Understanding and Treating "First-Episode" Schizophrenia

Peter J. Weiden, MD[a],*, Peter F. Buckley, MD[b],
Michael Grody, MD[c]

[a]Department of Psychiatry, University of Illinois Medical Center, Chicago, IL
[b]Department of Psychiatry, Medical College of Georgia, Augusta, GA
[c]The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, Glen Oaks, NY

"First-episode schizophrenia" is a clinical and research term that often is used to emphasize the special issues that arise when working with this patient population. Although the incidence rate of first-episode schizophrenia makes this population a relatively small percentage of a usual clinical caseload, it is a critically important time for the future of the course of the illness. The hope is that proper management during this critical period can influence favorably the long-term trajectory of illness and outcome for the individual patient. A growing body of evidence suggests that certain approaches and interventions are more helpful than others. The notion that schizophrenia has an inexorable downhill course or is a deteriorating illness is being challenged by more sophisticated understanding of what happens before the initial episode and new understanding of the complex interactions between predisposing genetic or biologic vulnerabilities and exposure to specific environmental risk factors during adolescence and early adulthood. One premise of this review is that proper understanding and treatment interventions during the early phases of the illness can make an enormous difference in the eventual long-term outcome. But, the concepts and definitions regarding "first-episode" are often murky, and treatment services can easily miss some of the treatment opportunities discussed below.

WHAT IS MEANT BY FIRST-EPISODE SCHIZOPHRENIA?

"First-episode" is a clinical term referring to a patient who has only recently formally presented, been evaluated, and been treated for schizophrenia within the treatment services of mental health system. At some point during this initial treatment, the person has been evaluated and received a diagnosis of probable or definite schizophrenia. A related term, "first-episode psychosis" is sometimes used to identify a person recently identified as acutely psychotic but for whom a formal diagnosis has not yet been established. In this instance, the presumption

*Corresponding author. E-mail address: pweiden@psych.uic.edu (P.J. Weiden).

is that the individual probably will receive a diagnosis in which psychosis is a common presenting sign–affective disorder, schizophrenia, or substance abuse. This distinction is more than merely semantic, because the term "first-episode schizophrenia" pertains only to the subgroup of individuals who have psychotic symptoms at initial diagnosis and who eventually are diagnosed as having schizophrenia. Given that the clinical presentation of a first episode of acute psychosis eventually will include other diagnoses, the reader needs to keep in mind the difference and the retrospective nature of matching the course of illness before diagnosis with the eventual course and outcome once the diagnosis is made. To clarify these issues, some of the terms and concepts pertaining to first-episode schizophrenia are shown in Table 1.

This article focuses on the group of individuals who, after presenting with psychotic symptoms, go on to receive a probable or definite diagnosis of schizophrenia. Given that the diagnosis has been made, the article then retrospectively considers three broad phases of the illness trajectory for such a patient:

1. The period in adolescence or adulthood between the first signal of a possible problem and the time the person is first seen for acute treatment of what later is diagnosed as schizophrenia
2. The initial treatment episode when the person is first evaluated, almost always in the setting of a clinical crisis when there are prominent psychosis symptoms
3. The period after the diagnosis of "first-episode schizophrenia" is made, when the patient is embarking on an initial period of treatment after stabilization

These three phases may not have clear boundaries and may overlap. Nonetheless, they represent distinct theoretical and practical divisions in understanding and treating the first-episode schizophrenia patient.

These phases also are translatable into certain transitions that are part of the illness trajectory (Fig. 1):

The transition from no identifiable symptom to the retrospectively identified onset of some sign, symptom, or behavioral abnormality that later is viewed as the initial phases of schizophrenia (the start of the prodromal period)

The transition from nonpsychotic prodromal symptoms to retrospectively identified psychotic symptoms that fulfill the necessary diagnostic criteria for the diagnosis of schizophrenia

The transition from living in the community with disturbances that are not formally evaluated or treated within a mental health care system to having had an initial treatment episode and formal mental health evaluation

The transition from being treated for an acute psychotic episode to being stabilized and receiving a psychiatric diagnosis consistent with schizophrenia that includes discussion of vulnerability of recurrence and a recommendation of ongoing antipsychotic treatment

Although not every first-episode patient goes through these exact transitions, the person, at the very least, makes a transition from not having been formally treated in a mental health care system to being identified as a patient who has

Table 1
Terms commonly used in the literature discussing first-episode schizophrenia

Term	Definition	Comments and Issues
First-episode schizophrenia	No consensus definition, but most studies anchor the definition to treatment exposure, either by time since diagnosis was made or duration of antipsychotic treatment. Note that the anchoring of the time point is based on the time of clinical presentation that triggered a formal diagnostic evaluation.	Perhaps more accurate to consider as "first-presentation" because the definition is anchored to the relatively brief time since initial treatment (medication) exposure rather than other specific disease markers over and above standard diagnostic criteria for schizophrenia and related psychotic disorders
Precursor signs and symptoms	Signs and symptoms from a diagnostic cluster that are observed to precede the disorder but are not specific and do not predict future diagnosis with certainty	Most of the nonpsychotic signs and symptoms occurring during prodromal period are nonspecific and are common signs of other disorders such as depression or substance abuse
Prodrome (or "prodromal period")	Period before meeting the full-blown criteria of disorder (schizophrenia), when some signs and symptoms are nevertheless present	Can be defined only retrospectively, after a diagnosis of schizophrenia is made and confirmed. In other words, initial prodromal symptoms are not specific to an eventual schizophrenia diagnosis.
Duration of untreated psychosis (also known as "DUP")	Time from first discernable psychotic symptom to the first point of treatment for a possible diagnosis of schizophrenia	Psychotic symptoms usually occur only after other nonpsychotic symptoms have been present for some time. Also, there may be challenges in accurately dating onset of first psychotic symptom.

a psychotic disorder of probable or definite schizophrenia. This definition is in keeping with much of the literature addressing the epidemiologic risk factors, initial presentation, and initial course of treatment after the diagnosis of schizophrenia is established. This article therefore does not address evaluation or treatment issues pertaining to patients who are considered at high risk for schizophrenia but
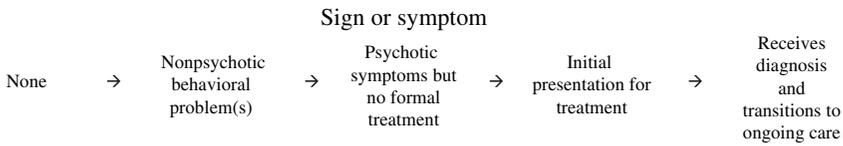
Sign or symptom

| None | → | Nonpsychotic behavioral problem(s) | → | Psychotic symptoms but no formal treatment | → | Initial presentation for treatment | → | Receives diagnosis and transitions to ongoing care |

Fig. 1. Transitions involved in the trajectory of first-episode schizophrenia.

who do not meet diagnostic criteria for schizophrenia or to persons presenting with first-episode psychotic symptoms who receive another psychiatric diagnosis.

ENVIRONMENTAL RISK FACTORS DURING ADOLESCENCE AND YOUNG ADULTHOOD

The epidemiology of schizophrenia is reviewed elsewhere in this issue. In this article the focus is narrowed to recent developments in the understanding of emerging environmental risk factors that may be considered causal risk factors for the diagnosis of first-episode schizophrenia. There has been a major shift from the previously accepted concept that the risk of schizophrenia arises primarily from a neurodevelopmental disorder that is extant by the time of infancy, remains latent during childhood, and environmental influences during adolescence or young adulthood have little effect on the ultimate risk of schizophrenia. More recent epidemiologic studies have shown that social environment may be an important risk factor in determining transition from ''at risk'' to actual ''first episode'' diagnosis. In other words, given that more people are vulnerable to develop schizophrenia than eventually develop schizophrenia, what are some of the identifiable concurrent risk factors that may add to the overall risk of transitioning from never having schizophrenia to the onset of a first episode? Causal risk factors are neither necessary nor sufficient for the development schizophrenia, but their presence would mean that some people who otherwise would not develop schizophrenia are exposed to this causal risk factor and go on to develop the illness. Research suggests that in the general population low-grade psychotic experiences are a common but transitory developmental phenomenon [1]. In other words, many more people in the general population are vulnerable to schizophrenia than actually develop the full-blown disorder that is called ''first-episode schizophrenia'' by the clinicians who treat the unfortunate individuals who make this transition. Using two independent general population samples, investigators examined the hypothesis that common, nonclinical developmental expressions of psychosis may become abnormally persistent when synergistically combined with developmental exposures, such as cannabis use, trauma, or urbanicity [2], that may impact on behavioral and neurotransmitter sensitization, ultimately leading to a first episode of schizophrenia.

Adolescents and young adults exposed to the following environmental risk factors may be at increased risk for developing schizophrenia: (1) living in a densely populated urban environment (''urbanicity''), (2) specific types of

social adversity related to discrimination, disconnection, or cultural isolation, and (3) exposure to cannabis by marijuana use in early adolescence or young adulthood before the onset of full schizophrenia symptoms. Remember that the term "causal risk factor" does not mean that these factors are necessary or sufficient; rather, they seem most relevant when a person is already at high risk for schizophrenia.

Urbanicity as a Risk Factor for Schizophrenia

There is a renewed interest in the social environment as a causal risk factor for the development of schizophrenia and other psychotic disorders. Estimates of the increased risk of urban environment as a causal risk factor for schizophrenia are as high as 30% of attributable risk within these high-risk populations. A Danish population registry study that took into account years spent living in urban environments found evidence for "a dose-response relationship between urbanicity during upbringing [at any time during childhood or adolescence] and schizophrenia risk" [3]. In a prospective study of risk factors in a cohort of 918 adolescents for future onset of psychotic disorder, baseline signs of psychotic types of experiences interacted with urban environment so that about 4 years later those exposed to both factors were more than twice as likely to develop a psychotic disorder than those who exposed to only one of these risk factors. These findings support the suggestion that the outcome of the developmental expression of psychosis is worse in urban environments. The environment may impact the risk for psychotic disorder by causing an abnormal persistence of developmentally common expressions of psychotic experiences [4]. "The excess incidence of [first-episode psychosis] in Southeast London compared with [less urban sites] of Nottingham or Bristol is consistent with a dose-response relationship with urbanicity demonstrated in several recent studies" [5].

Social Adversity as a Risk Factor for Schizophrenia

Although the association between minority ethnicity and risk of schizophrenia has been known for some time, the precise nature of this relationship has been a matter of debate. Recent prospective studies of new-incident cases of schizophrenia in three sites across the United Kingdom have shown a gradient effect of social adversity on the future risk of diagnosis of schizophrenia. The Etiology and Ethnicity in Schizophrenia and Other Psychoses study was "designed to better understand and disentangle the relationships between urbanicity, social class, ethnicity, immigration and other environmental factors that might contribute to the risk of schizophrenia and other psychotic disorders" [5]. This study evaluating the differential rates and risk factors for the higher incidence of cases of schizophrenia and other psychotic disorders among ethnic minorities and recent immigrants in the United Kingdom found that "black and minority ethnic" individuals had more than three times the risk of having an incident diagnosis of schizophrenia compared with "white British" (IRR, 3.6; 95% confidence interval

[CI], 2.7–4.9). This risk was not explained by urbanicity, which was itself an independent risk factor for new-onset psychosis, as discussed in the previous section. For example, although immigration is a risk factor for first-episode schizophrenia in United Kingdom, the percentage of others within the same immigrant group living in the local neighborhood also was found to be an independent risk factor. One ecologic study showed that minority adolescents growing up in neighborhoods that were less populated by the same minority had a higher risk of schizophrenia than minority adolescents living in neighborhoods that had greater minority representation [6]. Another cohort study also showed an interaction between baseline reporting of lifetime history of traumatic events and the subsequent emergence of psychotic symptoms on follow-up in a sample of community-dwelling adolescents [7].

Marijuana Exposure as a Causal Risk Factor

Substance and alcohol use is traditionally considered a precipitant but not a cause of schizophrenia. More recent studies challenge this attitude, especially for marijuana (cannabis). Findings in a series of studies suggest that exposure to marijuana may be a causal factor in some (but not all) episodes of new-onset schizophrenia among heavy marijuana users. The first major epidemiologic report suggesting some causal association came from a 15-year follow-up of 45,570 Swedish army recruits showing that those who had histories of moderate marijuana use (ie, used marijuana on more than 15 occasions) were six times more likely to develop schizophrenia than less-frequent users or nonusers [8,9]. Marijuana was the only substance associated with an increased risk for schizophrenia; exposure to other drugs of abuse or alcohol was not [10]. In a separate survey of non–mentally ill adolescents and young adults followed for 4 years after a baseline evaluation [11] (age range, 14–24 years; n = 2437), a report of cannabis use at the baseline evaluation increased the likelihood of reporting psychotic symptoms 4 years later (adjusted odds ratio, 1.67; 95% CI, 1.13–2.46). Consistent with a model of interaction with prior vulnerability, the effect of cannabis use was much stronger when the baseline evaluation also showed a predisposition for psychosis (23.8% adjusted difference in risk; 95% CI, 7.9–39.7%). Marijuana exposure is most detrimental to individuals who already are prone to psychosis before first marijuana use [12]. Marijuana seems to be a specific risk factor, and increased risk for schizophrenia does not generalize to other drugs or alcohol. Studies of drug use in non–mentally ill populations find a relationship between marijuana use, but not alcohol use, and tendencies toward psychosis [13]. A 3-year follow-up (1997–1999) is reported of a general population of 4045 psychosis-free persons and of 59 subjects in the Netherlands who had a baseline diagnosis of psychotic disorder. Substance use was assessed at baseline, at 1-year follow-up, and at 3-year follow-up. Baseline cannabis use predicted the presence at follow-up of any level of psychotic symptoms (adjusted odds ratio, 2.76; 95% CI, 1.18–6.47) as well as a severe level of psychotic symptoms (odds ratio, 24.17; 95% CI, 5.44–107.46). Results confirm previous suggestions that cannabis use

increases the risk of both the incidence of psychosis in psychosis-free persons and a poor prognosis for those with an established vulnerability to psychotic disorder [14].

This information linking marijuana use and increased risk of schizophrenia may be of tremendous importance in educating siblings and other family members of individuals who have schizophrenia. Although still controversial, the quality and sophistication of the epidemiologic research challenge the primacy of genetic or in utero/postnatal predisposition and suggest that there may be some causal risk factors for development of incident cases of schizophrenia that can be modified from a public health perspective. These new findings have important implications for the management of first-episode patients as well as the families who are exposed to the same environmental factors [15].

TIME PERIOD BETWEEN INITIAL ONSET AND INITIAL CLINICAL PRESENTATION

When considered from the perspective of disease onset, the term "first-episode schizophrenia" is misleading. When clinicians first encounter such a patient, usually in crisis only recently, the illness can seem to have "come out of nowhere." Despite the overwhelming nature of the acute symptoms at time of clinical presentation, the underlying neurobiologic processes already have been present for considerable time. A person who soon will receive a diagnosis of first-episode schizophrenia is likely to have been very symptomatic for some time. When the patient's history is better understood, it becomes clear that things have not been not completely "right" for a long time, even if there were no obvious or flagrant psychotic symptoms. The threshold that finally is crossed, resulting in a treatment assessment or intervention, usually involves a symptom or behavior that has been present for a while but finally has become so bad that it elicits a response. In other words, once the diagnosis of schizophrenia is established, it is usual to find that the person has met diagnostic criteria for schizophrenia for a considerable period of time already. In fact, the only thing that is "first-episode" is that the clinicians now are aware that the case exists. It is more precise, therefore, to think of "first-episode" schizophrenia as "first-clinical-presentation" schizophrenia.

Course of "Prodromal" Symptoms: What Comes First?

Psychotic symptoms are most likely to be the most prominent symptoms at time of diagnosis. Psychotic symptoms, however, are usually a late sign of schizophrenia, and only 25% of patients who have schizophrenia report having experienced psychotic symptoms sometime in childhood. In most patients the onset of psychotic symptoms occurs in early adulthood, typically in the mid 20s for men and late 20s for women. Rather than psychotic symptoms, the earliest signs usually are an array of developmental disturbances that include neurologic soft signs, minor physical anomalies, and mild cognitive, sensory, and motor impairments (eg, inattention at school, poor scholastic performance, motor "clumsiness") [16,17]. Although this pattern has been well described in large,

population-based studies, the signs are too subtle to be of any diagnostic value in individual patients. Current diagnostic criteria for schizophrenia do not include these early developmental signs, and generally they are not included in the retrospective category considered "prodromal" onset, as described in the next section.

Nature of "Prodromal" Symptoms Before the Onset of Psychosis

Social withdrawal, social anxiety, depression, and other interpersonal and functional problems often begin well before there is any signal of a more specific or more definitive psychotic disturbance. These behavioral changes usually cross a threshold into a noticeable and clinically significant problem well before the next threshold is crossed (the demonstration of psychotic symptoms or other criteria that permit a formal diagnosis of schizophrenia). From a developmental perspective, this experience supports the hypothesis that the initial neurochemical problems antecedent to schizophrenia probably are not caused by excess dopamine. In fact, this stage of prodrome is more consistent with hypotheses of dopamine hypoactivity in the frontal cortex.

Transition From Nonpsychotic "Prodromal" to Psychotic Symptoms

Because a diagnosis of schizophrenia requires persistent psychotic symptoms, it is inevitable that a person who later is diagnosed with first-episode schizophrenia will pass a threshold for psychosis and meet criteria for persistent psychotic symptoms. Although psychotic symptoms are part of the definition, the fact that they almost are always a later sign of the disorder is very important, both theoretically and clinically. The late arrival of psychotic symptoms is consistent with the hypothesis that psychosis is not a primary component of the disorder but is a secondary response to a perhaps more fundamental disturbance.

Unfortunately the onset of psychosis usually is not sufficient in its own right to trigger a prompt medical or psychiatric evaluation. Instead, the psychotic symptoms and all of the fallout from being psychotic usually fester for some time before receiving clinical attention or treatment. By the time the patient is initially seen for evaluation and help, there already is a good chance that significant psychosocial damage has resulted from the festering psychotic state. It is common for overt psychotic symptoms to have been present for a considerable period of time before the first treatment contact. Although there probably is a further delay between the onset of psychotic symptoms and their recognition as such by others, the delay often continues despite awareness of others that the person is seriously disturbed. Reasons for the further delay in getting treatment include stigma, inability to know how to respond, and, most common, lack of awareness on the part of the psychotic person himself or herself. In the first-episode literature, the time period between first established report of a psychotic symptom and initial treatment intervention for the acute psychotic episode is known as "duration of untreated psychosis," or DUP. A

meta-analysis of DUP found that the average DUP was 9 months but may be as long as 2 years. The fact that a long DUP exists across a wide range of cultures and treatment services speaks to the strength of the resistance and barriers to initial care for persons who have psychotic symptoms. In the meantime, DUP is a measurable baseline component of the first-episode experience and has been the subject of considerable academic interest, especially regarding its role as a potentially modifiable prognostic indicator of future long-term outcome beyond the initial treatment episode.

Most studies of DUP and outcome have shown a correlation between the length of the DUP and treatment outcome, in that a longer DUP predicts poorer outcomes. What is more controversial is why this seems to be the case. One hypothesis is that the stigma that was a barrier to seeking help remains a barrier afterwards. Another hypothesis is that the DUP is of itself neurotoxic and somehow alters the central nervous system in a way that makes the patient less responsive to medication. If that supposition is true, patients who have a longer period of untreated psychosis may be unable to achieve the level of recovery that would have been possible if the psychosis had been treated sooner. The data supporting this hypothesis are, at present, mixed. The qualitative signs and symptoms of the actual ''first-episode'' of psychosis do not seem to be affected strongly by the DUP, but the DUP does seem to be one of the predictors of initial response to antipsychotic medication (a shorter DUP predicting a better likelihood of antipsychotic response). In a meta-analysis of 43 publications, Perkins and colleagues [18,19] showed a shorter DUP to be associated with a better response to antipsychotic medication ''as measured by improvement or endpoint severity of global psychopathology (5 studies), positive symptom severity (13 studies), and negative symptom severity (14 studies).'' In addition, at the time of first treatment, duration of previously untreated psychosis was found to be associated with severity of negative symptoms [19]. Because the presence of psychotic symptoms means the crossing of a threshold that is an unequivocal sign of a serious condition for which antipsychotic medication is indicated, shortening the DUP becomes a measurable outcome for efforts to shorten the time between a diagnosis of schizophrenia being made and treatment for psychotic symptoms. The potential advantage of recognizing the significance of the DUP is that it may reveal potential interventional treatment strategies that improve outcome. Shortening the DUP is theoretically important in understanding the potentially toxic effects of untreated psychotic symptoms on eventual treatment response. From a public health and interventional vantage point, it should be explored whether the DUP is influenced by factors connected with the fundamental pathology of schizophrenia, such as poor premorbid function, by factors unrelated to disease pathology, such as access to care and socioeconomic status, or perhaps by a combination of the two [18]. Nonetheless, other neurobiologic findings of first-episode schizophrenia show that even by the time the first psychotic symptoms manifest, other biologic processes have taken place that signify that onset of psychosis is not a primary threshold of illness progression.

NEUROBIOLOGY AT THE TIME OF PRESENTATION OF FIRST-EPISODE SCHIZOPHRENIA

The observation in the mid 1970s that patients who have chronic schizophrenia have demonstrable brain abnormalities on CT was a "wake-up call" for psychiatrists. The evolution of brain imaging studies has confirmed and extended these early findings. In particular, this work has shown conclusively that these changes are present (to a similar extent and magnitude) in patients who have first-episode schizophrenia [20–28]. Two recent sequential MRI studies [29,30] provided evidence of subtle abnormalities in the brains of patients genetically at high risk of developing schizophrenia and found preliminary evidence of reduction in temporal lobe structures in ultra–high-risk patients who converted from high-risk status to actual schizophrenia. Although these observations are provocative, they are not yet clinically useful. Therefore, an MRI scan in a first-episode patient probably would be read as normal by a neuroradiologist, even though the overall pattern of MRIs shows subtle differences when contrasted with appropriately matched comparison groups.

Although clinically they are too subtle to be useful, there nevertheless is ample evidence of an array of structural and neurochemical brain changes detectable even at the first episode of schizophrenia [31]. Current theories concerning the origins of schizophrenia account for these changes as evidence of a neurodevelopmental basis for schizophrenia arising from early noxious events (in utero and perhaps also in early childhood or adolescence) that either are genetic or environmental or involve some combination of the two types of events. Although this neurodevelopmental model has held ascendancy in conceptualizing the onset and cause(s) of schizophrenia, there also is evidence that progressive brain changes (neurodegenerative processes) occur in some patients who have schizophrenia within the first 2 years of the course of illness [23,32]. These results make it harder for clinicians to translate the neuroanatomic findings from this body of research into a cohesive message about future outlook and prognosis. There is ample evidence paralleling neurobiologic findings that the clinical symptoms of schizophrenia are as pronounced in a first episode as in more chronic stages of the illness. Negative symptoms are common, with one study reporting prominent primary negative symptoms (not attributed to either depression or extrapyramidal side effects [EPS]) in more than one quarter of first-episode patients [33,34]. Cognitive deficits, including memory, attention, and executive performance, are common across a broad array of functions. In the Calgary first-episode study, deficits across a range of cognitive measures were found in 111 first-episode patients that were comparable to deficits found in 76 patients who had chronic illness [35]. Other studies have reported a similar extent of pervasive cognitive impairment in first-episode patients [36,37]. Short-term (1- to 2-year follow-up) studies of neurocognitive functioning suggest some improvement in selective measures such as attention and visual learning but persistent disability in other core functions such as verbal memory [38,39]. This observation is important because cognitive impairment is considered a greater barrier than psychotic symptoms to achieving

vocational rehabilitation [40]. Perhaps one way of describing these findings is to state that by the time of first clinical presentation of schizophrenia, the neurobiologic evidence indicates that significant changes to the brain have happened well before the immediate clinical crisis. This hard evidence goes along with the clinical evidence that the person probably has not been completely well for quite some time. Moving forward, the evidence suggests that further progression of illness, if it occurs, is not as severe as what has happened already. In other words, these data seem to be consistent with the possibility of recovery, analogous to rehabilitation after a nonprogressive central nervous system injury such as stroke.

CLINICAL PRESENTATION OF FIRST-EPISODE SCHIZOPHRENIA

Because social isolation and psychotic symptoms usually are present for some time before the initial contact with a mental health service, it is interesting to consider the sort of "tipping point" that marks the transition to receiving treatment. Most of the time, this transition is related to the degree of disturbance, disruption, or danger posed by the psychotic symptoms. Patients may present with either suicidal or violent behavior, perhaps because such triggering events finally lead to presentation to a treatment service [41]. The first presentation of psychosis is frightening and distressing. Patients are very perplexed, and family members are distraught. The patient's bizarre behavior and resistance to treatment make it all too easy to ignore how terrifying psychotic symptoms can be for the patient [42]. Therefore, by the time the clinician first sees the patient, the illness is further aggravated by a crisis that is the result of such behavior. The net result is that the initial contact with mental health services often happen in an atmosphere of extreme stress and social chaos.

To make matters worse, there is a lag time between the atmosphere of crisis and uncertainty and the eventual diagnosis and establishment of a clear treatment plan. It takes time to reconstruct what actually happened from history provided by the patient and family toward the end of the crisis, and after the treatment team has had a chance to complete a medical and psychiatric evaluation. As one might expect, pathways to care are many and diverse. Addington and colleagues [43] traced the presentation to services of 86 patients who had first-episode psychosis and found that most patients came into care through emergency services. The pernicious interaction between psychiatric symptoms and treatment delay is also shown by studies relating avoidance of health care to social isolation and impairments in social functioning [44]. Meanwhile, the mental health care system that is the initial point of entry generally is accustomed to caring for persistently ill, multiepisode patients and therefore is less likely to be attuned to the needs and emotional vulnerability of patients and families at this first stage of care. These systems barriers are even more challenging for first-episode patients who have multiple barriers to becoming engaged in the treatment process [45].

One of the most vexing and persistent problems in treating first-episode patients is "denial of illness" or "lack of insight," which for purposes of this article

are considered the same. Although "lack of insight" sometimes is a state-related part of an acute psychotic episode [46,47], lack of insight often persists as psychotic symptoms resolve [48]. More than 50% of stabilized patients who have first-episode schizophrenia deny that they are ill after the acute episode is over [49,50]. A growing convergence in the literature shows that denial of illness or "lack of insight" is one of the strongest predictors of future nonadherence to antipsychotic medication [51–54].

To address the clinical need of first-episode patients better, and also to provide a foundation for clinical research in this area, there has been an international trend to develop specialty programs focused on the needs of the first-episode patient. A specialty service with mental health staff focused on the initial onset may help reduce some of the overwhelming nature of the experience of entering into mental health care treatment for the first time, especially because such programs provide a more distinct entry point to appropriate services [55]. Of course, these services are useful only when available, and they are not yet universally available in a way that is analogous to having surgical trauma centers strategically placed for ready access in urban areas. What these centers have demonstrated is that it is possible to study the pathways to care for first-episode patients within communities. Another assumption of specialty services is that because first-episode schizophrenia is the first opportunity for mental health services to begin treatment for those who develop schizophrenia, it is important that every effort be made to "get it right" from the very beginning of the treatment process.

IMMEDIATE TREATMENT OF A FIRST-EPISODE PSYCHOSIS PATIENT

Before a Formal Diagnosis of Schizophrenia is Established

It is important to remember that the diagnostic evaluation may take some time, and that only when it is apparent that the person has a probable or definite diagnosis of schizophrenia is it possible to consider the initial presentation as one of schizophrenia. Although a diagnosis of first-episode schizophrenia sometimes can be be made with some confidence within days to weeks of initial clinical contact, it often may require considerable time and effort to work through the differential diagnosis and to make such a diagnosis with a reasonable degree of clinical certainty.

As discussed, for individuals eventually diagnosed as having schizophrenia there usually is little question about the presence or absence of psychotic symptoms. The DUP literature shows that for patients who ultimately receive a diagnosis of schizophrenia or schizophreniform disorder, the threshold for meeting criteria for psychotic symptoms probably was crossed long before the immediate evaluation. Therefore, often the diagnostic challenge is focused on the differential diagnosis of acute psychosis. Although a review of this topic is beyond the scope of this article, the evaluation often is handicapped by the absence of a reliable and accurate history of symptoms. The patient often is unwilling or unable to disclose the full extent of symptoms, the family is too

overwhelmed or shocked, and, almost by definition, medical records are unavailable. Furthermore, stigma and fear may impede the patient's or family's willingness to report fully the severity or magnitude of the problem. Therefore, clinicians must keep in mind that the true nature of the course of illness will tend to unfold over time, and that the history reported during the first days and weeks often underrepresents the severity and the duration of the problem. Establishing the longitudinal course before onset is feasible but requires training and consensus definitions [56,57]. Furthermore, the overlap between primary affective illness and schizophrenia is well known and becomes a differential that sometimes cannot be answered with 100% certainty at the initial evaluation. Once a diagnosis of schizophrenia (or schizophreniform disorder) is made by experienced mental health clinicians, however, it is likely that the diagnosis of schizophrenia will remain stable and valid over time. Many patients who have first-episode psychosis present with active substance abuse, which poses major diagnostic challenges, particularly in determining whether the drug abuse and schizophrenia are causally related [41].

Immediate Psychopharmacologic Intervention

Because psychotic symptoms are likely to be the primary focus of treatment, the primary pharmacologic question will be the choice of antipsychotic medication. Because this treatment is the "default" mode, a few considerations concerning medication issues should be kept in mind before prescribing an antipsychotic agent. Many first-episode patients have never received psychiatric medications. Once an antipsychotic medication is prescribed, that changes forever. Therefore, clinicians need to be mindful of the importance of obtaining and recording the physical and mental status before starting medication and to consider whether delaying initiation of medication is appropriate. Table 2 lists the newer antipsychotics, and suggested starting doses and intervals for dose increases. The reader should note that these doses and dose titration schedule would be considered to be on the low end of the therapuetic range for more persistently ill patients. This illustrates the importance of being able to rapidly identify "first episode" patients and systems to be able to implement pharmacologic treatment plans that address the treatment needs of this patient population.

Although the clinician may use an antipsychotic medication before a primary diagnosis is established, this class of medication will not help clarify the primary diagnosis. That is, antipsychotic agents treat acute psychotic symptoms regardless of whether the diagnosis ultimately turns out to be schizophrenia, bipolar disorder, or substance-induced psychosis. Perhaps a practical approach is to consider clinical situations when the use of antipsychotic agents should be delayed or is contraindicated. Before starting treatment with a medication, some of the issues that might need to be considered include (1) possible pregnancy and whether knowledge of pregnancy would affect the use of a medication; (2) whether there is any possibility of behavioral or neurologic toxicity from recent exposure to antipsychotic medication; (3) whether there is a need for

Table 2
Initial dose and titration schedule for a first episode patient with no complicating conditions affecting dosing*

	Usual starting dose (mg/day) Avg (range)	Interval between dose increases	Usual dose increment	Usual initial target dose range (mg/day)	
				Low Avg (range)	High Avg (range)
Aripiprazole	10 (5–15)	1 week	5 (or 10 mg)	10 (5–15)	25 (20–30)
Olanzapine	10 (5–15)	1 week	5 mg	10 (7.5–12.5)	22.5 (20–30)
Quetiapine	150 (50–250)	3 days (but wide range)	150 mg (but wide range)	300 (wide range)	800 (600–1000)
Risperidone	1.5 (1–2)	1 week (but wide range)	1.5 mg (but wide range)	2 (1–3)	6 (5–8)
Ziprasidone	60 (40–100)	4 days	40 or 60 mg	100 (60–140)	200 (160–240)
Haloperidol	3 (1–4)	1 week	2–4 mg	5 (2–8)	10 (10–15)

*Mean doses and standard deviations from survey results converted to ''real world'' doses.
From Weiden PJ, Preskorn SH, Fahnestock, P, et al. A roadmap: translating the psychopharmacology of antipsychotics to individualized treatment for severe mental illness. J Clin Psych 2007;68(Supp X):1–48. Copyright © 2007, Comprehensive NeuroScience Inc., White Plains, NY; with permission.

a careful neurologic examination unaffected by the possible neurologic side effects of antipsychotic medication.

MANAGING DIAGNOSTIC UNCERTAINTY

As discussed, there is a period of time after the assessment has been done and before a tentative diagnosis is made. Because of the stress on the family and the patient, the work-up should be timely, and basic aspects of the evaluation (physical examination, neurologic assessment, laboratory and interview screening for drug and alcohol use) should be undertaken as soon as possible. Clinicians should know that there is a tendency for both patients and family to underreport the duration of symptoms before the initial presenting episode; therefore, initial reports should be considered tentative, and the history of duration of untreated symptoms (psychotic and nonpsychotic) should be reassessed later. A retrospective life chart should be developed with a focus on assessing the degree of social isolation that may have been one of the earliest signs of a developing illness. Social withdrawal is a particularly useful diagnostic sign: if it occurred before the manifestation of recognizable psychotic symptoms, it may be possible to rule out affective symptoms (patient is not lonely or sad during protracted periods of social isolation) and substance abuse (the patient was too socially withdrawn to be able to purchase or use illicit drugs). Once psychotic symptoms occur, it may be more difficult to disentangle concurrent mood symptoms from those psychotic symptoms more consistent with schizophrenia [58,59]. Diagnostic stability is better for men than women, and a diagnosis of schizophrenia tends to be more stable than a diagnosis of schizophreniform disorder. Regardless of the theoretical aspects of diagnostic stability, patients and families should be prepared to contend with changes in their formal psychiatric diagnosis whenever they change psychiatrists or treatment services.

CHOICE OF ANTIPSYCHOTIC AGENT

Clinicians should aim for excellent results when treating a first-episode patient because first-episode status is associated with a higher likelihood of achieving an excellent medication response. In one of the classic studies of first-episode schizophrenia, Robinson and colleagues [60] found that 87% of first-episode patients achieved an excellent response to antipsychotic medication, with a median time to response of 9 weeks. This favorable response was achieved using older antipsychotics, so the theoretical feasibility of achieving excellent therapeutic responses is not just a characteristic of the newer, atypical antipsychotic medications. There are, however, several other crucial considerations in medication selection that, taken together, strongly favor the use of one of the newer atypical antipsychotic agents rather than an older medication when initiating treatment with an antipsychotic agent. The relative advantages of the newer agents include the reduced neurologic burden relative to older conventional agents, their superior effectiveness at relapse prevention, and their relatively favorable effects on mood and cognition.

In terms of efficacy, safety, and tolerability, the issues pertaining to the specific choice of an antipsychotic medication for first-episode patients are similar, but not exactly the same, to those pertaining to the choice of antipsychotic for more persistently ill patients who have schizophrenia. We will discuss some of the specific aspects of differences between antipsychotics that may be particularly relevant in the treatment of the "first-episode patient.

When choosing medications for patients with established medication histories, clinicians can guide the selection in part on the person's past history of efficacy and tolerability. Most of the time, information will be available about the patients treatment system and any constraints. By definition this is not available for first episode patients. The lack of prior treatment trials means that the patient's pharmacologic history cannot be used as one of the factors guiding the choice of medication. There often will be uncertainties as to the final diagnosis and therefore about the recommendation for ongoing antipsychotic therapy after the acute episode resolves. Moreover, practical concerns such as location or access to ongoing treatment and medication are unknown at the time of the initial medication choice. These uncertainties may represent practical constraints on possible medication selection. While this may sound obvious, these practical matters are sometimes forgotten when medication are started in crisis settings. Advanced planning about these service and access needs of first episode patients is a crucial aspect of the initial medication selection process.

Given the stress and frequent opposition to treatment that are such common elements of the first-episode experience, any distressing or unexpected reaction to medication may result in long-term rejection of further treatment and may fuel a sense of distrust and alienation from mental health care services. Therefore, in choosing the medication the prescriber needs to be mindful of the need to minimize the risk of sudden, unexpected adverse events that would result in long-term avoidance of medications. Similarly, the prescriber of antipsychotic agent must be mindful that first-episode patients are more sensitive and more vulnerable than patients who have more chronic disease to common and distressing side effects of antipsychotics. This vulnerability may present in several ways, with more severe side effects, faster onset of side effects, and greater distress and discomfort caused by the same side effect.

There is nothing beneficial about having any side effect. Formerly it was believed that EPS might be a marker for the efficacy of antipsychotics. It now is clear that EPS actually are a marker of poor response and should be avoided whenever possible, regardless of the agent chosen. It also has been the lead author's experience that there often is a routine procedure in emergency rooms or inpatient units regarding the as-needed administration of antipsychotics that can best be described as "one size fits all." The combination of lack of insight and fear about what is happening in an adversarial situation often coincides with a standard policy of an as-needed intramuscular administration of the haloperidol/lorazepam combination for "agitation." Even though the initial pharmacologic treatment plan may have taken into account the sensitivity of the first-episode patient to low doses and used a dose titration strategy meant to

minimize treatment-emergent side effects, this approach is obliterated by the automatic as-needed administration of haloperidol without regard to the needs of the first-episode patient. Once this medication is administered, it cannot be undone, and it may lead to persistent nonadherence or to irreversible neurologic effects [61]. Note that this case is different from the theoretical idea that it may be possible to use very low doses of conventional antipsychotics in a first episode of schizophrenia without necessarily inducing severe EPS [62].

The overall approach to medication choice has shifted overwhelmingly to the preferential use of the newer atypical antipsychotics instead of the older, first-generation antipsychotic medications. Although the short-term response rates of the newer and older antipsychotics are about equivalent, the newer medications have better long-term effectiveness for first-episode patients. One of the most compelling reasons to favor the newer agents is the lower likelihood of EPS, which translates to lower rates of sudden episodes of neurologic events that cause the patient to avoid long-term treatment and to lower coprescription of anticholinergic agents such as benztropine. Formerly, anticholinergic agents were overwhelmingly likely to be coprescribed with the antipsychotic agent, leading to distressing peripheral anticholinergic problems and exacerbating the cognitive dysfunction associated with the illness itself. Thus far, however, there is no consensus or clear evidence supporting use of one specific atypical antipsychotic over another, although the use of clozapine as a first-line agent does not seem to have clear-cut advantages [63]. Excellent reviews on medication treatment of first-episode schizophrenia have been published recently [62,64,65].

Although there is widespread agreement that the use of atypical antipsychotics for first-episode patients is preferred in theory, this use is not always followed in practice. In particular, a vexing problem is a "one size fits all" approach seen in many emergency psychiatric services. Often, clinicians working in these settings believe that the high-potency conventional antipsychotics such as haloperidol "work faster" than the newer medications or routinely prescribe intramuscular haloperidol to be used as needed in case of "agitation" or medication refusal. Unfortunately the net effect of this approach is that many first-episode patients are in fact exposed to older agents such as haloperidol under circumstances that are likely to pose significant neurologic risks as well as jeopardize the therapeutic engagement process that is fragile under the best of circumstances.

AFTER A DIAGNOSIS OF FIRST-EPISODE SCHIZOPHRENIA IS MADE

Once the clinician believes that the diagnosis is probable or definite schizophrenia, the issue of informing the patient and family becomes of critical importance. There is no debate that the patient and family need education and guidance about the nature of psychotic symptoms and the risk of possible recurrence. There is controversy in first-episode schizophrenia about the best

way to convey this information. In particular, there is concern that using the word "schizophrenia" too soon, even if the diagnosis of schizophrenia is very likely, might alienate and stigmatize the patient in a way that could do more harm than good. Many first-episode services have developed their own approaches to patient and family education. It is important to be mindful of the issues involved. Whether one uses the diagnostic term "schizophrenia," uses a more tentative approach ("it may be schizophrenia"), or focuses on the psychotic symptoms without extensive discussion of the diagnosis should be considered and discussed with involved colleagues before the meeting with the patient or family when the diagnosis is discussed.

Psychosocial Interventions for First-Episode Patients

Helping patients and families acquire insight into a potentially lifelong and debilitating illness while preserving hope and supporting morale during a first episode of schizophrenia is a challenge for clinicians. The issues that arise in providing psychotherapy during a first episode are somewhat different from those that are a focus of psychotherapy at more advanced stages of the illness. A recent review of psychosocial interventions targeting first-episode patients was most noticeable for the paucity of focused intervention studies in this vital area [66]. Most of the literature on psychosocial intervention for first-episode patients pertains to what are described as "multimodal interventions," that is, a programmatic effort made possible by a specialty service focusing on the unique needs of this target population during this critical time period. Studies have evaluated comprehensive interventions, which include community outreach and early diagnosis with broad and specialized focus on pharmacologic and psychosocial services designed for this phase of illness. On the one hand, specific treatment interventions ("single-element interventions") were focused primarily on family interventions and individual cognitive behavior therapy (CBT) interventions. Readers should keep in mind that these interventions often occur in the milieu of a highly motivated and trained specialty staff. Incorporating such interventions into nonspecialty clinical services actually may result in larger improvements in care given to "first episode" patients entering treatment service systems that did not have ways to identify these individuals.

A study of the possible long-term benefits of an intensive short-term CBT intervention given during the first-episode of treatment did not show any enduring benefits of CBT on persistent symptoms or subsequent relapse [43]. Known as the Study of Cognitive Reality Alignment Therapy in Early Schizophrenia, it compared two "active" psychotherapies–CBT or supportive counseling–with a standard-of-care comparison group [55,67,68]. The long-term outcome showed no differences in persistent symptoms, nonadherence, relapse or rehospitalization. Although disappointing to those hoping to show specificity of CBT, this study is very informative in guiding the design of other CBT-based interventions for first-episode patients.

Support for relatives also is crucial at this early stage. Relatives need clear, comprehensible information on schizophrenia that covers symptoms, biology,

course, and treatment. The National Alliance for the Mentally Ill (NAMI), founded in 1979, is a key source of information and support (available at NAMI.org). Most NAMI chapters run a very well-received program for relatives called the "Family-to-Family" program [69]. Dixon [70] has confirmed the benefit of this program in allaying anxiety and providing valuable information. Studies have found that psychoeducational programs for families produce an impressive reduction in relapse rates among ill family members [71]. One way that family approaches may differ for first-episode schizophrenia is that the multifamily approach, in which several families (along with their ill relatives) meet together, may be effective in theory [72] but may be logistically too difficult to implement when focused primarily on first-episode patients and their families [73], The unpredictability and inconsistent attendance of first-episode patients makes this treatment approach feasible only in tertiary services for first-episode patients. Under most clinical circumstances, family psychoeducation should be done for each family separately and tailored to the specific health beliefs and concerns of the particular family environment.

Psychopharmacology After the Diagnosis is Established
Transitioning from acute to maintenance pharmacotherapy
A major practical effect of establishing a diagnosis of schizophrenia is that it establishes the need for ongoing antipsychotic therapy beyond the end of the acute psychotic episode. If a diagnosis of schizophrenia can be made with confidence, then long-term maintenance antipsychotics are indicated. This is often a point of confusion. Many schizophrenia patients can achieve full remission after their first episode is successfully treated. But, the degree of improvement does not change the need for ongoing antipsychotic medication. It is the primary diagnosis that drives the recommendation. This is, of course, one of the most important consequences of the diagnostic endeavor. (Other possibilities include a presumptive diagnosis of an affective disorder, for which maintenance treatment might be changed to a mood-stabilizing agent, or a primary diagnosis of substance abuse/dependence, for which referral to a psychosocial treatment program specializing in drug and alcohol problems would become the primary focus.) In some cases it may not be possible to achieve a sufficient degree of confidence to recommend maintenance antipsychotic therapy even though clinical intuition suggests that a diagnosis of schizophrenia is most likely. In this discussion it is assumed that the diagnosis of schizophrenia is established and that maintenance antipsychotic treatment is clearly indicated.

Assuming that the treatment response has been adequate and that the antipsychotic medication is reasonably well tolerated, the current antipsychotic usually remains the choice for ongoing treatment. The time course of response to the acute psychotic episode is such that patients remain quite sensitive to symptom recurrence soon after responding to medication and being stabilized to continue with ongoing medication treatment. Accordingly, in theory, the antipsychotic dose needed to achieve acute efficacy should be continued well into the maintenance treatment period (eg, 3–6 months into outpatient treatment)

before any dose lowering is recommended. In practice this continuation of medication is easier said than done. First-episode patients typically are greatly relieved after the acute psychotic episode resolves, and are eager to put this experience behind them. The clinical import is that during the initial postacute treatment period (which often corresponds with the transition from inpatient to outpatient care), the patient attempts to put this experience behind them by ending treatment and stopping medication. Sometimes it is possible to work out a compromise so that the patient agrees to continue the medication but at a dose that is lower than before and lower than optimal for preventing relapse. In other words, the pharmacologic principle is that it is better for the patient to take some medication, even if it is not an optimal dose, if it is the only compromise that is acceptable. Likewise, the medication regimen needs to be tailored to what the patient is willing to take rather than to what has been prescribed. The medication regimen should be simplified even at the sacrifice of optimal efficacy. The overall approach here should be to prescribe the best pharmacologic regimen possible rather than the best possible pharmacologic regimen!

Changing antipsychotic medication

The time course of antipsychotic response is longer than the usual 4- to 6-week time period [74]. At the same time one should calibrate the response criteria to target a relatively complete control of positive and negative symptoms relative to what might be considered acceptable for a more persistently ill (chronic) patient. The initial goals of treatment should be aggressive and aim for resolution of positive symptoms and a return to premorbid (eg, before prodromal period) status. A detailed discussion of how to define a "good response" is beyond the scope of this article; it is important to note that full or almost full symptom remission is the goal of antipsychotic therapy. It is necessary to determine whether one antipsychotic agent works and to ensure that an appropriate dose of the antipsychotic was used before switching to another. Given the absence of fixed-dose studies of atypical antipsychotics in first-episode patients, dosing guidelines for using these agents in first-episode schizophrenia are generally extrapolated from available information on dosing in more chronic forms of schizophrenia. Typically, for first-episode patients, it is recommended that clinicians attempt to use the lower end of the therapeutic dosage range, at least during the initial phases of the first therapeutic treatment trial. Dosing recommendations for first-episode patients are derived from the *Expert Consensus Guidelines on Optimizing Pharmacologic Treatment of Psychotic Disorders* [75]. As in any other clinical situation, antipsychotic medications should be changed when the initial antipsychotic regimen does not have adequate efficacy or has unacceptable side effects. The caveat here is how the fact that the patient is early in the course of treatment may affect the operational criteria for "inadequate efficacy" or "intolerable side effects." The magnitude of weight gain and dyslipidemia from some of the newer agents is as large in first-episode cohorts as it is in chronically ill patients [76], however, and this weight gain is becoming

recognized as a significant limitation of some of the newer antipsychotic medications.

Treatment of postpsychotic depression

In contrast to other chronic mental illnesses, such as depression or alcoholism, suicide is likely to occur earlier in the course of schizophrenia. This observation, however, is a generalization, and suicidal behavior may be a risk for patients at any stage of the illness. Demoralization and consequent depression in reaction to the magnitude of impending lifelong disability can occur early in the course of schizophrenia [44] and are considered major risk factors—along with other general and demographic characteristics—for suicide in patients who have schizophrenia. Birchwood and colleagues [77] have described the chronology and course of depression in patients following an acute episode of schizophrenia. Although not a first-episode sample, patients whose depressive symptoms persisted as a postpsychotic depression had a higher rate of suicidal behavior than patients who had depressive symptoms only during the acute episode of psychosis. In a Scandinavian follow-up study of a cohort of 321 patients with a first episode of psychosis, 26% of patients had a history of suicidal behavior, and 26% had suicidal thoughts within the week before their initial assessment. During the 1-year follow-up of these patients, 31 (11%) attempted suicide. The presence of hallucinations and a history of suicidal behavior were predictors of suicidal behavior in this population [78].

Adherence to the primary antipsychotic medication should be evaluated before initiating adjunctive antidepressant therapy. Usually the risk of precipitating a relapse from prescribing antidepressants when patients are "covered" with a parallel antipsychotic is too high, and other strategies (eg, hospitalization) might be considered.

Medication nonadherence: it is not a matter of "whether?" but "when?"

To prevent relapse, maintenance antipsychotic treatment is as important for first-episode patients as it is for multiepisode, or "revolving door," schizophrenic patients [64]. Therefore, at least from a theoretical perspective, a diagnosis of schizophrenia establishes the need for ongoing maintenance antipsychotic medication, and the clinician should not waiver from the commitment to promoting long-term adherence to ongoing antipsychotic therapy. Translating this evidence-based knowledge into a useful treatment plan is easier said than done. Despite clinicians' recommendations otherwise, the question usually is not so much whether the first-episode patient will stop antipsychotic medications too soon. The answer to that question is almost always "Yes." The correct question is "When will the medication be stopped?"

Given the problem of poor compliance in first-episode schizophrenia, one treatment option is to consider the use of a long-acting route of medication. Until recently only the older antipsychotics were available in long-acting preparations. Given the other advantages of the newer antipsychotics, the older medications generally were not recommended for patients in such early stages of the illness, not because of the need for injection per se but because of their

side effect profile. The newer atypical antipsychotics now are the first-line treatment for schizophrenia [79,80]. Before long-acting risperidone became available, the major drawback of the first-line atypical agents was the lack of long-acting versions for continuous drug delivery. Clinicians had to struggle with the trade-off between recommending an oral atypical medication with superior efficacy and a reduced side burden or one of the older, less efficacious antipsychotic medications that can be given by long-acting injection [81,82]. This dilemma has changed with the availability of one of the atypical antipsychotics in a long-acting route of drug delivery [83–85]. Whether a long-acting route of medication delivery is more effective than oral administration within the class of newer atypical antipsychotics for first-episode patients is not known, but at least one randomized, prospective study has compared the long-term outcomes of first-episode patients treated with long-acting risperidone and those treated with an oral atypical antipsychotic agent. Preliminary findings show that most stabilized first-episode patients voluntarily accept a recommendation that they switch from an oral to a long-acting injection. The caveat here is that this acceptance is within the subset of first-episode patients who already had accepted a recommendation for outpatient follow-up, and that ''acceptance'' is defined as receiving one long-acting injection. Therefore, the impact of the long-acting route on first-episode outcome still is not known, but early results show that it is acceptable, and making the recommendation does not seem have any short-term detrimental effects on the therapeutic alliance or medication attitudes [82,86,87].

Choosing the maintenance antipsychotic medication for long-term treatment
Although the approach to choosing a maintenance antipsychotic is very similar to that used for choosing an antipsychotic before completing the final diagnostic evaluation for the ''first-episode'' patient during the acute psychotic episode, it is not the same. There is a general agreement within the expert community in the United States that, whenever possible, the first-line antipsychotic should be one of the first-line (nonclozapine) atypical antipsychotics. Provocative preclinical data and new neuroimaging data suggest that there may be differences in neuroprotective effects favoring the newer medications. Looked at another way, the older conventional antipsychotics may be more neurotoxic [88–90]. In a first-episode comparative treatment study, patients randomly assigned to either olanzapine or haloperidol received sequential neuroimaging assessments [88]. Over the course of 1 year, patients taking haloperidol showed a divergent pattern on MRI compared with patients treated with olanzapine. Patients treated with haloperidol showed a loss of gray and white cortical matter and enlarged ventricular volume. Because no comparable longitudinal MRI data exist for the other atypical antipsychotics, it is not known whether this finding is unique to olanzapine or is a class effect of the atypical agents relative to the older agents. Although the interpretation of MRI data is still speculative, it would parallel the clinical finding of lower rates of tardive dyskinesia from the newer medication [91]. Because tardive dyskinesia is a de facto marker

of central nervous system neurotoxicity, it is perhaps not a surprise that MRI studies show differential effects as well.

Beyond the general approach to favor one of the atypical antipsychotic, there is no consensus on the choice of the specific antipsychotic for long-term therapy. The issue of long-term safety is, of course, a very important consideration. The specific medication should take into account the patient's specific symptomatic profile, risk factors for adverse effects, and the adverse-effect profile of each antipsychotic agent under consideration. Of particular relevance in medication choice is minimizing the long-term medical risks of treatment, which include the neurologic risks of persistent EPS and tardive dyskinesia and the potential exacerbation of risk factors for diabetes mellitus and cardiovascular disease. Finally, medication adherence issues, if not already a central issue, are likely to be a major concern sometime within the first year of maintenance antipsychotic therapy.

The problem of poor adherence in first-episode schizophrenia
The treatment of a first-episode of schizophrenia is of critical importance in that it may establish–for better or worse–the acceptability of ongoing treatment in the years ahead. Despite responding relatively well, most will stop their medication within the first year of treatment. Naturalistic follow-up studies of ecologic samples find that only 25% of first-episode patients take antipsychotic medication consistently for the first year after starting treatment [92,93]. Many clinicians feel that being a ''first episode'' reduces the risk of relapse after medication discontinuation. Not so. The chances of relapsing from medication discontinuation are no different than chronically ill populations. In follow-up, nonadherence to medication is the greatest predictor of relapse [60,94]. Looked at another way, in terms of achieving improvements and recovery, continued medication adherence is by far and away the strongest clinical predictor of a patient's remaining stable and being able to achieve a sustained remission [95,96]. No pharmacologic or psychosocial treatment intervention studied so far has been able to prevent medication nonadherence among first-episode patients [97–99]. In a naturalistic follow-up study of a first-episode cohort treated in routine practice settings [92,93], less than one fifth of the first-episode cohort took antipsychotic medication consistently throughout the follow-up, and 65% had discontinued the antipsychotic medication for more than 2 weeks. The slope of the nonadherence curve shows that about one third of the cohort had a medication gap in the first 3 months after discharge. The slope then becomes more gradual, with another one third showing a first gap between 3 and 12 months. A first-episode patient has much to lose from stopping medication. The patient will probably suffer the pain and consequences of another acute psychotic episode much sooner rather than later. Today, nonadherence is a greater obstacle to the successful treatment of first-episode schizophrenia than any limitations in the efficacy of the newer medications.

Why do first-episode patients stop their medication? Many factors contribute to nonadherence, including efficacy problems, access barriers, and illness-related factors.

One of the basic elements of adherence, at least when it is self-directed, is to acknowledge that there is a problem that might need treatment. Therefore, failure to acknowledge or understand that there is a problem for which medications might be helpful becomes the primary motivational barrier to ongoing voluntary adherence. There is ample evidence that insight is impaired at the first onset of illness. Accordingly, it follows that for these patients adherence would be a substantial problem even when treatment for schizophrenia is first introduced. Novac [100] reported that medication noncompliance was best predicted by positive symptoms at admission and by lack of insight at discharge. In a similar study assessing compliance over the first 3 months of treatment among 59 Finnish first-episode patients, poor compliance was associated with side effects, male gender, lack of social activities, and global, but not positive, symptom severity [101,102]. First-episode patients are especially reluctant to accept a formal diagnosis of schizophrenia, or any other similar disorder with the associated stigma or a future of illness-based limitations and the need for ongoing treatment [103]. Refusal to accept such a diagnostic label may or may not extend to rejecting possible benefits from medication. This consideration is of particular importance for understanding nonadherence in immediate aftermath of a first episode of schizophrenia. The linking of medications to diagnosis is problematic for many first-episode patients who do not accept a diagnosis of mental illness but who otherwise might be willing to acknowledge that medications may be helpful for recovery.

Interventions for impending medication nonadherence in first-episode schizophrenia. One possible strategy to address the adherence problem in first-episode schizophrenia is to stop trying to fight against the overwhelming likelihood that a first-episode patient will stop antipsychotic medication too soon. Instead of trying to prevent nonadherence, perhaps it is better to focus on an overall strategy that reduces the harm from nonadherence. It might be more realistic to consider initial medication nonadherence as an expectable part of the recovery process. This expectation might change the therapeutic attitude from a pointless struggle to stop nonadherence and instead place a greater emphasis on maintaining the therapeutic alliance at all times regardless of the person's current adherence status. Such a long-term perspective may prevent the initial episodes of nonadherence after a first-episode from becoming entrenched in the years to come. From a research perspective, first-episode cohorts comprise an ideal population to study the potential impact of innovative therapeutic approaches. First-episode randomized pharmacologic studies comparing different antipsychotic agents show, at best, only marginal differences among medications in time until nonadherence [97,104]. These same studies show that nonpharmacologic factors such as the therapeutic alliance or insight are much more relevant predictors than are the side effects of the medication [99]. The authors' research group at SUNY Downstate Medical Center currently is conducting a prospective study evaluating the effectiveness of recommending a long-acting atypical antipsychotic (long-acting risperidone

microspheres) shortly after an initial episode of schizophrenia has been treated and the patient has stabilized. Early findings show that the majority of first-episode patients who successfully engage in outpatient treatment during the first month after discharge are willing to accept a recommendation of trying a long-acting route of antipsychotic medication. Initial reluctance to try a long-acting injection is usually amenable to a tailored psychoeducation intervention focusing on matching the goals of antipsychotic therapy to the long-term goals of the patient and family [105]. Whether the acceptance of a long-acting atypical antipsychotic translates into better clinical outcomes in terms of better adherence, stability, and sustained recovery is still under investigation.

SUMMARY

The understanding and therapeutic focus in schizophrenia have shifted, in part from the recognition that neurobiologic damage occurs early and often in the course of the illness. First-episode schizophrenia therefore constitutes a window of opportunity for timely, comprehensive, and effective therapeutic interventions. The next phase of longitudinal studies evaluating treatment outcome in first-episode schizophrenia will provide information about whether improved care at the onset of illness can translate into a better long-term outcome. Simultaneously, studies in high-risk persons and prodromal studies will determine whether shifting the definition of onset to an earlier ''incipient'' stage and intervening assertively at that point can result in improved outcomes and perhaps even a reduction in the incidence of schizophrenia. Gathering information from these lines of inquiry will take some years, but if they converge it will be possible to offer a much more optimistic view of schizophrenia to patients and relatives when they present to mental health care services. In fact, the awareness of these research efforts and promotion of such work in the public domain is already a powerful source of encouragement for individuals who currently struggle with schizophrenia.

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