CHILDREN WITH PRODROMAL SYMPTOMS OF PSYCHOSIS:
Translating Research Into Clinical Practice

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Clinical Presentation: *A 10 year old female presents to your office with her mother. The mother reports that the child was healthy and "normal" for years, but lately refuses to bathe and talks about odd beliefs, including seeing ghosts. There was a death in the family about six months ago, but the symptoms preceded the death. She avoids her favorite toys because she thinks that they look at her "funny." The patient continues to perform well in school and tend to her chores. The mother asks you what to do. She is afraid because she always heard that her grandmother had "bipolar schizophrenia" but has no additional details.*

Severe psychotic illnesses like schizophrenia produce significant psychosocial and economic disability, particularly when they first present during youth.[1] In the United States, it is estimated that the total cost of schizophrenia is over 60 billion dollars, which includes both direct costs from patient care and housing and indirect costs from unemployment, reduced workplace productivity, and premature mortality.[2] As with many psychiatric disorders, where treatment begins after the onset of illness, psychotic disorders are often treated after the first psychotic episode. However, there has been increasing neurobiological and clinical research indicating the existence of a prodromal period prior to the first psychotic episode, which could be detected by clinical monitoring.

The Prodrome

It is estimated that some psychotic symptoms are present in 7.5% of adolescents[3] and 5% of the general adult population,[4] which may represent a subgroup at genetic risk of psychosis.[5] A large majority of individuals with psychotic illnesses display subthreshold or "prodromal" signs of psychosis during adolescence and transition to adulthood.[3,5]

The "prodromal period" is the time during which a disease process has begun but has not yet clinically manifested with sufficient severity or compromise that it meets criteria for full-blown illness. In the case of psychotic disorders, this is often described as a prolonged period of attenuated and nonspecific thought, mood, and perceptual disturbances accompanied by poor psychosocial functioning, which are typically identified retrospectively. Clinical high-risk (CHR), at-risk mental state (ARMS), or ultra-high-risk (UHR) are terms to identify prospectively individuals who are potentially in the prodromal phase of psychosis. The DSM has included attenuated psychosis syndrome as a category for further study in section 3.[6]

It is important for pediatric healthcare providers to understand psychosis and how to identify prodromal symptoms. Table 1 provides a list of symptoms commonly reported in the prodromal phase.

Who Converts from Prodrome to Psychosis?

A meta-analysis of 27 studies (with 2,502 participants) demonstrated that of the total number of untreated people with prodromal symptoms, 18% transitioned to psychosis after six month follow-up, 22% after 1 year, 29% after 2 years, and 36% after 3 years.[8] The mean transition risk to a psychotic state was 29.2% (95% CI 27.3%-31.1%) with a mean follow up of 31 months.[8] Another meta-analysis of ten randomized prevention trials demonstrated that the risk of onset of disorder was reduced by 52% after 12 months and by 35% at 2-4 years follow-up. These promising outcomes are also reflected in small numbers needed to treat (NNT) of nine at 12 months follow up and an NNT of 12 after longer-term followups.[9] Overall the risk reduction at 12 months was 54% (RR = 0.463; 95% CI = 0.33–0.64) with a NNT of 9 (95% CI = 6–15).[9] Box 1

Table 1: Examples of Symptoms During the Prodromal Period

Symptoms	Examples
Positive prodromal thought content	Perplexity, delusional mood, non-persecutory ideas of reference, over-valued beliefs, distrustful, exaggerated
Negative prodromal thought con-	Social isolation or withdrawal, avolition, diminished emotional responsiveness,
Disorganization symptoms	Odd behavior, mannerisms, poor focus and attention, social inattentiveness
Other symptoms	Sleep disturbances, dysphoric mood,

Note: Adapted from Structured Interview for Prodromal Symptoms (SIPS).[7]

HOME

reflects signs and symptoms that increase risk for transition to clinical psychosis.

Assessment Tools

The Comprehensive Assessment of At-Risk Mental States (CAARMS) and Structural Interview for Prodromal Symptoms (SIPS) are tools used to identify and classify the ARMS or UHR as falling under 1) Attenuated Psychotic Symptoms (APS) group, which describes subthreshold attenuated positive psychotic symptoms in the last 12 months; 2) Brief Limited Intermittent Psychotic Symptoms (BLIPS) group, consisting of psychotic symptoms lasting for less than one week and spontaneously remitted; or 3) Trait and State Risk Factor Group, describing an individual with a first degree relative who has a psychotic disorder or schizotypal personality disorder and who has experienced psychosocial decline over the last one year.[7, 12] The Prodromal Questionnaire is another frequently used screening tool.[13] Of these tools, CAARMS and SIPS require specialized training, whereas the Prodromal Questionnaire-Brief Version is available freely.

Psychotherapeutic Interventions

Meta-analysis of five cognitive-behavioral therapy (CBT) trials reported that CBT reduced the risk of transition to psychosis at the end point by 48% when compared to controls (pooled risk ratio = 0.52, 95% confidence interval 0-79) .[9] A study examining the effects of an integrated psychological intervention, combining individual CBT, group skills training, cognitive remediation, and multifamily psychoeducation versus supportive counseling showed that the integrative psychological intervention was superior to supportive counseling in preventing progression to psychosis at 12 month follow-up (3.2% vs. 16.9%; p=.008) and at 24 month follow up (6.3% vs 20.0%; p =.019) .[14]

Psychopharmacological Interventions

There have been a few trials evaluating the efficacy of antipsychotic agents in preventing transition to a psychotic episode. Transition rates at 12 months in a study comparing CBT and risperidone, CBT and placebo, and supportive therapy and placebo, were 10.7%, 9.6%, and 21.8%, respectively, and the differences were not statistically significant. The dropout rate was 37% for the risperidone arm.[15] Another double-blind, placebo-controlled study did not find statistical differences in one-year conversion rates between olanzapine (5-15 mg/day) and placebo. The participants on olanzapine gained a statistically significant amount of weight compared to placebo, with an average weight gain of 8.7kg over 12 months (SD=9.05). The dropout rate was 54% for the olanzapine arm, and 34% for the placebo arm.[16] Open label trials with amisulpride and aripriprazole have shown some efficacy but placebo-controlled trials are needed.[17, 18] Long-chain omega-3 fatty acids have been shown to be superior to placebo in a 12-week randomized control trial. The trial needs to be replicated.[19]

Box 1: Clinical variables that predict a higher risk of transition to psychosis include:[10,11]

- high unusual thought-content scores
- low social functioning
- social decline in an individual with genetic risk
- high suspicion/paranoia scores
- early adolescent social maladjustment
- history of substance abuse

Conclusion

Youth who present with prodromal symptoms (as listed in Table 1) may be at increased risk for developing clinical psychosis, which can be a chronic, debilitating condition. Clinicians should be diligent for screening for prodromal symptoms by monitoring for evolving symptoms on a regular basis (see Box 2 for practical tips). Several screening measures exist to aid clinicians. Preventative efforts are under investigation. Currently, psychotherapeutic modalities and some pharmacological interventions hold promise.

Furthermore, early detection and intervention in people at risk of developing psychosis can be successful to pre-

Box 2: Practical Tips for Child and Adolescent Psychiatrists and Clinicians:

- Identify prodromal or at-risk Individuals via screening measures and clinical interviews, and conduct an individualized appraisal of symptoms, functional changes, and environmental/ genetic risk factors.
- Carefully and closely monitor for emergence of a full - fledged psychotic episode and other comorbidities like anxiety, mood symptoms, suicidality, and substance abuse.
- Psychoeducation, education and employment support, and family involvement are of paramount importance.
- Approximately 30% of individuals with prodromal symptoms transition to a psychotic disorder at a 30-month follow-up. 70% do not develop a primary psychotic disorder. The risk of transition can be decreased by over 52% at 12 months and by over 35% at 2-4 years with early intervention.
- Psychotherapeutic interventions like cognitive behavioral therapy and skills training have shown to be effective in preventing a psychotic episode
- The use of antipsychotics as a preventive tool has not been shown to be effective, is not recommended, and has significant risks.

vent or delay a first psychotic episode. Additional research is needed to determine the benefit of antipsychotics at this stage, as current studies are limited by high drop-out rates.

Other Resources:

International Early Psychosis Association (IEPA)
http://iepa.org.au/

North American Prodromal Longitudinal study (NAPLS)
http://napls.psych.ucla.edu/

Headspace
http://www.headspace.org.au/

Take-Home Summary:

Evidence is lacking on how to treat prodromal symptoms, although psychopharmacological and psychotherapeutic interventions are showing some preliminary potential benefits. More research is needed before these can be recommended to prevent the onset of psychosis.

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HOME