The Early Stages of Schizophrenia: Speculations on Pathogenesis, Pathophysiology, and Therapeutic Approaches

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Schizophrenia is commonly considered a neurodevelopmental disorder that is associated with significant morbidity; however, unlike other neurodevelopmental disorders, the symptoms of schizophrenia often do not manifest for decades. In most patients, the formal onset of schizophrenia is preceded by prodromal symptoms, including positive symptoms, mood symptoms, cognitive symptoms, and social withdrawal. The proximal events that trigger the formal onset of schizophrenia are not clear but may include developmental biological events and environmental interactions or stressors. Treatment with antipsychotic drugs clearly ameliorates psychotic symptoms, and maintenance therapy may prevent the occurrence of relapse. The use of atypical antipsychotic agents may additionally ameliorate the pathophysiology of schizophrenia and prevent disease progression. Moreover, if treated properly early in the course of illness, many patients can experience a significant remission of their symptoms and are capable of a high level of recovery following the initial episode. Because the clinical deterioration that occurs in schizophrenia may actually begin in the prepsychotic phase, early identification and intervention may favorably alter the course and outcome of schizophrenia. Biol Psychiatry 2001;50:884–897 © 2001 Society of Biological Psychiatry

Introduction

Schizophrenia is widely considered to be a genetically mediated neurodevelopmental disorder. The neurodevelopmental theory of schizophrenia postulates that etiologic and pathogenic factors occurring long before the formal onset of the illness (probably in gestation) disrupt the course of normal neural development, resulting in subtle alterations of specific neurons and circuits, which confer vulnerability and may ultimately lead to malfunction (Figure 1) (Bloom 1993; Lewis and Lieberman 2000; Murray and Lewis 1987; Weinberger 1987). The consequences of these neurodevelopmental aberrations, however, do not immediately cause clinical manifestations in schizophrenia as in other neurodevelopmental disorders, such as autism, fragile X, or Down's syndrome. Rather, symptoms typically present after a latency period of 1–3 decades. At the same time, high-risk and longitudinal birth cohort studies have identified social, motor, and cognitive dysfunctions and mild physical anomalies during childhood and adolescence, before the onset of illness (Jones 1997). These features, however, are mild in severity and have low predictive validity as individual markers of schizophrenia (Erlenmeyer-Kimling and Cornblatt 1987; Fish 1977).

Clinical Course of Schizophrenia

The onset of the formal symptoms of schizophrenia is generally preceded by a prodromal phase. So-called prodromal symptoms and behaviors (i.e., those that herald the approaching onset of the illness) include attenuated positive symptoms (i.e., illusions, ideas of reference, magical thinking, superstitiousness), mood symptoms (i.e., anxiety, dysphoria, irritability), cognitive symptoms (i.e., distractibility, concentration difficulties), social withdrawal, or obsessive behaviors to name a few (McGlashan 1996). Because many of these prodromal phenomena extensively overlap with the range of mental experiences and behaviors of persons in the ages of risk who do not subsequently develop schizophrenia, prodromal symptoms cannot be considered diagnostic. It is precisely their nonspecificity and lack of high predictive validity that limits their utility for the purposes of early intervention (Gottesman and Erlenmeyer-Kimling 2001; Schaffner and McGorry 2001).
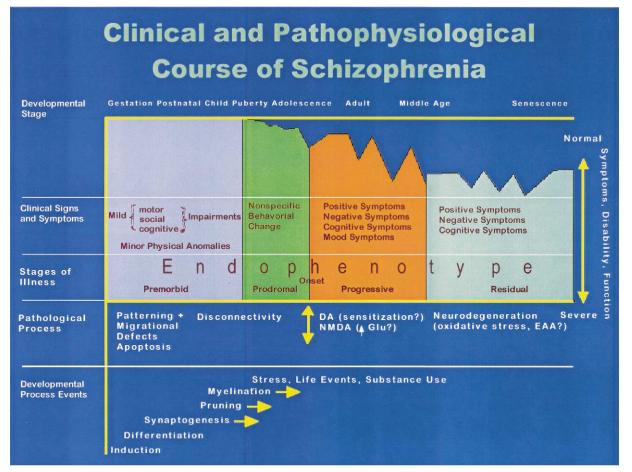
Figure 1. Clinical and pathophysiologic course of schizophrenia. This diagram attempts to integrate and schematically depict the clinical and pathophysiologic course of schizophrenia in its various clinical stages. To orient the reader starting from the top row: Developmental Stage describes the stage of life during which the various events and phenomena occur; Clinical Signs and Symptoms refers to the mental and behavioral manifestations of the illness; Stage of Illness describes all premorbid and morbid phases of the illness; Pathologic Process refers the hypothesized pathogenic and pathophysiologic mechanisms that underlie and are causal to the clinical manifestations of the disorder; Developmental Process and Events indicates the neurobiologic maturational processes and environmental events that may unmask or destabilize the neural circuits made vulnerable by etiologic and pathogenic factors. DA, dopamine; NMDA, N-methyl-D-aspartate; Glu, glutamate.

The development of frank psychotic symptoms marks the formal onset of first- episode schizophrenia, although this is usually not diagnosed for some time until the patient seeks or is brought to medical attention. Indeed, the duration of psychotic symptoms before diagnosis and treatment averages about 1 year, and if time from first appearance of prodromal symptoms is considered the average duration is about 3 years (McGlashan 1996). Despite this, most individuals recover symptomatically from the first episode; however, the majority of patients proceed to have one or more subsequent episodes in the form of psychotic relapses from which some proportion fail to recover, at least to the same degree as they had during their first or prior episode (Lieberman et al 1993, 1996; Robinson et al 1999b). This process of psychotic relapses, treatment failure, and incomplete recovery leads

many patients to a chronic course of illness, and persistent disturbances and deficits in perceptions, thought processes, and cognition (Lieberman 1999; McGlashan 1988). In this way, patients accumulate morbidity in the form of residual or persistent symptoms and decrements in function from their premorbid status. The process of accruing morbidity in the context of exacerbations and (relative) remissions has been attributed to progression of the illness (Kraepelin 1919) and described as "clinical deterioration" (Bleuler 1980).

Interestingly, although the majority of patients with schizophrenia exhibit this pattern of deterioration, this occurs to different degrees and different temporal sequences in the illness. Despite this variation, the deterioration process predominantly occurs in the early phases of the illness—in the prepsychotic prodromal period and

Table 1. Clinical and Pathologic Stages of Schizophrenia

Illness stage	Developmental stage	Clinical features	Pathophysiological process	Treatment
Premorbid	Gestation, infancy, childhood, early adolescence	Mild physical anomalies, poor motor coordination, mild cognitive impairments, social deficits	Neurodevelopmental: inductive, patterning, and synaptogenetic anomalies	None proven; potential for gene therapy
Prodromal	Adolescence and early adulthood	Nonspecific mood symptoms: anxiety, sadness, lability, irritability; sleep disturbances; cognitive impairment in attention, concentration; mild psychotic symptoms: illusions, suspiciousness, magical thinking; behavioral changes: substance use, social withdrawal, preoccupations	Maturational events (postpubertal hormonal effects, myelination, synaptic regression) interact with developmental anomalies to unmask vulnerabilities to neuroplastic dysfunction	None proven; potential for supportive and stress reduction therapies, potential use of GABA agonists, NMDA allosteric modulators, antioxidants, atypical antipsychotics
Onset/deteriorative	Adolescence and early adulthood	Psychosis, cognitive impairment, negative symptoms, and social deficits	Endogenous neurochemical sensitization involving meso-limbic-cortical-striatal circuits mediated by dopamine and glutamate	Antipsychotic drugs proven efficacy; potential use of neuroprotective agents
Chronic/residual	Adulthood, middle age, senescence	Negative symptoms, cognitive impairment, social deficits, and psychosis	Neuroprogression with limited neurotoxicity, loss of cell processes, possible induction of apoptosis of cortical-limbic striatal neurons.	Antipsychotics proven but limited efficacy; potential for use of experimental agents as adjuncts

Table 1 describes the hypothesized pathologic stages of schizophrenia from a developmental, clinical, and pathophysiological perspective and the corresponding therapeutic strategies currently utilized or considered. The prodromal stage is transitional from the premorbid to the onset/deteriorative phase.

GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate.

during the first 5–10 years after the initial episode (Figure 1). Following this, the illness stabilizes and, although there may be subsequent exacerbations, there is no continued illness-driven decline in functioning and increase in residual symptoms (although the most severe variants may continue to decline through senescence [Harvey et al 1999]).

Measures of Vulnerability and Pathophysiology

Schizophrenia emerges over time, and the illness can be conceptualized as having three pathophysiologic stages, which correspond to distinct clinical stages: neurodevelopmental (premorbid) stage, neuroplastic (prodromal, onset, and deteriorative) stage, and neuroprogressive (deteriorative and chronic/residual) stage (Table 1) (Lieberman et al 1997).

Measures of Vulnerability

It is well established that having a first-degree relative with a psychotic disorder increases risk of developing schizophrenia and related psychotic disorders (Gottesman 1991). Prenatal or birth complications (i.e., hypoxia, infection, toxic exposure) also are associated with increased risk for schizophrenia (Buka and Fan 1999; Cannon et al 2000). Although specific genes and epigenetic factors (i.e., occurring during gestation and birth) are believed to confer vulnerability for the development of schizophrenia, there are no clear and specific manifestations by which at-risk persons can be identified. High-risk and longitudinal birth cohort studies have identified several premorbid factors that indicate increased risk for schizophrenia, including family history, prenatal and perinatal complications, body dysmorphias, and mild premorbid deficits in social, motor, and cognitive functions during childhood and adolescence (Jones 1997). For example, subtle motor abnormalities during infancy (Walker and Lewine 1990) and deficits in social functioning, organizational ability, and intellectual functioning at ages 16–17 years have been associated with the later appearance of schizophrenia (Davidson et al 1999). In addition, individuals with schizophrenia have subtle but measurable

body dysmorphias, particularly of body structures that are derived from neural crest tissue and develop during the late first and second trimesters of fetal life (Maynard et al, 2001; Waddington et al 1999). All of these features, however, are mild in severity and have low predictive validity as individual markers.

Studies of individuals at risk for schizophrenia (such as first-degree relatives and individuals with schizotypal personality disorders) and first-episode patients have found that information processing deficits are one of the earliest clinical and cognitive markers of vulnerability for schizophrenia (Carter et al 1997; Nuechterlein and Dawson 1984; Nuechterlein et al, 1991, 1994; Pert et al 1992; Posner 1988; Weiss et al 1992). Attention deficits are present before the onset of the illness, and the clinical expression of the illness in high-risk adolescents (Cornblatt and Keilp 1994). Executive function impairments, including working memory, are also consistently demonstrated in patients with schizophrenia, as well as those with schizophrenia-spectrum disorders (Goldberg and Gold 1995). Although attention and executive function deficits have been associated with prefrontal cortical pathology in schizophrenia, other information processing deficits suggest a significant breakdown in hippocampal and temporal cortical functions.

Neurophysiologic studies of patients with schizophrenia have revealed abnormal auditory information selection processes during oddball tasks. These deficits have been found as early as the initial sensory processing stage of information, and suggest that sensory gating and attention deficits are core components of the pathophysiology of schizophrenia (Adler et al 1982; Boutros and Belger 1999). The observation of decreased P50 suppression in over half of the first-degree relatives of schizophrenic patients (Siegel et al 1984) suggests that P50 may be a vulnerability marker for schizophrenia and schizotypal personality disorder (Cadenhead et al 2000; Clementz et al 1998; Siegel et al 1984; Waldo et al 1991).

Recently, in utero ultrasonography was used to examine the brain structure in high-risk fetuses and showed that high-risk fetuses exhibited enlarged lateral ventricles compared with matched normal fetuses (Gilmore et al 2000). This evidence suggests that a genetic developmental diathesis of vulnerability for schizophrenia manifest in brain morphology is present long before the onset of symptoms and is reflected by characteristic features that are neither severe nor always specific.

Neuropathology of Schizophrenia

The proximal events that trigger the formal onset of schizophrenia are not known but may include normal neurobiologic maturational processes (i.e., experience-dependent axonal and dendritic proliferation, programmed cell death, axonal myelination, synaptic pruning) and environmental interactions, including gestational insults, trauma, stress, and substance abuse. This suggests the possibility that schizophrenia is unmasked or provoked by developmental biological events and/or environmental perturbations (Lieberman et al 1997; Weinberger 1987).

Evidence for a progressive, as well as a developmental, component to the illness is derived from recent neuroimaging studies in first-episode patients. These studies have found evidence of neuroanatomical changes at first treatment contact, as well as evidence of limited neuroanatomical progression. Comparisons of studies evaluating chronic patients with the few available studies of recent onset or first-episode patients with schizophrenia have revealed somewhat greater rates of morphologic abnormalities (reflected in the number of regions affected and the size of volume differences) in older and chronic patients (Bogerts et al 1993; Lieberman et al 1992).

Progression of neuropathology is suggested by the cross-sectional brain imaging studies that show that chronically ill schizophrenic patients have more numerous and severe structural brain abnormalities compared with first-episode patients; however, prospective imaging studies provide the most direct test of whether there is progression or stasis of brain abnormalities in schizophrenic patients. Three prospective studies of first-episode patients (DeLisi et al 1992, 1995, 1997; Gur et al 1998; Lieberman et al 1996, 2001) and five prospective studies of chronic patients (Davis et al 1998; Garver et al 1997; Gur et al 1998; Mathalon et al 2001; Rapoport et al 1999) have examined the progression of structural brain abnormalities and/or the relationship of progression to clinical course in patients with schizophrenia. These studies have produced mixed findings, but generally suggest that a subset of patients with poor treatment outcome or a more severe course are more likely to show progressive changes in brain morphology, with ventricular enlargement and cortical gray matter volume reductions as the most consistent findings. Some investigators have also found a negative correlation between patient compliance with antipsychotic medications and morphologic changes, suggesting that use of antipsychotics may slow disease progression in some patients (DeLisi et al 1992, 1995, 1997; Lieberman et al 2001; Nair et al 1997). There is also convincing evidence that patients with treatment-refractory childhood onset and geriatric schizophrenic patients have progressive ventricular enlargement (Davis et al 1998; Rappaport et al 1999).

Proton magnetic resonance spectroscopy (^{1}H MRS) is used to measure compounds such as N-acetylaspartate (NAA), which is a neuronal marker that reflects cell number and density (Stanley et al 1995b). Most ^{1}H MRS

studies, as well as postmortem studies, of patients with schizophrenia have shown reductions in NAA in either the frontal or temporal lobes (Akbarian et al 1993a, 1993; Bertolino et al 1996b; Buckley et al 1994; Choe et al 1994; Fukuzako et al 1995; Maier et al 1995; Nasrallah et al 1994; Renshaw et al 1995; Shioiri et al 1996; Yurgelun-Todd et al 1996), with some exceptions (Bartha et al 1997; Stanley et al 1996).

There is increasing evidence that NAA is a metabolically active metabolite that is influenced by pharmacologic treatment as well as disease state (Vion-Dury et al 1995). Bertolino et al (1996a) reported a highly significant effect of antipsychotic treatment in increasing the concentration of NAA in the dorsolateral prefrontal cortex (DLPFC) of patients with schizophrenia. Antipsychotic medications affect the concentration and activity of glutamate in the prefrontal cortex (Stanley et al 1996). Therefore, increases in NAA in the DLPFC associated with antipsychotic treatment may be mediated by increases in glutamate in this region.

Using ^{1}H MRS and ^{31}P MRS, investigators have found that patients with schizophrenia exhibit differences in the concentrations of NAA and various phosphomonoester (PME) and phosphodiester (PDE) moieties in specific brain regions, including the temporal and prefrontal cortex. N-acetylaspartate is an abundant amino acid located in neuronal cell bodies and processes. The PMEs are phospholipids involved in membrane synthesis, and PDEs are byproducts of lipid metabolism that are believed to reflect membrane turnover. Thus, these biochemical measures can be used to indirectly assess neuronal and glial mass, integrity, and turnover, which may reflect pathophysiologic processes. Investigators have found that NAA is consistently reduced in the temporal cortex in patients with schizophrenia (including first-episode patients), but less consistently so in other brain regions, notably the prefrontal cortex (Keshavan et al 2000). There have been no reports of longitudinal ^{1}H MRS studies of NAA.

^{31}P MRS studies of first-episode patients have described reduced concentrations of PMEs and elevated levels of PDEs primarily in the prefrontal cortex, suggesting increased phospholipid metabolism, possibly due to membrane turnover in response to a pathologic process, such as excessive synaptic pruning (Keshavan et al 1994; Pettegrew et al 1991; Stanley et al 1995b). Stanley et al (1995a) found that PMEs were generally lower in patients with schizophrenia at all stages of the illness, but PDEs were elevated in first-episode patients, perhaps reflecting a more fulminant process during that stage.

In another study of patients with schizophrenia in various stages of illness, Stanley and coworkers, using ^{1}H MRS, found higher glutamine concentrations in patients with schizophrenia compared with controls (Stanley et al 1996). In addition, glutamine concentrations were positively correlated with illness duration, and this relationship was not associated with the effects of age or treatment. Moreover, glutamine levels were reduced by antipsychotic drug treatment. The role of the excitatory amino acids (EAA), glutamate and aspartate, have been studied in detail in various preparations and animal models of neurodegeneration (Lieberman 1999). It has been proposed that the glutamate may induce slow excitotoxic effects that in turn induce the loss of cell processes, possibly through apoptosis in a manner that would not induce reactive gliosis (Jarskog et al 2000; Lieberman 1999b; Wang et al 1999). Abnormally elevated glutamine levels, therefore, may be associated with schizophrenia and disease progression.

Several investigators have described pathophysiologic processes that involve or could lead to neurodegeneration. These specifically implicate N-methyl-D-aspartate (NMDA) receptor hypofunction and excitotoxicity (Olney and Farber 1995), antagonism of NMDA receptors by N-acetylaspartylglutamate (NAAG) and consequent oxidative stress (Coyle and Puttfarcken 1993), reduction in γ-aminobutyric acid (GABA) interneuron-mediated inhibition of pyramidal neurons in the cingulate cortex (Benes 1995), and dopamine-mediated neurochemical sensitization (Laruelle et al 1999; Lieberman et al 1997) and neurotoxicity (Wyatt 1995) as pathogenic mechanisms (Table 1).

Treatment Strategies to Alter Course and Prevent Progression of Schizophrenia

Some authors have suggested that pharmacologic treatment suppresses the symptoms of schizophrenia but does not alter the course or potential progression of the disease (Hegarty et al 1994). In contrast, others have postulated that antipsychotic drugs ameliorate the pathophysiologic process that causes psychotic symptoms and leads to clinical deterioration (Jody et al 1990; Lieberman et al 1997; Wyatt 1991). Some of the most important evidence for the latter hypothesis is derived from treatment studies of first-episode patients and has shown associations between the duration of pretreatment psychosis and outcome (see references in Table 2).

Specifically, many, but not all, of these studies found that longer periods of active psychotic symptoms before first treatment were associated with worsened outcome. What is remarkable is that this relationship was present for outcomes measured in multiple ways, including the time to or level of recovery from the first episode, the time to or likelihood of relapsing after recovery from the first episode, and long-term outcomes measured globally for up to 5 years after beginning treatment for first-episode schizo-

Table 2. Duration of Untreated Psychosis and Outcome in First-Episode Schizophrenia

Reference	Study sample	Duration of illness	Duration of illness and outcome
Wyatt et al 1997	25 initially nonmedicated and 71 initially medicated patients with schizophrenia	DUP of initially non-medicated subjects is about 6 mos longer than DUP of initially medicated subjects	The initially nonmedicated subjects required more rehospitalization days during year 2 after discharge from the index hospital admission and had worse global functioning across a period of 6–7 y following index discharge
Waddington et al 1995	DUP has been regarded as a continuous variable in a multiple regression analysis in 88 subjects and as a dichotomous variable in between-groups comparisons of 49 short DUP (13.7 y ± 11.8 y) and 39 long DUP (21.2 y ± 12.9 y) subjects	DUP: mean 17.1 y, range 0–51 Duration of illness: mean 34.6 y, SD = 11.5	Longer DUP predicts more severe negative symptoms and general cognitive impairment at follow-up
Scully et al 1997	52 subjects	DUP: mean 13.9 y, SD = 11.9 Duration of illness: mean 43.1 y, SD = 10.3	Longer DUP predicts more severe negative symptoms and general cognitive impairment at follow-up, DUP is not associated with level of positive symptoms and executive dysfunction at follow-up
Jablensky et al 1992	78.2% of the 1379 initially examined patients completed 2-year follow-up and were included in the analysis of course and outcome	Not reported	Type of onset is a significant predictor of a 2-year pattern of course, % time spent in psychotic episodes, % time spent in complete remission, % time spent in unimpaired social functioning, and % time on antipsychotic medication. Patients with acute onset had the most favourable outcomes, patients with gradual onset had the least favourable outcomes, those with subacute onset were in the middle
Loebel et al 1992	$n = 70$ (54 with schizophrenia, 16 with schizoaffective disorder)	DUP: mean 51.9 wks, SD = 82.3 Duration of untreated illness: mean 150.8 wks, SD = 176.6 Duration of prodrome: Mean = 98.5 wks, SD = 156.6	Long DUP is associated with longer time to remission and lower level of remission after first psychotic break
Robinson et al 1999a	$n = 118$ dichotomized to long (more than 1 year) and short (less than 1 y) DUP groups	DUP: mean 71 wks, SD = 150 Duration of untreated illness: mean 143 wks, SD = 205	DUP is associated with treatment response at a level of significance $p = .03$
Robinson et al 1999b	$n = 104$	DUP: mean 64 wks, SD = 146 Duration of untreated illness: mean 119 wks, SD = 181	DUP of 1 y or longer does not predict first relapse
Szymansky et al 1996	n total = 70, duration of illness (DUP for the first-episode patients) is analyzed as a continuous variable	DUP of the 34 first-episode patients: Mean 3.2 y, SD = 4.3	Longer duration of untreated psychosis correlates with less improvement of positive symptoms in the first 6 mos of neuroleptic treatment

Table 2. (Continued)

Reference	Study sample	Duration of illness	Duration of illness and outcome
McGorry et al 1996a Harrigan et al 2000	200 first-episode cases with schizophrenia, schizophreniform, schizoaffective, delusional disorder, bipolar disorder with psychotic features, major depression with psychotic features, brief reactive psychosis, induced psychosis, and psychosis NOS	DUP total sample: mean 193.7 d, SD = 615.6, median 25; schizophrenia only: mean 1035, median 122; schizophreniform only: mean 28.1, median 10.5; nonschizophrenia/schizophreniform: mean 69.7, median 14 Duration of prodrome: mean 455.7 days, SD = 818.8, median 172.5	Longer DUP is correlated with longer duration of psychotic symptoms at first hospitalization. Better levels and rates of recovery are seen with DUP < 28 d. DUP is independent predictor of QOL at 12 mos. Longer DUP is correlated with more positive and negative symptoms, and poorer global functioning and quality of life at 12-month follow-up. DUP is an independent predictor of 12-month QLS, SANS negative, and BPRS positive symptoms
Edwards et al 1998	15 prolonged recovery cases compared to 212 non-prolonged recovery cases	DUP in the prolonged recovery group: mean 418.4 d, median 153, SD = 695.8 d	Association between long DUP and treatment resistance
Haas et al 1998	$n = 80$ with short DUP (less than 1 y) and $n = 23$ with long DUP (1 y or longer)	DUP of the short DUP group: mean 0.6 y, SD = 2.1 Duration of illness of the short DUP group: mean 5.9 y, SD = 6.9 DUP of the long DUP group: mean 4.3 y, SD = 4.0 Duration of illness of the long DUP group: mean 8.1 y, SD = 7.0	Long DUP is associated with more severe negative symptoms, but not with level of positive symptoms on admission. Short vs. long DUP groups did not differ in terms of length of index hospitalization. Long DUP is associated with more severe SAPS positive and SANS negative symptoms at discharge from index hospitalization. Greater improvement in GAS global functioning, from admission to discharge, for the short DUP group
Linszen et al 1998	$n = 76$ dichotomized to long (more than 1 y) and short (less than 1 y) DUP groups	Duration of untreated illness: mean 5.4 mos, SD = 11.0	DUP did not predict psychotic relapse during 12-month follow-up
Wiersma et al 1997	63 subjects with first-ever episode of nonaffective psychosis	Not reported	The duration of the first remission period is not predicted by mode of onset or DUP
Larsen et al 2000	43 first-episode patients of whom 32 had schizophrenia, 3 schizophreniform, 1 schizoaffective disorder, 5 delusional disorder, 2 brief reactive psychosis	DUP: Mean 114, median 26 wks	Long DUP is significantly corcorrelated with more negative and positive symptoms and poorer global functioning, and poorer level of remission at 1 year
Larsen et al 1998	34 first-episode patients with schizophrenia divided into long ($n = 17$, mean 244, median 182 wks, range 52–936, SD 203) and short ($n = 17$, mean 15, median 9 wks, range 1–52, SD 14) DUP groups	DUP: mean 130 wks median 54, range 1–936, SD = 203	Long DUP is associated with deteriorating course of premorbid functioning, weaker social network and more social withdrawal. DUP is not associated with PAS total scores, baseline GAF, and baseline PANSS positive, negative, and general symptoms scores

Table 2. (Continued)

Reference	Study sample	Duration of illness	Duration of illness and outcome
Madsen et al 1999	21 first-episode schizophrenic patients, 10 patients with other psychotic disorders, and 9 healthy volunteers	Not reported	DUP is not associated with nonresponsiveness to antipsychotic medications at 5-year follow-up. DUP is significantly correlated with cortical (mainly frontal) atrophy and sulcal enlargment at baseline as measured by CT
Craig et al 2000	For every diagnostic category DUP was divided into three groups	DUP: median 98 d (95% CI = 36.3-159.7) for patients with schizophrenia/schizoaffective disorder Median 9 d (95% CI = 5.7–12.3) for bipolar disorder Median 22 d (95% CI = 6.6-37.4) for psychotic depression	DUP is not associated with remission of positive symptoms, global functioning, and negative symptoms at 24 mos
Hoff et al 2000	50 subjects divided into short ($n = 15$) and long ($n = 35$) DUP groups with 1 y as the cutoff point	DUP: mean 11.4 mos, SD = 16.2, range 1–72 Duration of behavioral change: mean 3.4 y, SD = 6.1, range <1–41	No association between DUP and baseline MRI brain structure volumetric measurements or neuropsychologic summary scores
Ho et al 2000	74 subjects, DUP is treated as a continuous variable	DUP: mean 60.8 wks, median 13.5 SD = 130.5 Duration of untreated illness: mean 130.5 wks, SD = 204.5, median 53.5	DUP is not associated with time to positive symptom remission. DUP is not significantly correlated with quality of life or the severity of negative, psychotic, and disorganized symptoms at 6-month follow-up
Barnes et al 2000	53 subjects split around the median of 26 wks into short and long DUP groups	DUP: mean 59 wks, median 26, SD = 93 Duration of prodrome: mean 113.5 wks, SD = 232	No difference between the short and long DUP groups on measures of IQ or intellectual decline from premorbid level, oculomotor and neurocognitive function, psychomotor poverty, reality distortion, and disorganization syndrome scores at baseline. DUP is not associated with response to first exposure to antipsychotic medication as measured by the Brenner scale (Brenner et al 1990)
Drake et al 2000	248 subjects, DUP regarded as a continuous variable	DUP: mean 38 wks, median 12, range 4–624 16 patients had DUP between 2 and 16 y	Longer DUP was correlated with more positive and general PANSS symptoms, but not with more negative symptoms at baseline. Longer DUP predicts less improvement of PANSS during 6–12 wks of treatment
Whooley et al 1997	53 subjects dichotomized into short-term symptom (DUP less than 1 y, $n = 30$) and long-term symptom (DUP group of 1 y or longer, $n = 23$) groups. Patient's report was used for estimating DUP	DUP per patient report: mean 22.7 mos, median 6, SD = 36.8, range 1–240 DUP per family report: mean 15.9 mos, median 3, SD = 34.5, range 0–240	DUP is not associated with PANSS total and syndrome scores, but long DUP predicts significantly poorer quality of life at baseline evaluation
Bottlender et al 2001 (personal communication)	58 subjects, DUP is categorized in three groups: ≤6 mos ($n = 39$); >6 mos and ≤1 y ($n = 5$); and >1 y ($n = 14$)	DUP is less than 6 mos in 39 patients (67%), between 6 mos and 1y in 5 patients (8.6%), and more than 1 y in 14 patients (24.1%)	Longer DUP is associated with more pronounced negative, positive, and general psychopathological symptoms as well as lower global functioning 15 y after first hospitalization

Table 2. (Continued)

Reference	Study sample	Duration of illness	Duration of illness and outcome
Black et al 2001	19 subjects categorized into short (*n* = 9) and long (*n* = 10) DUP groups split around the median DUP of 57 wks	DUP total sample: median 57 wks Mean short DUP group 11.28 wks, Median 8.14 Mean long DUP group 147.8 wks, median 116.6	Long DUP is associated with more severe PANSS negative symptoms. DUP is not associated with PANSS positive or total PANSS ratings. Long DUP is associated with more severe positive symptoms and poorer global functioning at 6-month follow-up
Verdoux et al 2001	65 subjects divided into short (<3 mos) and long (≥3 mos) DUP groups	DUP: mean 22.7 mos, median 3, SD = 59.3	Subjects with long DUP are more likely to present with psychotic symptoms and continuous illness course over the 2-year follow up period

DUP, duration of untreated psychosis; NOS, not otherwise specified; QOL, quality of life; QLS, quality of life scale; SANS, scale for the assessment of negative symptoms; BPRS, Brief Psychiatric Rating Scale; SAPS, scale for the assessment of positive symptoms; GAS, global assessment scale; PANSS, positive and negative syndrome scale; CT, computed tomography; MRI, magnetic resonance imaging.

phrenia. Moreover, maintenance treatment studies have demonstrated the prophylactic effect of antipsychotic drugs in preventing relapse. Treatment may be responsible for mitigating the course of illness and producing more favorable outcomes (Davis and Andriukaitis 1986). With the advent of the second generation or atypical drugs, the question is asked whether they have any selectively beneficial effects that would improve outcome if used in first episode patients (Lieberman et al 1996). Preclinical studies suggest that antipsychotic drugs may do more than just suppress symptoms and ameliorate the underlying pathophysiology, forestall disease progression, and prevent morbidity from increasing (Mohn et al 1999; Olney and Farber 1995; Duncan et al 2000). Such a hypothesized effect could be achieved in a variety of ways. On a clinical level these drugs have superior efficacy in their rapidity and degree of symptom remission and prevention of relapse. Because they are better tolerated they should have higher rates of treatment adherence, which should result in fewer relapses. At a biologic level atypical drugs may be more effective at alleviating the pathophysiology of schizophrenia and may have a more efficient and effective mechanism of action. Preclinical studies suggest a possible basis for this hypothesized effect (Mohn et al 1999; Olney and Farber 1995; Duncan et al 2000). Based on the glutamate/NMDA receptor hypofunction model of schizophrenia, the ability of antipsychotic drugs to alter glutamate-mediated behavioral and cellular functions induced by NMDA antagonists have been examined. These studies show that conventional drugs can alleviate only some of the behavioral effects of NMDA antagonists (i.e., increased locomotor activity but not social isolation and acoustic startle responses) but that they do not block the cellular effects reflected by early immediate gene expression and uptake of 2-deoxyglucose, a marker of cellular metabolism. Moreover, studies with an NMDA knock-down mouse strain that only partially expresses the NR1 subunit of the NMDA receptor have demonstrated that the atypical drug clozapine blocks the abnormal behaviors (i.e., increased locomotor activity) at 1/40 the dose of haloperidol (Mohn et al 1999). Several clinical studies have also begun to examine this question. Preliminary reports from these suggest that there may be advantages in the use of atypical drugs that would lead to better long-term outcomes (Emsley 1999; McEvoy et al 2000).

The theory that schizophrenia is a genetically mediated, neurodevelopmental disorder suggested that affected individuals were "doomed from the womb" and consequently was pessimistic as to prognosis; however, recent studies have shown that most patients experience a substantial reduction and even remission of psychotic symptoms following the initial episode if treated properly early in the course of their illness, although associated negative and cognitive symptoms can persist (Whitesides et al 1998). These studies also revealed that individuals suffering first-episode psychosis experienced an alarming delay between onset of psychotic symptoms and initiation of treatment that averaged between 1 and 2 years (Table 2) (McGlashan 1999).

If the pathophysiology of schizophrenia is progressive, beginning at or before the onset of psychosis, then the potential for prompt or even early intervention would seem very compelling. Thus, the prospect that early intervention favorably alters the course and outcome of schizophrenia has exerted a powerful influence on psychiatric research and treatment strategies. If recovery and improved outcomes occur with earlier treatment that reduces the duration of active psychosis, then it is logical to try to intervene before the onset of illness. For this reason, the prodromal stage of schizophrenia has become a prime target for research and development of therapeutic strategies (McGlashan 1996; McGorry et al 1999).

The prodromal stage is believed to be a critical juncture in the course of schizophrenia because, not only does it herald the onset of psychosis and the manifestations by which the illness is diagnosed (and then treated), but because the clinical deterioration that occurs in the early stages of the illness may actually begin in the prepsychotic phase (Carpenter et al 1991; Hafner et al 1998). Indeed, the momentum toward early effective treatment intervention is so great that outreach programs for early identification and psychosis prevention services are now being developed and evaluated worldwide (McGlashan 1996).

Although overall, this represents a substantial advance in the attitude and approach to the clinical care of patients with schizophrenia, this movement has stimulated many questions and controversies (Lieberman and Fenton 2000). Among these is the feasibility and safety of early intervention, particularly with pharmacologic agents, before the establishment of a clear diagnosis. The effectiveness of such potentially powerful preventive strategies is dependent on the soundness of the methods, the certainty with which persons truly at risk for imminent illness can be identified, and understanding of the potential risks and benefits of careful watching versus preemptive treatment. There is a critical need for a better understanding of the natural history of the early stages of schizophrenia and how patients progress from the prodromal stage to the onset of psychosis.

Conclusions

There has been remarkably little study of the earliest stages of schizophrenia and the reasons why the duration of active first-episode psychosis is so prolonged. For example, the actual nature and time-course by which patients develop symptoms is largely unknown. Moreover, whether the mode and nature of the onset differs by gender, age of onset, or in relation to premorbid characteristics (i.e., intelligence quotient). Regarding treatment, it is not known how much of the duration of active psychosis is accounted for by delay in patients seeking treatment and how much is because of delay in establishment of diagnosis and initiation of treatment. If it is the former, then the question is whether this is associated with lack of disease awareness and recognition among patients, families, and friends. If the latter, then the question must be asked whether patients have ready access to mental healthcare. This is a public health problem of some magnitude. It is not clear how knowledge, skills, attitudes, beliefs, and barriers operate as determinants of help-seeking in individuals experiencing symptoms or in persons who notice symptoms in family members, friends, or acquaintances, and how these factors can be modified. Clearly, delay in seeking treatment by symptomatic pa-

tients potentially may be reduced by various measures, including development of community outreach programs and increasing public awareness of mental illness. Strategies, such as the integration of early detection teams into youth services in Australia (McGorry et al 1996b) and sustained antistigma-oriented social marketing in Norway (McGlashan 1996), are important pilot tests of innovative models to meet this challenge.

Historically, schizophrenia has been regarded with therapeutic pessimism; however, demonstration of good treatment outcomes in first-episode and recent-onset patients and the association between duration and episodes of active psychosis with progression and outcome of the disorder has generated efforts and hope that morbidity may be limited and the course of illness altered by early intervention. The advent of atypical antipsychotic drugs may be a consequential factor in this evolving therapeutic strategy, because their improved safety and efficacy profile compared with standard neuroleptics increases the likelihood that patients will adhere to treatment and potentially experience improved therapeutic effects. In addition, preliminary evidence suggests that atypical antipsychotics may have undefined properties that will more efficiently ameliorate the pathophysiology of schizophrenia associated with psychosis and thereby prevent disease progression; however, future studies of the onset of schizophrenia and advances in drug discovery may lead to new even more effective intervention and prevention strategies.

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