient-specific decision.

How long should you continue therapy after symptom remission?

There is a lack of consensus on the duration of therapy for a patient treated for first-episode schizophrenia because a small percentage (10% to 20%) do not relapse after the first psychotic episode.[3] In general, treatment guidelines and expert consensus statements recommend at least 1 to 2 years of treatment before considering a discontinuation trial.[7,10-11] Discuss the benefits and risks of maintenance treatment with your patient and obtain informed consent. With patients with minimal insight, obtaining proper consent is not possible and the physician must exercise judgment unilaterally, if necessary, after educating the family.

continued

Clinical Point

Prescribed dosages should be based on symptom improvement and tolerability

First-episode psychosis

Related Resources

- Recovery After an Initial Schizophrenia Episode (RAISE) Project Early Treatment Program. National Institute of Mental Health. http://raiseetp.org.
- Martens L, Baker S. Promoting recovery from first episode psychosis: a guide for families. Centre for Addiction and Mental Health. http://www.camh.ca/en/hospital/Documents/www.camh.net/About_CAMH/Guide_to_CAMH/Mental_Health_Programs/Schizophrenia_Program/3936PromotingRecoveryFirstEpisodePsychosis_final.pdf.

Drug Brand Names

Aripiprazole • Abilify
Asenapine • Saphris
Clozapine • Clozaril
Fluphenazine • Prolixin
Iloperidone • Fanapt
Haloperidol • Haldol
Lurasidone • Latuda
Olanzapine • Zyprexa
Paliperidone • Invega
Quetiapine • Seroquel
Risperidone • Risperdal
Ziprasidone • Geodon

Clinical Point

An adequate antipsychotic trial may be longer in first-episode patients, 8 to 16 weeks, compared with 4 to 8 weeks in multi-episode patients

After at least 12 months of treatment, antipsychotic therapy could continue indefinitely, depending on patient-specific factors. There are no predictors for identifying patients who do not require maintenance therapy beyond the first psychotic episode. The absence of negative and cognitive deficits could provide clues that a patient might be a candidate for antipsychotic tapering.

Predicting the treatment course

Research investigating clinical predictors or biomarkers that forecast whether a patient will respond to treatment is preliminary. Many characteristics have been identified (***Table 3, page 39***[1,3,4,23,25,40]) and include shorter DUP,[1] poorer premorbid function,[3] antipsychotic discontinuation,[3] a trusting patient-doctor relationship,[41] and antipsychotic-related adverse effects,[23,25] which are predictive of response, nonresponse, relapse, adherence, and nonadherence, respectively.

Editor's note: *The second article in this series in the July 2015 issue reviews the rationale and evidence for non-standard, first-line therapies, including long-acting injectable antipsychotics and clozapine.*

References

1. Perkins DO, Gu H, Boteva K, et al. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry. 2005;162(10):1785-1804.
2. Bradford DW, Perkins DO, Lieberman JA. Pharmacological management of first-episode schizophrenia and related nonaffective psychoses. Drugs. 2003;63(21):2265-2283.
3. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following a response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry. 1999;56(3):241-247.
4. Weiden PJ, Buckley PF, Grody M. Understanding and treating "first-episode" schizophrenia. Psychiatr Clin North Am. 2007;30(3):481-510.
5. Madaan V, Bestha DP, Kolli V. Schizophrenia prodrome: an optimal approach. Current Psychiatry. 2014;13(3):16-20, 29-30.
6. Lehman AF, Lieberman JA, Dixon LB, et al; American Psychiatric Association; Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004;161(suppl 2):1-56.
7. Barnes TR; Schizophrenia Consensus Group of British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2011;25(5):567-620.
8. Canadian Psychiatric Association. Clinical practice guideline. Treatment of schizophrenia. Can J Psychiatry. 2005;50(13 suppl 1):7S-57S.
9. McEvoy JP, Scheifler PL, Frances A. Treatment of schizophrenia 1999. Expert consensus guideline series. J Clin Psychiatry. 1999;60(suppl 11):4-80.
10. National Institute for Health and Care Excellence (NICE). Clinical guideline 178: Psychosis and schizophrenia in adults: treatment and management. London, United Kingdom: National Institute for Health and Care Excellence (NICE); 2014.
11. Buchanan RW, Kreyenbuhl J, Kelly DL, et al; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010;36(1):71-93.
12. Scottish Intercollegiate Guidelines Network (SIGN). Management of schizophrenia. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network; 2013. SIGN publication no. 131.

continued on page 42

Bottom Line

The goals of pharmacological treatment of first-episode schizophrenia are to minimize the duration of untreated psychosis and target full remission of positive symptoms using the lowest possible antipsychotic dosages. Pharmacotherapy should continued for 1 to 2 years, with longer duration considered if it is discussed with the patient and with vigilant monitoring for adverse effects and suboptimal medication nonadherence to prevent relapse.

continued from page 40

First-episode psychosis

Clinical Point

There are no predictors for identifying patients who do not require maintenance therapy beyond the first psychotic episode

13. Argo TR, Crismon ML, Miller AL, et al. Texas Medication Algorithm Project procedural manual. Schizophrenia treatment algorithms. Austin, Texas: Texas Department of State Health Services; 2008.
14. Marder SR, Essock SM, Miller Al, et al. The Mount Sinai conference on the pharmacotherapy of schizophrenia. Schizophr Bull. 2002;28(1):5-16.
15. Bandelow B, Zohar J, Hollander E, et al; WFSBP Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. World J Biol Psychiatry. 2008;9(4):248-312.
16. Robinson DG, Woerner MG, Alvir JMJ, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psych. 1999;56(3):241-247.
17. Green AI, Tohen MF, Hamer RM, et al. First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr Res. 2004;66(2-3):125-135.
18. McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry. 2007;164(7): 1050-1060.
19. Henry LP, Amminger GP, Harris MG, et al. The EPPIC follow-up study of first-episode psychosis: longer-term clinical and functional outcome 7 years after index admission. J Clin Psychiatry. 2010;71(6):716-728.
20. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. New Engl J Med. 2005; 353(12):1209-1223.
21. Crossley NA, Constante M, McGuire P, et al. Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis. Br J Psychiatry. 2010;196(6): 434-439.
22. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia: a controlled study of the neuroleptic threshold and higher haloperidol dose. Arch Gen Psych. 1991;48(8):739-745.
23. Lieberman JA, Tollefson G, Tohen M, et al; HGDH Study Group. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. Am J Psychiatry. 2003;160(8):1396-1404.
24. Schooler N, Rabinowitz J, Davidson M, et al; Early Psychosis Global Working Group. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry. 2005;162(5):947-953.
25. Kahn RS, Fleischhacker WW, Boter H, et al; EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 2008;371(9618):1085-1097.
26. Emsley RA; Risperidone Working Group. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Schizophr Bull. 1999;25(4): 721-729.
27. Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naïve first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. Neuropsychopharmacology. 2003;28(5):995-1003.
28. Girgis RR, Phillips MR, Li X, et al. Clozapine v. chlorpromazine in treatment-naive, first-episode schizophrenia: 9-year outcomes of a randomised clinical trial. Br J Psychiatry. 2011;199(4):281-288.
29. Robinson DG, Woerner MG, Napolitano B, et al. Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. Am J Psychiatry. 2006;163(12):2096-2102.
30. Zipursky RB, Gu H, Green AI, et al. Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. Br J Psychiatry. 2005;187:537-543.
31. Taylor M, Waight A, Leonard B. Advances in the understanding and challenges facing the management of first-episode schizophrenia. J Psychopharmacol. 2012; 26(suppl 5):3-5.
32. Merlo MC, Hofer H, Gekle W, et al. Risperidone, 2mg/day vs. 4mg/day, in first-episode, acutely psychotic patients: treatment efficacy and effects on fine motor functioning. J Clin Psychiatry. 2002;63(10):885-891.
33. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry. 2000;157(4):514-520.
34. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. Am J Psychiatry. 2006;163(4):743-745.
35. Gallego JA, Robinson DG, Sevy SM, et al. Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months? J Clin Psychiatry. 2011;72(12):1691-1696.
36. Gardner KN, Bostwick JR. Antipsychotic treatment response in schizophrenia. Am J Health Sys Pharm. 2012;69(21): 1872-1879.
37. Stauffer VL, Case M, Kinon BJ, et al. Early response to antipsychotic therapy as a clinical marker of subsequent response in the treatment of patients with first-episode psychosis. Psychiatry Res. 2011;187(1-2):42-48.
38. Schennach-Wolff R, Seemüller FH, Mayr A, et al. An early improvement threshold to predict response and remission in first-episode schizophrenia. Br J Psychiatry. 2010;196(6): 460-466.
39. Perkins DO, Gu H, Weiden PJ, et al; Comparison of Atypicals in First Episode study group. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. J Clin Psychiatry. 2008;69(1):106-113.
40. Garner B, Berger GE, Nicolo JP, et al. Pituitary volume and early treatment response in drug-naïve first-episode psychosis patients. Schizophr Res. 2009;113(1):65-71.
41. Sapra M, Weiden PJ, Schooler NR, et al. Reasons for adherence and nonadherence: a pilot study comparing first- and multi-episode schizophrenia patients. Clin Schizophr Relat Psychoses. 2014;7(4):199-206.

First-episode psychosis

Table 4

Adverse effects of antipsychotics in first-episode psychosis

Study/design	Drug	Neurologic outcomes
McEvoy et al, 2007[18]; N = 400, double-blind, flexible dosing	Olanzapine, 2.5 to 20 mg/d (MMD 11.7 mg/d) Risperidone, 0.5 to 4 mg/d (MMD 2.4 mg/d) Quetiapine, 100 to 800 mg/d (MMD 506 mg/d)	No differences in EPS among SGAs over 52 weeks Increased use of adjunctive medications with olanzapine vs quetiapine
McEvoy et al, 1991[22]; N = 106, controlled study	Haloperidol at neuroleptic threshold dosage (MMD 3.4 ± 2.3 mg/d) Haloperidol at higher dosages (2 to 10 × increase or continue at neuroleptic threshold (MMD 11.6 ± 4.7)	FES neuroleptic threshold = 2.1 mg/d Chronic neuroleptic threshold = 4.3 mg/d
Lieberman et al, 2003[23]; N = 263, double-blind, flexible dosing	Haloperidol, 2 to 20 mg/d (MMD 4.8 mg/d) Olanzapine, 5 to 20 mg/d (MMD 10.2 mg/d)	Increased akathisia at 12 and 24 weeks with haloperidol Increased tardive dyskinesia at 24, 52, and 104 weeks with haloperidol Increased use of adjunctive medications throughout the study with haloperidol Increased discontinuation rates secondary to adverse drug event at 24 and 104 weeks with haloperidol
Schooler et al, 2005[24]; N = 555, double-blind, flexible dosed	Haloperidol, 1 to 4 mg/d (MMD 2.9 mg/d) Risperidone, 1 to 4 mg/d (MMD 3.3 mg/d)	Increased EPS (akathisia, parkinsonism) with haloperidol Increased use of adjunctive medications with haloperidol No tardive dyskinesia differences at 1 year between groups
Kahn et al, 2008[25]; N = 498, open-label, flexible dosing	Haloperidol, 1 to 4 mg/d (MMD 3 mg/d) Amisulpride, 200 to 800 mg/d, (MMD 450.8 mg/d) Olanzapine, 5 to 20 mg/d, (MMD 12.6 mg/d) Quetiapine, 200 to 750 mg/d, (MMD 498.6 mg/d) Ziprasidone, 40 to 160 mg/d (MMD 107.2 mg/d)	Increased use of adjunctive medications with haloperidol Increased akathisia with haloperidol and ziprasidone Increased parkinsonism with haloperidol vs SGA No tardive dyskinesia differences Increased discontinuation rate secondary to more adverse drug events with haloperidol vs olanzapine and quetiapine
Emsley et al, 1999[26]; N = 183, double-blind, flexible dosing	Haloperidol, 2 to 16 mg/d (MMD 5.6 mg/d) Risperidone, 2 to 16 mg/d (MMD 6.1 mg/d)	Increased severe EPS on all ESRS items with haloperidol Increased use of adjunctive medications throughout with haloperidol Increased total adverse drug events and discontinuation with haloperidol Increased EPS severity and adjunctive med use in high-dose risperidone (>6 mg/d; post hoc analysis)
Lieberman, 2003[27]; N = 160, double-blind, flexible dosing	Chlorpromazine, max 600 mg/d (MMD 400 mg/d) Clozapine, max 400 mg/d (MMD 300 mg/d)	Increased EPS (akathisia, parkinsonism) at 12 weeks but not 52 weeks with chlorpromazine
Girgis et al, 2011[28]; N = 124 (follow-up of Lieberman et al 2003[27]), 2-year randomized controlled trial and 7-year naturalistic treatment	Chlorpromazine, max 600 mg/d (MMD 400 mg/d) Clozapine, max 400 mg/d (MMD 300 mg/d)	No differences in tardive dyskinesia for subjects who remained on the drug to which they were randomized for the entire study period; however, significantly more subjects initially randomized to chlorpromazine vs clozapine developed tardive dyskinesia
Robinson, 2006[29]; N = 112, open-label, flexible dosed	Risperidone, 1 to 6, mg/d (MMD 3.9 mg/d) Olanzapine, 2.5 to 20 mg/d (MMD 11.8 mg/d)	No EPS differences

EPS: extrapyramidal side effects; ESRS: extrapyramidal symptom rating scale; FES: first-episode schizophrenia; MMD: mean modal dosage; SG

Source: References 18, 22-29

	Comments
	Comparison among SGAs only
	This study provides evidence for targeting 50% lower antipsychotic dosages in FES
	Larger haloperidol dosage range compared with other studies More EPS occurred in haloperidol group despite increased use of adjunctive medications such as anticholinergics, benzodiazepines, and beta-blockers
	This dosage range was lower relative to the Emsley et al[26] study but haloperidol was still associated with more EPS
	More EPS occurred in haloperidol despite a lower dosage range being used relative to the Leiberman et al[23] study
	Haloperidol was associated with more EPS, despite a similar risperidone dosage range and mean modal dosage
	More EPS occurred despite the chlorpromazine group receiving prophylactic benztropine, 4 mg/d
	The high attrition rate and group crossover (eg, 30% of original chlorpromazine group took clozapine at some point during follow-up period) limit interpretation of results
	Comparing 2 SGAs, including risperidone, a strong D2 receptor antagonist

A: second-generation antipsychotic