Delayed Detection of Psychosis: Causes, Consequences, and Effect on Public Health

Although the pathophysiology and cause of schizophrenia remain unknown, the natural history of this vexing illness has been well described (1). The onset of schizophrenia typically occurs in late adolescence or early adulthood. Manifestations of the disorder in the form of positive, negative, cognitive, and mood symptoms develop gradually over a period of weeks, months, or even years. In the majority of cases, the symptoms and behaviors on which a clinical diagnosis is based are preceded by less specific and severe "prodromal symptoms." Prodromal symptoms and behaviors may include attenuated positive symptoms (e.g., illusions, ideas of reference, and magical thinking), mood symptoms (e.g., anxiety, dysphoria, mood lability, and irritability), cognitive symptoms (e.g., distractibility and difficulty concentrating), social withdrawal, and obsessive behaviors—to name a few (2). Because many of these prodromal phenomena extensively overlap with the mental experiences and behaviors of persons in the age group at risk for schizophrenia who do not subsequently develop schizophrenia, they cannot be considered diagnostic. Thus, it is only after the formal symptoms of the disorder reach a threshold of severity and are sustained that a person is said to be experiencing a first psychotic episode or break.

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Recent research has demonstrated that the first episode of schizophrenia is a critical therapeutic opportunity. If patients are treated promptly and effectively, good outcomes can be achieved. However, these same studies have revealed that throughout the world, individuals suffering a first episode of psychosis experience an alarming delay between the onset of psychotic symptoms and the initiation of treatment. More than 10 studies conducted on several continents have described typical durations of untreated psychosis that average 1–2 years (3).

This disturbing finding raises several questions. What are the consequences of a diagnostic delay regarding psychosis? Can the course of schizophrenia be modified by earlier detection and treatment? A controversial hypothesis suggests that untreated psychosis may result in neurotoxicity, which induces irreversible brain damage that is clinically detectable as deterioration and treatment resistance (4, 5). If this hypothesis is correct, a long duration of untreated psychosis can have serious consequences, including enduring and perhaps lifelong deficits and disability.

Associations between the duration of untreated psychosis and time to treatment response (6) and relapse (7) have been interpreted as consistent with a neurotoxic effect of psychosis. In this issue of the *Journal,* two reports bring new evidence to bear on the "toxic psychosis" hypothesis by direct measurement of biological indices. Hoff et al. evaluated the relationship among the duration of untreated psychosis, brain magnetic resonance imaging (MRI) volumetric measurements, and neuropsychological test scores in 50 consecutively admitted patients in the Suffolk County (New York) Longitudinal Study. The patients had an average duration of untreated psychosis of about 1 year and an average duration of behavioral change of 3 years (both retrospectively determined). Among the patients recovering from a first episode of psychosis, no relationships among duration of prior illness, severity of cognitive deficits, or structural brain anomalies were observed.

In a second carefully conducted MRI study, Fannon et al. examined 37 never or minimally treated patients with a first episode of psychosis (schizophreniform disorder, schizophrenia, or schizoaffective disorder) and 25 matched normal comparison subjects. Patients had a relatively short (31-week) average duration of psychosis (retrospectively determined). Confirming the results of previous reports, the authors found that the patients with psychosis revealed significantly smaller whole brain volumes and smaller cortical and temporal gray matter volumes and significantly larger lateral and third ventricle volumes than comparison subjects. However, no relationship between the duration of prior psychosis and any regional brain volumes was detected.

Other *Journal* reports published this year also found no association between the duration of prior or untreated psychosis and clinical outcome at 6 (8) and 24 months (9) after the onset of psychosis. When we group the newer data with these findings, the cognitive and morphologic data of Hoff et al. and Fannon et al. offer important new information that militates against the hypothesis that measurable neurotoxicity and lifelong disability are frequent or inevitable consequences of untreated psychosis. Although they offer some reassurance, the results of these studies should be interpreted in the context of the research methods used and their inherent limitations. A decisive test of the neurotoxicity hypothesis will require a prospective longitudinal study that integrates repeated measures with state-of-the-art neuroimaging, neuropsychological evaluation, and clinical outcome assessment in patients in the early stages of schizophrenia and, ideally, before the onset of psychosis. Such important studies will take time to complete.

In the meantime, however, and apart from the frightening prospect of permanent brain damage, there are other compelling reasons for making the early detection and treatment of psychosis a public health priority—first and foremost the fact that untreated psychosis damages lives.

Undiagnosed and untreated psychosis imposes a significant burden of terror, suffering, and bewilderment on patients and their families. Impairments in functioning that accompany untreated psychosis wreak havoc on the normative processes of young adult development. The maturational tasks of establishing and maintaining a peer group, achieving independence from family, cultivating romantic interests, acquiring independent living skills, and preparing for productive work may all be disrupted at a most critical stage of development. These disruptions too often alter the trajectory of a young person's life in a way that is not easily repaired. In addition, an untreated person with psychosis is at risk for episodes of behavioral dyscontrol, including violence, with the potential for long-lasting consequences for himself or herself and others.

A serious and surprising question is why is the duration of untreated psychosis so long throughout the world? The duration of untreated psychosis can be measured—albeit imperfectly, as it is usually performed retrospectively—but its causes are remarkably understudied and poorly understood. How much of untreated psychosis is accounted for by patient delay (time between onset of symptoms and actually initiating contact with a health professional) and how much by diagnostic delay (time between first contact with the health care system and the time when definitive diagnosis and treatment is achieved)? How often are the symptoms of psychosis recognized by the patient as an indication of illness? Or is a family member, friend, or teacher usually the first to notice that something is wrong? To whom do these individuals characteristically turn for help? To guidance counselors, clergy, or primary health care professionals? How ready is their access to mental health care? What knowledge, skills, attitudes, beliefs, and barriers operate as determinants for help-seeking individuals experiencing symptoms themselves or for persons who notice symptoms in family members, friends, or acquaintances? How can these determinants be modified?

An effective public health response as well as a reasoned scientific approach to the unacceptably long duration of untreated psychosis worldwide must be informed by a

clear understanding of the at-risk states that precede psychosis. This includes the phenomenology, neurobiology, and course of the early stages of psychotic illness and the individual, interpersonal, and social processes that contribute to a delay in treatment. Indeed, the protracted average delays until diagnosis and treatment seem to be present throughout the world, with the only consistent exception thus far reported being the military (10).When these phenomena and processes are identified and understood, potent and modifiable risk factors for a delay in treatment can be isolated and the optimal time and method of therapeutic intervention can be determined.

The prospect of early intervention favorably altering the course and outcome of schizophrenia has exerted a powerful influence on psychiatric research and treatment strategies and captured the attention of the clinical and lay communities (see articles in the *Wall Street Journal* and *New York Times*; e.g., references 11, 12, and 13). If we can enable recovery and improve outcome with earlier treatment, is it logical—in fact, imperative—to intervene before the onset of illness? Thus, the prodromal stage of the illness has become a prime target for research and the development of therapeutic strategies. Although, on the whole this represents a substantial advance in our attitude and approach to the clinical care of patients with schizophrenia, this movement has stimulated many questions and controversies. Among these is the feasibility and safety of intervention, particularly with pharmacologic agents, in the putative prepsychotic and prediagnostic stages of psychotic disorders. The effectiveness of such potentially powerful preventive strategies is dependent on the soundness of the methods, the certainty with which we can identify persons truly at risk for imminent illness, and our understanding of the potential risks and benefits of careful watching versus preemptive treatment. The decision to participate in preventive trials ultimately rests with the informed and competent prospective participant, who must weigh the risks and benefits. Although research has laid much of the scientific foundation for the implementation of such strategies, it is uncertain whether the evidence is sufficient to assure all the stakeholders in this illness of the readiness of this new model of care. Strategies such as the integration of early detection teams into youth services in Australia (14) and sustained anti-stigma-oriented social marketing in Norway (3) are important pilot tests of innovative models to meet this challenge.

In the meantime, developing approaches to early detection to reduce the duration of untreated psychosis in those who are already ill is an immediate public health challenge and opportunity. Delay in diagnosis and treatment is a concern across many medical conditions, and progress is possible: a recent report (15) described a median prehospital delay of 2 hours among patients hospitalized for the evaluation of heart attack symptoms; after self-discovery of breast cancer symptoms, about two-thirds of woman seek evaluation within 3 months (16). A delay in the treatment of psychosis is unacceptably long; it must be understood and remedied. We have the means to do so.

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