Early Intervention for Schizophrenia: The Risk-Benefit Ratio of Antipsychotic Treatment in the Prodromal Phase

In schizophrenia, once psychosis and negative symptoms have manifested, most patients will suffer from persistent illness and declining social and vocational functioning; hence prevention has been contemplated for many years (1). In the early 1990s, the perception that second-generation antipsychotics improved the risk-benefit ratio of antipsychotic treatment was the impetus for investigators to attempt to diagnose and treat the illness before the appearance of full-blown psychosis. It was hypothesized that early intervention, including supportive therapy and treatment with antipsychotics, might prevent or delay the first psychotic episode and the subsequent deterioration (2). In order to identify these future patients, diagnostic criteria for this prodromal phase of the illness were developed and agreed upon, based on the presence of attenuated or brief positive symptoms or decreased functioning in persons with a first-degree relative with schizophrenia. Initial results indicated that 40% of patients who met these criteria transitioned to full-blown psychosis within a year (3). Specialty clinics were established, professional organizations were formed to promote investigation in this field, and new assessment tools were developed to quantify prodromal symptoms. The National Institute of Mental Health funded the North American Prodromal Longitudinal Study, in which the leading prodromal researchers in the United States and Canada pooled their data to further the study of the prodromal phase. Impressive prediction models were published in prestigious journals, positive treatment trials encouraged the use of second-generation antipsychotics in these patients (4, 5), and more and more clinicians began to administer antipsychotics to patients with attenuated psychotic symptoms (6). However, as time went on, the rates of transition from prodrome to psychosis dropped below a range of 15%–20% (7, 8). There are several possible explanations for the decline. Publicity and increased awareness led to earlier referrals, and hence patients were assessed earlier in the period of risk, leading to the recruitment of a more dilute sample, including more false positives. In addition, increased exposure of putative prodromal patients to pharmacological and psychosocial interventions might result in fewer transitions to psychosis (9). Around the same time, it became clear that the second-generation antipsychotics were marginally if at all more efficacious than the old drugs and had significant metabolic side effects, which led to a reshifting of the risk-benefit ratio (10).

"The challenge is to identify the minority of patients…who are on their way to their first episode."

This issue of the *Journal* includes an important article by Addington et al. (11) that sheds light on this pioneering project. The authors reported on the patients in the North American Prodromal Longitudinal Study clinics who did not receive antipsychotic medication and did *not* transition to full-blown psychosis over 2 years. It turns out that the clinical status of the majority of these patients was *improved*, with fewer positive symptoms and somewhat better functioning. First and foremost, this finding encourages clinicians treating patients with these symptoms *not* to initiate antipsychotic treatment, as the majority of them are not on their way to a psychotic disorder. Second, these findings force us to reconsider the validity of this diagnostic category, including

the members of the DSM-5 Task Force, who are contemplating inclusion of a diagnostic category of an "at risk" syndrome based on these criteria in DSM-5.

But why does not this apparently straightforward preventive approach work? Many patients do have a prodromal phase in which milder psychotic symptoms are present before they escalate into full-blown psychosis. However, it appears that attenuated psychotic symptoms are quite frequent in the nontreatment-seeking general population, and about 10% of persons in the community endorse having attenuated positive symptoms (unpublished data available upon request from Kaymaz et al.), which generally do not cause great distress or lead to treatment seeking. Crucially relevant to the issue of prodromal research, these symptoms are often transient, waxing and waning over the years. Hence, a person with attenuated positive symptoms might be misclassified as being in the prodromal phase of the illness, as in the following scenario: a 22-year-old man who has these psychotic experiences has an emotional crisis when his girlfriend leaves him. He might be upset, have difficulty sleeping at night, have difficulties concentrating, have decreased functioning at school or at work, and have more attenuated positive symptoms. If this person goes to a psychiatrist presenting with this clinical picture, he might very well meet criteria for the prodromal phase. Of course, the most likely outcome is that after a while our patient meets another girl with whom things work out better, and his symptoms improve. He will decrease the rates of transition in a prodromal study and would be similar to one of the people studied in Dr. Addington's article, while in fact this whole episode has little to do with schizophrenia.

There are additional reasons why this prodromal strategy might not have an overall effect on the incidence or outcome of schizophrenia. The criteria have a relatively low positive predictive value, even in the highly selected and enriched samples in the specialty clinics, which are not representative of the general population. Some patients do not have an appreciable prodromal phase, and the time between the first change in behavior and overt psychosis is measured in days or weeks. Others have an insidious onset of psychosis, do not seek treatment, and spend years at home with unidentified and untreated psychosis. Also, data (12, 13) indicate that the decline in cognitive and social functioning sometimes occurs years before the first psychotic episode, and even if we could identify these individuals premorbidly, there are no data indicating what would help them.

That being said, many schizophrenia patients do have a prodromal phase. The challenge is to identify the minority of patients meeting prodromal criteria who *are* on their way to their first episode of schizophrenia, as they often respond well to antipsychotics and might very well benefit from early intervention. This lofty goal awaits improvement of our understanding of the biology of schizophrenia and is not possible today.

What are the broader implications of the Addington et al. article? Closer scrutiny shows that although the majority of the persons meeting prodromal criteria are better, they are not well. Many of them suffer from nonpsychotic disorders (depression, anxiety, substance abuse, personality disorders), and they have significant cognitive, social, and vocational difficulties. It is clear that although these individuals do not have schizophrenia, they are not well and need help. This point is also apparent in the article by Carrión et al. (14), also in this month's issue, showing that teenagers meeting these prodromal criteria have poor cognitive and social abilities as well as decreased functioning. Although most will not transition to a psychotic disorder, they do need intervention.

But there are a lot of people with nonpsychotic disorders and/or decreased cognitive, social, and vocational functioning in the community. Most are not found in psychiatric clinics, rather in unemployment agencies, welfare offices, and jails. For society, these problems are far more costly than schizophrenia. One possible direction for future research is to study the phenomenology and biological underpinnings of cognitive and social dysfunction as well as nonpsychotic symptoms. If we can better understand what makes some people more or less socially able and/or intelligent, this might have a pro-

found effect on society and, in addition, will further our understanding of schizophrenia and other severe mental disorders.

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