

A woman in a white lab coat is sitting on a bench, looking down thoughtfully. The image is overlaid with a yellow tint and horizontal motion blur lines. The text is overlaid on the upper part of the image.

# First psychotic episode—

## Seize the moment to build

# a window of opportunity a therapeutic alliance

Intervening early and building a therapeutic alliance can improve medication adherence, reduce relapse risk, and favorably alter the course of schizophrenia

**Christoph U. Correll, MD**

Child and adolescent psychiatry fellow  
Schneider Children's Hospital  
Long Island Jewish Medical Center,  
New Hyde Park, NY

**Alan J. Mendelowitz, MD**

Assistant professor, Albert Einstein College of Medicine  
Department of psychiatry, The Zucker Hillside Hospital  
North Shore - Long Island Jewish Health System,  
Glen Oaks, NY

A first psychotic episode offers the opportunity to build a therapeutic alliance at a teachable moment—while patients and their families are dealing with a devastating diagnosis. With a proactive approach, you can influence how patients view themselves and their experience, including psychotic illness, your efforts to treat its symptoms, and the costs and benefits of interventions.

Unfortunately, the typical first psychotic episode goes undiagnosed and untreated for 1 to 2 years, which some studies suggest may allow schizophrenia to progress. Although controversial, evidence links a prolonged duration of untreated psychosis to poorer outcome.<sup>1</sup> Interventions during a prodromal (ie, pre-psychotic but already symptomatic) phase of schizophrenia also is being investigated, with the goal of attenuating—or perhaps even preventing—progression to frank psychosis.<sup>2-6</sup>

The implication for clinicians: timely identification and treatment may improve response, reduce relapse rates, and ultimately improve schizophrenic patients' quality of life.

**High rates of response—and relapse**

Patients with a first psychotic episode show a higher response rate to antipsychotics—up to 87% within 1 year<sup>7</sup>—and are more sensitive to side effects than are multi-episode patients.<sup>8</sup> Yet despite their high response rate, new-onset patients often suffer from residual symptoms, even when treated in controlled settings. They also have a high rate of relapse—82% within 5 years.<sup>9</sup>

The strongest modifiable predictor of relapse is medication non-adherence, which has been shown to increase the risk

Box

## CASE REPORT: A FIRST EPISODE OF PSYCHOSIS

**M**r. C, a 19-year-old college student, was brought for psychiatric admission after he told his roommates he was a new messiah who “needed to starve himself during the sunlight to enhance his holiness.” Approximately 7 months earlier he had become socially withdrawn and less able to do his college work. Two months later, he started using cannabis frequently. About 5 weeks prior to admission, he developed paranoid ideas involving his roommates and immersed himself in Eastern religions.

**History and work-up.** Mr. C was overweight and presented with mild dehydration. He did not report relevant signs of depression or mania and had no history of medical or psychiatric problems. Admission work-up included physical and neurologic exams, head CT, and blood work, which were unremarkable except for a positive cannabis toxicology. Family history was significant for one grandfather with alcohol abuse and one uncle who required psychiatric hospitalization in his 20s and never recovered functionally.

**Family concerns.** Mr. C’s parents were convinced a new diet was causing his symptoms and demanded that he be admitted to a medical ward. His brother insisted the symptoms were secondary to some “bad weed” and that everything would clear up in a few days. Although a brief medication-free observation period was considered to rule out substance-induced psychosis, the prodromal pattern of functional decline for more than 6 months and the bizarre quality of his delusions led to the diagnosis of a first episode of schizophrenia.

**Treatment strategy.** The treatment team met with Mr. C and his family to educate them about psychotic illness, the risks and benefits of novel antipsychotics, and the need to begin immediate treatment. With the patient’s and family’s consent, risperidone was initiated at 0.5 mg at bedtime and slowly increased over 1 week to 3 mg/d, with only mild and transient sedation. Within 3 weeks, Mr. C responded robustly and was discharged back to his family. Over the next 7 months, he continued taking risperidone, 3 mg/d, with some residual negative symptoms (social isolation without depression) and full remission of positive symptoms, which enabled him to return to college.

of relapse five-fold.<sup>7</sup> The first treatment experience provides a window of opportunity to help the patient accept taking medications as a normal part of life.

**Therapeutic alliance.** Your approach is key to building a therapeutic alliance with a person whose reality often is clouded by paranoia and referential thinking. Trust begins with the first clinical contact—during history-taking, ordering of tests, answering questions about the diagnosis, and discussing treatment options. Patients and their families must be informed about:

- target symptoms
- medication side effects
- predictors of response and relapse
- lack of certainty about how or when a patient will respond to any antipsychotic
- and the importance of rapid and uninterrupted treatment.

**Supportive therapy.** Support groups for the patient and family can help destigmatize the illness and reduce stress. Information about schizophrenia’s nature and course is available from the National Alliance for the Mentally Ill, National Mental Health Association, and other sources (see “Related resources,” p. 67).<sup>10</sup>

**CBT.** Adjunctive cognitive-behavioral therapy (CBT) may speed up acute symptom response,<sup>11,12</sup> reduce rates of non-response, and shorten hospital stays<sup>13</sup> by helping patients deal with uncertainty about outer and inner realities. CBT approaches are understudied but so far have not been found to reduce relapse rates.

**A moving target.** As treatment moves from acute to consolidation and maintenance, target symptoms may change, side effects can limit the preferred approach, and partial or nonresponse may require drug or dosing adjustments. It is prudent to be prepared to re-evaluate the initial diagnosis as new symptoms emerge, response patterns develop, additional test or historical data become available, or as the illness’ course becomes more clear. To improve outcome, address comorbid or concurrent diseases—such as substance abuse or dependence, mood disorders, anxiety and obsessive-compulsive symptoms, or eating disorders.

### Diagnostic work-up

As in Mr. C’s case (*Box*), a first psychotic episode is characterized by DSM-IV diagnostic criteria for schiz-

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**Table 1**

**WORK-UP OF PATIENTS PRESENTING WITH A FIRST EPISODE OF PSYCHOSIS**

Priority	Mode of evaluation
<b>Routine</b>	History Symptoms, time course, medical conditions, current/previous medications, herbs, drugs Medical and neurologic exam Blood work: CBC with differential, complete metabolic panel, thyroid and liver function tests, syphilis serology, pregnancy test, toxicology Urinalysis, toxicology ECG
<b>Recommended</b>	Fasting glucose and lipid profile (ideally before starting atypical antipsychotic) Head CT (especially if history of recent trauma) or brain MRI
<b>Optional</b>	Erythrocyte sedimentation rate, antinuclear antibodies, lumbar puncture, sleep-deprived EEG

psychosis, including hallucinations, delusions, disorganized thoughts or speech, disorganized behavior(s), or negative symptoms (such as anhedonia, amotivation, asociality, alogia, or affective flattening). The work-up is more comprehensive than that for subsequent episodes and includes a thorough history, complete physical examination, and brain imaging (Table 1) to explore other possible medical and psychiatric diagnoses (Table 2).

The history—ideally gathered from the patient and others—includes:

- medical and psychiatric diagnoses
- medications (prescribed and over-the-counter remedies)
- presence of stressors/triggers
- chronology of symptoms
- potential for the episode to endanger the patient or others.

**Imaging.** Despite a relatively low yield, we recommend that every patient with a first psychotic episode undergo a brain CT or MRI to rule out a potentially treatable organic cause for the psychosis.<sup>14</sup>

**Other tests.** Because of the increased risk of hyperglycemia, dyslipidemia, and possible cardiac conduction abnormalities with atypical antipsychotics, obtain a baseline fasting blood glucose, lipid profile, and ECG. A sleep-deprived EEG is recommended for patients with unclear motor movements or family history of epilepsy.

**Choosing medications**

Medication choices for the patient with first-episode schizophrenia are influenced by:

- target symptoms
- whether the symptoms endanger the patient or others
- the patient’s personal or family history of medication response or side effects
- a generally increased sensitivity to side effects in patients who have never been exposed to antipsychotics
- concurrent medical and/or psychiatric disorders
- prescriber, patient, and family preferences.

Psychiatrists generally select psychotropic classes by symptom domains (Table 3) and individual agents in each class by side effect profile.

Except for clozapine’s superior effectiveness in patients with refractory psychosis, controlled studies have shown no clinically significant differences in efficacy among the drugs in each class—including the antipsychotics. Individual patients, however, may respond differently to different agents.

**Principles of prescribing antipsychotics**

Antipsychotics are effective in treating most psychotic core symptoms, such as hallucinations, delusions, agitation, aggression, and disorganized thinking and behavior. Other medications can be added to speed up or enhance treatment response or to target other domains.

**Dosages.** First-episode patients often require lower dosages and slower titration than multi-episode patients. As a rule, antipsychotics are started at about one-half the dosage given to patients with a chronic treatment history, although symptom severity and absence of side effects at lower dosages can help individualize titration.

**Side effects.** Atypical antipsychotics are preferred because of

Table 2

## DIFFERENTIAL DIAGNOSIS OF FIRST-EPISEDE PSYCHOSIS

Possible diagnosis	Key points for differentiation
<b>Schizophrenia</b>	6 months of psychosis* (including prodromal symptoms); total duration of mood episodes brief relative to active and residual psychotic phases; not directly caused by medical condition or substance
<b>Schizophreniform disorder</b>	Same as above, except symptoms are present 1 to 6 months
<b>Brief psychotic disorder</b>	Same as above, except symptoms are present 1 day to 1 month
<b>Delusional disorder</b>	Apart from non-bizarre delusions, functioning not markedly impaired; total duration of mood episodes brief relative to active and residual psychotic phases; not caused by direct physiologic effects of medical condition or substance
<b>Psychotic disorder NOS</b>	Psychotic symptoms insufficient to make a specific diagnosis
<b>Schizoaffective disorder</b>	Like schizophrenia for at least 2 weeks, but with mania or major depression present for much of the active and residual psychotic periods
<b>Mood disorder with psychosis</b>	Psychotic symptoms occur exclusively during mood disorder episodes
<b>Psychosis due to general medical condition</b>	Psychotic symptoms caused by direct physiologic effects of a general medical condition
<b>Delirium due to general medical condition</b>	Psychotic symptoms associated with a disturbance in consciousness and other cognitive deficits; characterized by a fluctuating course
<b>Dementia due to general medical condition</b>	Psychotic symptoms associated with memory impairment and other cognitive deficits
<b>Substance-induced psychotic disorder</b>	Psychotic symptoms caused by direct physiologic effects of a substance; reaction exceeds that usually encountered with intoxication or withdrawal
<b>Substance-induced psychotic delirium</b>	Similar to above, but associated with a disturbance in consciousness and other cognitive deficits; characterized by a fluctuating course
<b>Substance intoxication or withdrawal</b>	Caused by direct physiologic effects of a substance; reaction is typically encountered with intoxication or withdrawal
<b>Conversion disorder</b>	Contradictory and inconsistent history and presentation; secondary gain
<b>Malingering</b>	Contradictory and inconsistent history and presentation; primary gain

\* Psychotic symptoms must interfere with functioning, and at least two of the following are required: delusions, hallucinations, disorganized thoughts or speech, disorganized behavior, or negative symptoms (avolition, alogia, affective flattening, asociality, or anhedonia), unless delusions are bizarre (impossible), or hallucinations consist of a running commentary or of two or more voices conversing with each other.

Source: Adapted from *DSM-IV handbook of differential diagnosis*. Washington, DC: American Psychiatric Press, 1995.

their reduced risk of extrapyramidal symptoms (EPS), positive effects on depressive and cognitive symptoms, and improved patient satisfaction and adherence, compared with the older antipsychotics.<sup>15-17</sup> Atypicals' potential side effects include weight gain, hyperglycemia, and dyslipidemia,<sup>18</sup> as well as often-overlooked sexual side effects.<sup>19</sup>

Consider the patient's risk for side effects when choosing an atypical antipsychotic, as each drug has strengths and weaknesses. For example, it may be reasonable to consider:

- risperidone, ziprasidone, or aripiprazole—rather than olanzapine or quetiapine—for patients at high risk for weight gain or with a family history of diabetes
- avoiding risperidone for patients with an early indication of sensitivity to EPS or prolactin-related side effects
- an agent that can be loaded rapidly, such as olanzapine or aripiprazole—rather than an agent that requires titration, such as quetiapine—for a patient presenting with severe agitation.

Clozapine—because of its side effect potential—is generally reserved for patients who have not responded to at least two antipsychotic trials of at least 4 to 6 weeks duration and have a steady-state clozapine level >350 ng/dl.

**Acute agitation.** Short-acting IM formulations can be used effectively for acute agitation and impulsivity or for patients who refuse oral antipsychotics. Until recently, only first-generation antipsychotics such as haloperidol and fluphenazine were available in IM formulations. Injectable ziprasidone mesylate is now available for acute agitation and has been found to be as safe and effective as haloperidol. Lorazepam may be used to treat agitation or as an adjunct to a patient's antipsychotic agent.

### Adjunctive therapies

When antipsychotic monotherapy is inadequate, adjunctive medications may be considered:

- to treat catatonia, obsessive-compulsive disorder, or depression
- to resolve agitation or mania more quickly
- to control agitation or anxiety while an antipsychotic dosage is being titrated
- when side effects emerge or residual symptoms remain despite adequate dosage and duration of antipsychotic treatment.

Deciding if and when to add another drug depends on

the nature and severity of target symptoms, the degree and time course of response, and whether side effects appear. If you use adjunctive therapies during acute stabilization, attempt to taper and discontinue them after the patient's symptoms have improved. Avoid combining antipsychotics, as no clinical data support the effectiveness and safety of this practice.<sup>20</sup>

Benzodiazepines are often used adjunctively for agitation, anxiety, or temporary insomnia in patients with schizophrenia. Common dosages are:

- for agitation or anxiety, lorazepam, 0.5 to 2 mg bid or tid, or clonazepam, 0.5 mg bid to 2 mg tid
- for insomnia, lorazepam or clonazepam, 1 to 2 mg at bedtime, or zolpidem, 5 to 10 mg at bedtime.

Benzodiazepines also are effective for catatonia, which may be misdiagnosed as negative symptoms or depression when it presents as marked psychomotor retardation, staring, selective mutism, negativism, mild posturing, or stereotypies.

If undiagnosed, catatonia may worsen during antipsychotic titration. Symptoms usually respond to high-dose lorazepam, 1 mg bid or tid, with increases up to a maximum dosage of 12 mg/d.

Mood stabilizers are often used adjunctively to treat acute agitation and disinhibition<sup>21</sup> or as add-on

agents for residual psychotic or affective symptoms. Recommended dosages and blood levels, as tolerated, are:

- valproic acid, starting at 10 to 20 mg/kg bid, with a target serum level of 60 to 120 µg/ml. A once-daily, extended-release formulation may improve compliance.
- lithium, starting at 300 mg bid to tid, aiming for a serum level of 0.8 to 1.2 mEq/L.

Manic symptoms in a schizoaffective presentation may require one or even two mood stabilizers.

Lamotrigine may be the treatment of choice for depressed patients with schizoaffective disorder, bipolar type.<sup>22</sup> However, it must be started at 25 mg/d and titrated extremely slowly—by 25 mg every other week, up to a target 200 to 400 mg/d—to avoid the risk of potentially fatal Stevens-Johnson syndrome.

Gabapentin, 300 mg tid to 1,500 mg tid, may help treat anxiety—particularly in patients with comorbid substance abuse, in whom benzodiazepines should be used sparingly after stabilization.

**Catatonia may be misdiagnosed as negative symptoms or depression**



Table 3

SYMPTOM-BASED DRUG TREATMENT OF FIRST-EPISODE SCHIZOPHRENIA

Target symptom	Medication choices	Dosage range	Comments
<b>Agitation</b>	Atypical antipsychotic Mood stabilizer Benzodiazepine ECT	Depends on level of agitation and individual agent	Ziprasidone IM may be useful for acute agitation
<b>Psychosis</b>	Atypical antipsychotic ECT	≈ 50% of dosage used for multiple episode patients	Start low/go slow, monitor side effects
<b>Catatonia</b>	Lorazepam ECT	1 mg/d bid to 4 mg/d tid	Use sedation, symptom resolution as threshold
<b>Negative symptoms</b>	Atypical antipsychotic Glycine, cycloserine may help	Dictated by positive symptom response	Effect on functioning, quality of life unclear
<b>Cognitive symptoms</b>	Atypical antipsychotic	Same as above for negative symptoms	Same as above
<b>Insomnia</b>	Lorazepam Zolpidem Trazodone Mirtazapine	1 to 2 mg HS 5 to 10 mg HS 50 to 200 mg HS 7.5 to 15 mg HS	Short-term treatment preferred
<b>Depression, obsessive-compulsive symptoms, anxiety/panic</b>	SSRI, SNDRI, NDRI, SARI, NASA	As per individual agent	Possible interference with antipsychotic blood levels*
<b>Parkinsonism</b>	Benzotropine Trihexyphenidyl	0.5 to 2 mg/d 1 to 15 mg/d	Possible effect of decreased cognition
<b>Akathisia</b>	Propranolol	20 to 160 mg/d	Monitor blood pressure
<b>Weight gain</b>	Ziprasidone Aripiprazole	Dictated by positive symptom response	Prevention more effective than remediation
<b>Non-adherence</b>	Olanzapine oral disintegrating tablets Risperidone liquid  Risperidone microspheres	5 to 20 mg/d 1 to 4 mg/d  IM injections every 2 weeks	Dissolves instantly  Can be mixed with water, coffee, orange juice, or low-fat milk  Not yet available

\* Fluoxetine and paroxetine increase risperidone levels by CYP-P450 2D6 inhibition; fluvoxamine increases clozapine and olanzapine levels by CYP-P450 1A2 inhibition; fluvoxamine and nefazodone increase quetiapine and may increase ziprasidone levels by CYP-P450 3A4 inhibition; all three CYP-P450 inhibitors may increase aripiprazole levels, but the extent is not known.

ECT: electroconvulsive therapy; SSRI: selective serotonin reuptake inhibitor; SNDRI: serotonin-norepinephrine-dopamine reuptake inhibitor; NDRI: norepinephrine-dopamine reuptake inhibitor; SARI: serotonin antagonist and reuptake inhibitor; NASA: norepinephrine-antagonist and serotonin antagonist.

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**Antidepressants.** Patients with schizophrenia can develop depression, even if they do not meet diagnostic criteria for schizoaffective disorder. Untreated depression can lead to non-adherence, self-medication with alcohol or illicit substances, and increased risk of suicide.

Differentiating depression from negative symptoms may be difficult, but there are subtle distinctions:

- Patients with negative symptoms appear more emotionally flat and unconcerned about their lack of motivation and diminished social and role functioning.
- Depressed persons often verbalize their demoralization, hopelessness, and desire to feel and behave differently.

Treat depression with any selective serotonin reuptake inhibitor or other newer-generation antidepressant such as mirtazapine, nefazodone, or venlafaxine at usual doses, as tolerated.

**Miscellaneous medications.** Use anticholinergic medications such as benztropine, 0.5 to 2 mg bid, or trihexyphenidyl, 1 to 5 mg bid, if parkinsonian symptoms occur and changing to an antipsychotic with a lower EPS potential is not feasible.

For akathisia, propranolol (10 mg bid or tid; titrate up to 160 mg/d if pulse rate and blood pressure remain stable) or benzodiazepines may be useful. Amantadine may also be used at dosages between 50 and 150 mg bid.

Insomnia may be treated with low dosages of sedating antidepressants, such as trazodone, 50 to 200 mg HS, or mirtazapine, 7.5 to 15 mg HS.

### Preventing relapse during maintenance

Medication adherence depends on patient insight and attitude towards medications.<sup>23</sup> Once you start a first-episode patient

on drug therapy, encourage adherence by monitoring symptoms and anticipating side effects. Every 3 months after the acute phase:

- Use a structured evaluation, such as the Brief Psychiatric Rating Scale,<sup>24</sup> to plot symptom severity, response, and risk for relapse.
- Rate EPS with the Simpson-Angus Scale<sup>25</sup> and tardive dyskinesia (TD) with the Abnormal Involuntary Movement Scale<sup>26</sup> because EPS and TD are associated with poor symptom response, adherence, and outcome.<sup>7</sup>

Reinforce information about the chronic nature of schizophrenia, especially when the patient or family question why treatment is needed if symptoms have resolved. Continue to counsel them about the patient's need for:

- regular sleep of sufficient duration and without sleep-wake reversal
- gradual return to premorbid social, educational, and vocational activities/responsibilities
- ongoing treatment.

Encourage vigilance for relapse warning signs, including insomnia, social withdrawal, anxiety, refusal to eat or take medications, suspiciousness, agitation, disorganization, preoccupation with overvalued ideas, or responses to internal stimuli.

If the patient is noncompliant with antipsychotics in tablets or capsules, options include:

- liquid risperidone or olanzapine in a rapidly dissolving form that the patient cannot hide and spit out later
- long-acting depot formulations if the patient cannot be supervised and monitored daily. Older antipsychotics (such as haloperidol decanoate and fluphenazine decanoate) are available in depot formulations, and the FDA is considering risperidone in a microsphere formulation that would allow biweekly injections.

### Medication withdrawal

Although the ideal duration of maintenance treatment after a first psychotic episode is debatable, we recommend that antipsychotics be continued at the full dosage that achieved symptom remission for at least 1 year.<sup>27</sup> Then, if the patient has returned to the premorbid baseline, you can attempt a gradual medication withdrawal across 2 to 4 months, ideally when the patient's environment is stable.

Be cautious when withdrawing antipsychotics from

**A** first episode of schizophrenia presents a unique opportunity to favorably alter a patient's quality of life. Intervening early with antipsychotics and encouraging medication adherence are most likely to prevent relapse and chronicity. Building a therapeutic alliance is key to stabilizing patients and maintaining function.

**BottomLine**



## Related resources

- ▶ National Alliance for the Mentally Ill (800) 950-NAMI (6264); [www.nami.org](http://www.nami.org)
- ▶ National Mental Health Association (800) 969-NMHA (6642); [www.nmha.org](http://www.nmha.org)
- ▶ National Alliance for Research on Schizophrenia and Depression (516) 829-0091; [www.narsad.org/index.html](http://www.narsad.org/index.html)
- ▶ Miller R, Mason SE. *Diagnosis schizophrenia. A comprehensive resource*. New York: Columbia University Press, 2002.

### DRUG BRAND NAMES

Aripiprazole • Abilify	Nefazodone • Serzone
Bupropion • Wellbutrin	Olanzapine • Zyprexa
Citalopram • Celexa	Paroxetine • Paxil
Clozapine • Clozaril	Quetiapine • Seroquel
Escitalopram • Lexapro	Risperidone • Risperdal
Fluoxetine • Prozac	Sertraline • Zoloft
Fluvoxamine • Luvox	Trazodone • Desyrel
Gabapentin • Neurontin	Venlafaxine • Effexor
Lamotrigine • Lamictal	Ziprasidone • Geodon
Lorazepam • Ativan	Zolpidem • Ambien
Mirtazapine • Remeron	

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patients with a family history of psychosis. Consider a more gradual dose reduction, ongoing group and/or individual psychotherapy, and at least monthly monitoring. When possible, involve people who are significant in the patient's life and educate them to look for deterioration's warning signs, such as insomnia, irritability, anxiety, social withdrawal, preoccupation with overvalued ideas, or pacing.

If relapse occurs, carefully assess how well the patient has adhered to medication. Once a second psychotic episode occurs, his or her medication probably should be continued indefinitely.

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