Psychotic prodrome: Are antipsychotics effective? Ethical?

Evidence is mixed but risk is high when abnormal cognition falls short of schizophrenia

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Because 40% of individuals with a psychotic prodrome develop schizophrenia, detecting and preventing this transition could improve many patients' lives. Unfortunately:

- psychotic prodrome lacks clear-cut symptoms and is difficult to identify
- little evidence exists to help clinicians select psychotropics and decide how long to use them
- treating all prodromal patients would expose those who never develop psychosis to the risk of psychotropics' side effects.

How, then, can psychiatrists help patients who present with possible prodromal symptoms? Based on research and our experience, this article describes the psychotic prodrome and offers a

pragmatic, evidence-based approach to diagnosis and treatment.

WHAT CAUSES PSYCHOTIC CONVERSION?

Reduced gray matter volumes in certain brain regions may be associated with conversion to psychosis *(Box 1)*. Stress also may play a role; elevated stress-reactive cortisol levels are associated with positive symptom severity in the prodrome.[1] Other factors being investigated include obstetric complications at birth, maternal age >30, premorbid schizotypal personality disorder, and impaired olfaction.

Symptoms. Nearly 80% of patients with schizophrenia experience a psychotic prodrome that lasts a few months to several years.[2] Common features include:

- gradual worsening of perceptual disturbance
- referential thinking
- paranoia
- mild cognitive deficits
- mood lability
- impulsivity
- suicidality
- declining social function and academic performance.[3,4]

Patients with these symptoms may be at imminent risk; if untreated, an estimated 40% progress to schizophrenia within 1 year.[5]

A premorbid phase often precedes the prodrome, with symptoms such as impaired attention, soft neurologic signs, and subtle social deficits. These changes may be harbingers of the prodrome but are too nonspecific to be diagnostic. Other functional impairments—including anxiety, depression, drug abuse, and psychosocial factors such as school stress—may mimic schizophrenic prodrome.

Prognosis. Studies of patients' first schizophrenia episodes suggest that prodrome duration may predict outcome. A longer prodrome is thought to indicate a poor prognosis,[6] such as in patients who wait a year before seeking treatment.[7] A review of 22 studies of first-episode psychosis found early psychosocial and pharmacologic interventions improved long-term prognosis, and medication discontinuation predicted more-severe and chronic disease.[8]

Genetic risk. Schizophrenia has a strong genetic predisposition, although not everyone in the genetic high-risk group develops schizophrenia. Persons with a family history of schizophrenia have a 10% to 20% risk of psychotic conversion.[9]

Pioneering work by McGorry et al[10] identified an "ultra high-risk group" with a psychotic

Box 1

Neuroimaging detects brain changes during psychotic prodrome

Reduced gray matter volumes in certain brain regions may be associated with conversion to psychosis. Imaging studies have found medial temporal lobe changes—specifically, hippocampal volume alterations—in persons with schizophrenia, genetic high-risk groups, and those thought to be at risk for imminent psychosis.[11]

MRI imaging of patients with prodromal signs has shown less gray matter in the right medial temporal, lateral temporal, inferior frontal cortex, and bilateral cingulate regions in those who have developed psychosis, compared with those who have not. In the psychotic patients, 12-month longitudinal follow-up has found reduced gray matter in the left hippocampal, fusiform, orbitofrontal, cerebellar cortices, and cingulate gyrus.[12]

Brain structure is related to genetic liability for schizophrenia in high-risk patients, who seem to have smaller right and left prefrontal lobes and smaller right and left thalami. These findings are consistent with the prodrome's neurocognitive deficits, which are less than those reported in schizophrenia and greater than those seen in healthy subjects.

Table 1

3 patient groups considered at 'ultra high risk' to develop schizophrenia

Patients with…	Symptoms
Attenuated psychotic symptoms	Overvalued ideas, perceptual disorders Present at least 1 week; not >5 years At least 1 symptom several times a week
Brief intermittent psychotic episodes	Frank psychotic features Resolve spontaneously within 7 days Can be drug-induced
Genetic risk and recent deterioration syndrome	Psychotic disorder in a first-degree relative Schizotypal personality disorder Present at least 1 month; not >5 years Significant functional decline

Source: Adapted from reference 10

conversion rate of 40% to 60%. These patients present with three symptom patterns:

- attenuated positive symptoms
- brief intermittent psychotic episodes
- genetic risk and recent deterioration syndrome *(Table 1)*.

Early identification of these high-risk individuals with perceptual distortions, frank psychotic symptoms, family history of psychosis, and schizotypal personality disorder may aid in early recognition and treatment.

The Edinburgh High Risk Study of 162 individuals ages 16 to 25 showed more marked psychopathology in those with at least two close relatives with schizophrenia, compared with control groups. A direct correlation was seen between genetic liability and poor neurocognitive performance.[11]

PRODROME RATING SCALES

Researchers are using outcome measures to diagnose prodromal symptoms and assess their severity. Operational, validated assessment tools include:

- **Bonn Scale for the Assessment of Basic Symptoms (BSABS)**: captures subtle changes in thinking, feeling, and perception.
- **Schizophrenia Prediction Instrument for Adults (SPI-A):** defines prepsychotic deviations and rates symptoms that are subjectively experienced by the patient.
- **Comprehensive Assessment of At Risk Mental State (CAARMS):** defines ultra high-risk criteria and incorporates eight dimensions of psychopathology.
- **Scale of Prodromal Symptoms (SOPS):** rates psychosis severity. When embedded within the Structured Interview for Prodromal Syndromes (SIPS), the SOPS determines the presence or absence of psychosis and predicts progression to psychopathology.
- **Criteria for Prodromal Symptoms (COPS):** defines ultra high-risk categories.
- **Presence of Psychosis Scale (POPS):** rates severity, intensity, and duration of positive prodromal symptoms.[12]

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These instruments may identify prodromal symptoms in psychiatric practice, but further validation of clinical criteria is needed before they could be recommended for routine patient assessment.

PROPHYLACTIC ANTIPSYCHOTICS?

Atypical antipsychotics may be the standard of care for patients with a first psychotic episode, but this intervention is based on few double-blind controlled trials. Not surprisingly, only a handful of studies have examined antipsychotic therapy for the prodrome's less clear-cut symptoms.

Risperidone. An 8- to 12-week open-label study in adolescents with first- and second-degree relatives with schizophrenia[13] included four prodromal and six first-episode psychosis patients who met criteria for a cluster A personality disorder. Risperidone, 1.0 mg/d and 1.8 mg/d, respectively, improved thought disorder and attention symptoms, as measured with the Child Behavior Checklist. Verbal memory improved minimally, and no medication side effects were reported.

An open-label observational study[14] identified four middle-aged subjects with a genetic risk of schizophrenia who reported negative symptoms and neurocognitive deficits. Risperidone, started at 0.25 mg/d and gradually increased to a maximum of 2 mg/d, improved negative symptoms, attention, and working memory. Mild side effects including tremors, sedation, dry mouth, and anxiety symptoms were reported.

An open-label, randomized, comparator trial[15] examined psychotic transition rates in 59 subjects (mean age, 20) who met ultra high-risk criteria. They received:

- a needs-based intervention (NBI) comprising case management, psychotropics excluding antipsychotics, and supportive psychotherapy
- or a specific preventive intervention (SPI) that included risperidone, 1 to 2 mg/d, and a modified cognitive-behavioral therapy (CBT).

After 6 months, 10 of 28 (36%) in the NBI group had converted to a first episode of psychosis, compared with 3 of 31 (10%) in the SPI group ($P = 0.03$). At this point, risperidone was stopped, and all patients were offered NBI for 6 more months.

At 12-months' follow-up, another 3 SPI patients who had been partially adherent or non-

Table 2

Should you intervene with patients in suspected psychotic prodrome?

Arguments for:

- Early treatment may prevent psychosocial decline
- Treatment may delay or ameliorate psychosis onset
- Treatment may improve patient awareness and acceptance of diagnosis
- Antipsychotics are effective for symptoms and may be neuroprotective
- Medications may improve overall outcome
- Neuroimaging findings may predict psychosis
- Outcome scales have improved diagnosis
- Treatment may reduce prodrome duration and improve prognosis

Arguments against:

- Treatment would likely be given to persons who would not develop psychosis
- Treatment would unnecessarily stigmatize individuals who do not have schizophrenia
- Exposing patients with uncertain diagnoses to treatment risks is an ethical dilemma
- Antipsychotics are associated with side effects
- Psychotic prodrome studies are inconclusive, with small sample sizes and short follow-up
- No biological markers exist to predict psychosis

Table 3

Psychotic prodrome: Unanswered clinical questions

- **Does prodrome** reflect a vulnerability for progression to psychosis?
- **Can prodrome** progress to psychosis in the absence of early interventions?
- **Does duration** of untreated psychosis predict prognosis?
- **Do treatments** reduce the risk of conversion to psychosis?
- **Do interventions** alter disease severity and prevent relapses?
- **Can early interventions** prevent cognitive and functional impairment?

adherent to antipsychotic therapy had converted to psychosis. For adherent SPI patients, protection against conversion appeared to persist for 6 months after risperidone therapy ended. All medication side effects were mild and transient.

Olanzapine. One double-blind, randomized, placebo-controlled trial has been published using olanzapine in patients with a prodromal syndrome.[16] Sixty patients received olanzapine, 5 to 15 mg/d, or placebo. The olanzapine group showed significant reductions in positive, negative, and disorganization subscale scores and total SOPS and Positive and Negative Syndrome Scale scores, compared with the placebo group.

In the first year, 11 of 29 placebo-group patients and 5 of 31 receiving olanzapine converted to psychosis. Among patients receiving no treatment in the second year, 2 of 8 former placebo patients and 3 of 9 former olanzapine patients converted to psychosis.

Discontinuation rates were 35% and 28%, respectively. Compared with the placebo group, patients taking olanzapine experienced greater weight gain, suggesting that risks associated with antipsychotic therapy may exceed unproven benefits in this population.

Discussion. Little information exists on using quetiapine, ziprasidone, or aripiprazole in prodromal patients. As cited above, preliminary studies with risperidone and olanzapine suggest that these agents may improve several domains of psychotic prodrome. The evidence does not support firm conclusions, however, given the trials' small sample sizes and brief duration.

The prevalence of obesity and metabolic syndrome in patients with schizophrenia and the added metabolic risks associated with atypical antipsychotics make their use during the prodrome controversial. Weighing the potential advantages and disadvantages *(Table 2, page 37)*, we consider antipsychotics to be the last resort after psychosocial interventions have failed to improve prodromal symptoms.

Low-dose atypical antipsychotics may be warranted for some patients, but their use requires stringent monitoring of:

- weight and waist circumference
- vital signs
- metabolic parameters such as fasting blood glucose and lipid profile
- abnormal involuntary movements
- prolactin elevations.

Lifestyle modification—including diet and exercise to counteract the risk of weight gain—must be part of the treatment plan. Because the exact risks of antipsychotics are unknown—particularly their weight-gain potential among children and adolescents—we recommend specialist consultation (see *Related resources, page 46*) and careful documentation of all treatment decisions and discussions.

OTHER THERAPIES

Antidepressants. Researchers are also exploring the efficacy of using antidepressants and anxiolytics in the prodromal phase. The only published naturalistic study of adolescents found antide-

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pressants alone or in combination with mood stabilizers or anxiolytics to be as effective as atypical antipsychotics in treating prodromal symptoms.[17] A more substantial study is ongoing.

Psychotherapy. For patients with a suspected psychotic prodrome, nondrug strategies may help minimize functional and cognitive impairments, ease distress, and improve coping skills.

CBT has been shown to reduce psychotic progression over 12 months.[18] Use CBT to help patients cope with the illness while focusing on:

- symptom monitoring
- premorbid and present functioning
- establishing a therapeutic alliance
- assessing the patient's experience of psychosis and any thought distortions.

Also assess and treat co-occurring conditions such as alcohol and drug abuse. Involving the family in early intervention has been shown to improve prognosis.[19]

'REAL WORLD' EARLY INTERVENTION

Patients with prodromal symptoms are often referred to psychiatrists by family members, primary care physicians, or other mental health professionals. They tend to be young adults, and a few may present in their teens. Most are experiencing behavioral changes such as social isolation, feeling suspicious, perceptual disturbances, depression, and/or anxiety symptoms that seem abnormal but fall short of DSM-IV criteria for schizophrenia diagnosis.

Many clinical questions about schizophrenia's prodromal phase remain unanswered *(Table 3, page 38)*. Our primary aim is to adequately assess these patients and provide treatment and follow-up, taking into account:

- the individual's presentation
- risks and benefits of available interventions.

Begin by educating patients and their families and providing social and emotional support to alleviate their distress that a mental illness may be developing *(Box 2)*. Psychosocial and pharmacologic treatment options are based on presenting symptoms and other patient-specific variables.

Psychotherapy should emphasize coping strategies, education about warning signals of psychotic conversion, establishing a therapeutic alliance, assessing thought distortions, and monitoring premorbid and present functioning.

Consider atypical antipsychotics for patients with distressing psychotic symptoms, rapidly deteriorating function, increased agitation, and safety risks. Consider antidepressant and/or anxiolytic therapy for depression and anxiety, respectively.

Discuss at length with patients and families the risks and benefits of pharmacologic treatments. When clinically appropriate, cautiously discontinue or taper any medication with patients' consent, while monitoring for side effects and symptoms.

Box 2

Early interventions when you suspect psychotic prodrome

- **Provide** patients and families information and emotional support; a strong therapeutic alliance may help keep the patient in treatment if schizophrenia develops
- **Offer** early psychosocial interventions such as vocational training, relapse prevention, substance abuse treatment, family therapy, supportive and CBT
- **Explore** using low-dose atypical antipsychotics as a last resort for patients with pronounced prodromal symptoms; explain risks of weight gain and other metabolic changes, obtain consent, and document need for such interventions
- **Consider** referral, if feasible, to a center specializing in psychotic prodrome diagnosis, treatment, and research

continued

Related resources

- Issue devoted to early prodrome research. *Schizophr Bull* 2003;29(4):621-879.
- Diagnostic and therapeutic intervention during psychotic prodrome. *CNS Spectrums* 2004;9(8):578-606.
- PRIME (Prevention through Risk Identification, Management & Education) Research Clinic. Department of Psychiatry, Yale University. http://info.med.yale.edu/psych/prime/pintro.html.
- Youth Mental Health Update. *Schizophrenia: New strategies for early detection and treatment.* RAPP Clinic, Zucker Hillside Hospital, Glen Oaks, NY. http://schoolnet.lij.edu/eshare/files/rapp.html

DRUG BRAND NAMES

Aripiprazole • Abilify
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal
Ziprasidone • Geodon

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Bottom Line

Schizophrenia's prodrome is not quite ready for clinical prime time. In the absence of guidelines, psychotherapy is preferred for high-risk patients along with screening and symptom monitoring. Atypical antipsychotics may protect against psychotic conversion, but limited data and side effect risks make them a treatment of last resort.